Applied Clinical Pharmacokinetics

LARRY A. BAUER

APPLIED CLINICAL PHARMACOKINETICS

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APPLIED CLINICAL PHARMACOKINETICS

Second Edition

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For all of the late dinners, all of the even later bedtimes, and all of the understanding, forgiveness, unconditional love, and support, I continue to be eternally grateful to my wife (S.P.B.) and my daughters (L.A.B. and L.E.B.) for allowing me the time and effort to produce another edition. Isn't it supposed to get easier each time?

—L.A.B.

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ABOUT THE AUTHOR

Larry A. Bauer, PharmD, is a Professor at the University of Washington School of Pharmacy and has been on the faculty since 1980. He also holds an adjunct appointment at the same rank in the Department of Laboratory Medicine where he is a toxicology consultant. He received his Bachelor of Science in Pharmacy degree (1977) from the University of Washington and his Doctor of Pharmacy degree (1980) from the University of Kentucky under the supervision of Dr. Robert Blouin. He also completed an ASHP-accredited hospital pharmacy residency (1980) specializing in clinical pharmacokinetics from A. B. Chandler Medical Center at the University of Kentucky under the preceptorship of Dr. Paul Parker. Dr. Bauer is a fellow of the American College of Clinical Pharmacology and the American College of Clinical Pharmacy.

Dr. Bauer's specialty area is in clinical pharmacokinetics; he teaches courses and offers clinical clerkships in this area. His research interests include the pharmacokinetics and pharmacodynamics of drug interactions, the effects of liver disease and age on drug metabolism, and computer modeling of population pharmacokinetics. He has over 155 published research papers, abstracts, books, and book chapters. Dr. Bauer is a member of several clinical pharmacology and clinical pharmacy professional organizations. He was consulting editor of *Clinical Pharmacy* (1981–1990), field editor of *ASHP Signal* (1981–1983), and a member of the editorial board of *Clinical Pharmacology and Therapeutics*. Currently, he is on the editorial board of *Antimicrobial Agents and Chemotherapy* and reviews for many other scientific publications. Dr. Bauer has precepted three postdoctoral fellows in clinical pharmacokinetics who currently have faculty appointments in schools of pharmacy or positions in the pharmaceutical industry.

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PREFACE

Upon beginning my thirtieth year as a pharmacist, the number of new approaches that continue to be developed for therapeutic drug monitoring impresses me. The second edition of *Applied Clinical Pharmacokinetics* includes new methods to dose immunosuppressants (2-hour postdose cyclosporine concentrations, area under the curve methods for cyclosporine and tacrolimus), and the elevation of what were new methods of dosing antibiotics to the mainstream (extended interval and area under the curve methods for aminoglycosides, trough-only monitoring for vancomycin). Other additions include more complete coverage of pediatric patients, dosing during hemoperfusion, an overview of methods preceding the initial and dosage adjustment sections, and a dosing strategies section that groups together initial and dosage adjustment techniques into a logical sequence. Of course, relevant sections, examples, problems, and references have been updated as needed for each chapter. However, one thing that remains unchanged is the general organization and philosophy of the book (please see the excerpt from the first edition following this section).

> Bernard of Chartres used to say that we are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size.—in Metalogicon (1159 A.D.), by John of Salisbury.

Depending on one's point of view, the discipline of therapeutic drug monitoring is entering its fifth decade. Some brilliant scientists and practitioners who have made significant contributions to the area (and whose names are in the reference list or attached to the methods recommended in this text) and changed the lives of countless patients are no longer with us. I extend my humble thanks to all of these exceptional individuals for making things a little bit clearer and a lot easier for the rest of us.

Larry A. Bauer, PharmD
June 2008

FROM *APPLIED CLINICAL PHARMACOKINETICS,* FIRST EDITION

The structure of this book is uniform for each chapter and is derived from my lectures in clinical pharmacokinetics. The introduction, which consists of a brief discussion of the clinical pharmacology and mechanism of action for the drug, is followed by sections that describe the therapeutic concentration range and anticipated adverse effects for the drug as well as a general monitoring scheme for the agent. Clinical monitoring parameters for therapeutic response and toxicity and basic clinical pharmacokinetic parameters for the compound are discussed next. The next sections describe the effects of disease states and conditions on the pharmacokinetics and dosing of the drug, and drug interactions that may occur with concurrent use of other agents. Each chapter concludes with a comprehensive presentation (with examples) of various methods to compute initial drug doses and to modify drug therapy regimens using serum concentrations to adjust doses. All dosing methods used in this text are ones that are published in peer-reviewed literature. Additionally, they are techniques that I have personal clinical experience with and have produced acceptable results in my practice and clinical clerkships. Finally, problems (with solutions) are included for each chapter so that the various dosing methods can be practiced. The problems are made up of brief clinical vignettes which, given a brief background, request that initial doses be computed or that dosage regimens be modified using drug concentrations.

This text is meant to teach clinical pharmacokinetic and therapeutic drug monitoring techniques to all clinical practitioners regardless of professional background. Pharmacists, physicians, nurse practitioners, and physician assistants are among the

individuals who could benefit from the text. With the advent of the almost-universal Doctor of Pharmacy degree in colleges of pharmacy, this book could be used in a pharmaceutics, pharmacokinetics, therapeutics, or clinical pharmacy course sequence. It is also possible to use this textbook in a self-directed manner to teach oneself or review important concepts and techniques. Every effort was made to make the chapters "student-friendly." Abbreviations are held to an absolute minimum. When abbreviations are used, they are defined near the place where they are used. Rather than using appendices, important information is repeated in each drug section so that readers do not need to jump from section to section for critical data. Multiple dosage computation and adjustment techniques for each drug, ranging from the simplest to the sophisticated, are presented. The easiest pharmacokinetic equations that produce accurate results are used in each instance.

It is my strong belief that clinical pharmacokinetics cannot be practiced in a vacuum. Individuals interested in using these dosing techniques for their patients must also be excellent clinical practitioners. Although it is true that "kinetics = dose," clinicians must be able to select the best drug therapy among many choices and appropriately monitor patients for therapeutic response, adverse drug effects, potential drug interactions, disease states and conditions that alter drug dosage, and so on. Thus, it is not acceptable to simply suggest a dose and walk away from the patient, satisfied that the job has been done. It is my sincere hope that this book will help clinicians increase their knowledge in the area of therapeutic drug monitoring and improve care to their patients.

Larry A. Bauer, PharmD
June 6, 2000

Part I

BASIC CONCEPTS

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1

CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC CONCEPTS

INTRODUCTION

Clinical pharmacokinetics is the discipline that applies pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens which optimize the therapeutic response of a medication while minimizing the chance of an adverse drug reaction. Pharmacokinetics is the study of the *absorption*, *distribution*, *metabolism,* and *excretion* of drugs.[1] When drugs are given extravascularly (e.g., orally, intramuscularly, applied to the skin via a transdermal patch, etc.), *absorption* must take place for the drug molecules to reach the systemic circulation. In order to be absorbed, the drug molecules must pass through several physiological barriers before reaching the vascular system. For example, when a medication is given orally, the drug dosage form must release drug molecules via dissolution, and the molecules must pass through the various layers of the gastrointestinal tract where they enter capillaries. *Distribution* occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart. *Metabolism* is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a *metabolite.* The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects. *Excretion* is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.

Pharmacodynamics is the relationship between drug concentration and pharmacological response. It is extremely important for clinicians to realize that the change in drug effect is usually not proportional to the change in drug dose or concentration (Figure 1-1). For example, when a drug dose or concentration is increased from a baseline value, the increase in pharmacological effect is greater when the initial dose or concentration is low compared to the change in drug effect observed when the initial dose or concentration is high. Thus, the

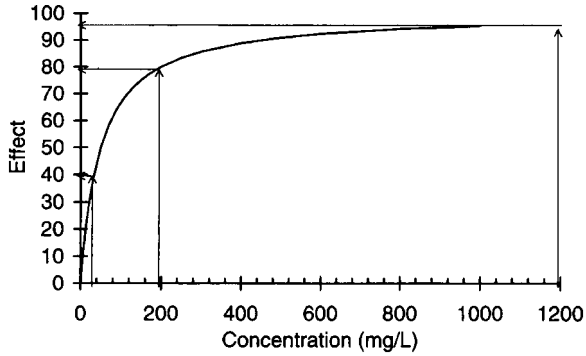

FIGURE 1-1 The relationship between drug concentration and response is usually a hyperbolic function: Effect = $(E_{max} \cdot C)/(EC_{50} + C)$, where E_{max} is the maximum effect and EC_{50} is the drug concentration where the drug effect equals $E_{max}/2$. After a dosage change is made and drug concentrations increase, the drug effect does not change proportionally. Further, the increase in pharmacological effect is greater when the initial concentration is low compared to the change in drug effect observed when the initial concentration is high. In this graph, the drug effect changes ~50% (from ~40 to 80 units) with a fivefold increase in concentrations at low levels (from ~40 to 200 mg/L), but only ~20% (from ~80 to 95 units) when the same five-fold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L).

increase in pharmacological effect that one observes in a patient as the dose is increased is subject to the law of diminishing returns and will eventually reach a maximum. The reason that most drugs follow this pattern is because their pharmacological effect is produced by forming a complex with a drug receptor. Once the drug-receptor complex is formed, the pharmacological effect is expressed. Often, toxic side effects of drugs follow the same type of dose- or concentration-response relationship, albeit shifted to the right on the dose or concentration axis. In clinical situations, patients may need to tolerate some side effects in order to obtain the maximal pharmacological effect of the agent.

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

When drugs are given on a constant basis, such as a continuous intravenous infusion or an oral medication given every 12 hours, serum drug concentrations increase until the rate of drug administration equals the rate of drug metabolism and excretion. At that point, serum drug concentrations become constant during a continuous intravenous infusion or exhibit a repeating pattern over each dosage interval for medications given at a scheduled time (Figure 1-2). For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic metabolism and renal excretion equals 50 mg/h. If cyclosporine is given orally at a dose of 300 mg every 12 hours, cyclosporine blood concentrations will follow a repeating pattern over the dosage interval which will increase after a dose is given (due to drug absorption from the gastrointestinal tract) and decrease after absorption is complete. This repeating pattern continues and eventually drug concentrations for each dosage interval become superimposable when the amount of cyclosporine absorbed into

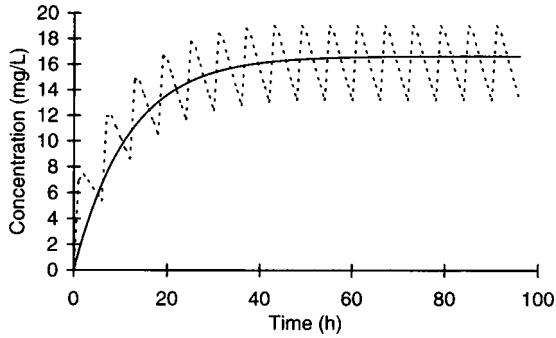

FIGURE 1-2 When medications are given on a continuous basis, serum concentrations increase until the rate of drug administration equals the elimination rate. In this case, the solid line shows serum concentrations in a patient receiving intravenous theophylline at a rate of 50 mg/h (solid line) and oral theophylline 300 mg every 6 hours (*dashed line*). Since the oral dosing rate (dose/dosage interval = 300 mg/6 h = 50 mg/h) equals the intravenous infusion rate, the drug accumulation patterns are similar. For the intravenous infusion, serum concentrations increase in a smooth pattern until steady state is achieved. During oral dosing, the serum concentrations oscillate around the intravenous profile, increasing during drug absorption and decreasing after absorption is complete and elimination takes place.

the body from the gastrointestinal tract equals the amount removed by hepatic metabolism over each dosage interval. Regardless of the mode of drug administration, when the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value. This equilibrium condition is known as *steady state* and is extremely important in clinical pharmacokinetics because usually steady-state serum or blood concentrations are used to assess patient response and compute new dosage regimens.

If a patient is administered several different doses until steady state is established, and steady-state serum concentrations are obtained from the patient after each dosage level, it is possible to determine a pattern of drug accumulation (Figure 1-3). If a plot of steady-state concentration versus dose yields a straight line, the drug is said to follow *linear pharmacokinetics*. In this situation, steady-state serum concentrations increase or decrease proportionally with dose. Therefore, if a patient has a steady-state drug concentration of 10 μg/mL at a dosage rate of 100 mg/h, the steady-state serum concentration will increase to 15 μg/mL if the dosage rate is increased to 150 mg/h (e.g., a 50% increase in dose yields a 50% increase in steady-state concentration).

While most drugs follow linear pharmacokinetics, in some cases drug concentrations do not change proportionally with dose. When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow *nonlinear pharmacokinetics*. When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the processes removing the drug from the body have become saturated. This phenomenon is known as *saturable* or *Michaelis-Menten pharmacokinetics*. Both phenytoin[2] and salicylic acid[3] follow Michaelis-Menten pharmacokinetics. When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations. Some drugs, such as valproic acid[4] and disopyramide,[5] saturate plasma

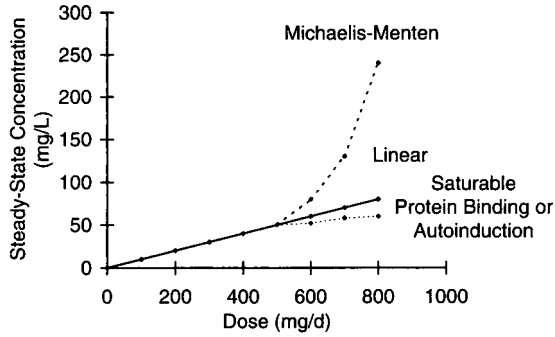

FIGURE 1-3 When doses are increased for most drugs, steady-state concentrations increase in a proportional fashion leading to linear pharmacokinetics (*solid line*). However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (*upper dashed line*), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (*lower dashed line*), saturable plasma protein binding or autoinduction are likely explanations.

protein binding sites so that as the dosage is increased steady-state serum concentrations increase less than expected. Other drugs, such as carbamazepine,[6] increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than anticipated. This process is known as *autoinduction* of drug metabolism. In either case, the relationship between steady-state concentration and dose for drugs that follow nonlinear pharmacokinetics is fraught with significant intersubject variability. Drugs that exhibit nonlinear pharmacokinetics are oftentimes very difficult to dose correctly.

Steady-state serum concentrations/dose plots for medications are determined in humans early during the drug development process. Because of this, by the time a new drug is available for general use it is usually known if the drug follows linear or nonlinear pharmacokinetics, and it is not necessary to determine this relationship in individual patients. Thus, the clinician treating a patient knows whether to anticipate linear or nonlinear pharmacokinetics and can assume the appropriate situation when adjusting drug doses. Dealing with drugs that follow linear pharmacokinetics is more straightforward and relatively easy. If a patient has been taking a medication long enough for steady state to have been established, and it is determined that a dosage adjustment is necessary because of lack of drug effect or the presence of drug toxicity, steady-state drug concentrations will change in proportion to dose for drugs that follow linear pharmacokinetics. For example, if a patient is taking sustained-release procainamide 1000 mg every 12 hours for the treatment of a cardiac arrhythmia, but is still having the arrhythmia, a clinician could obtain a steady-state procainamide serum concentration. If the procainamide concentration was too low (e.g., 4 μg/mL before the next dose), a dosage increase could help suppress the arrhythmia. Using linear pharmacokinetic principles, one could determine that a dosage increase to 1500 mg every 12 hours would increase the steady-state procainamide serum concentration to 6 μg/mL (e.g., new steady-state concentration = (new dose/old dose) × old steady-state concentration; new steady-state concentration = (1500 mg/1000 mg) × 4 μg/mL = 6 μg/mL).

CLEARANCE

Clearance (Cl) is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css): MD = Css · Cl. If one knows the clearance of a drug, and wants to achieve a certain steady-state serum concentration, it is easy to compute the required maintenance dose. Target steady-state concentrations are usually chosen from previous studies in patients that have determined minimum effective concentrations and maximum concentrations that produce the desired pharmacological effect but avoid toxic side effects. This range of steady-state concentrations is known as the *therapeutic range* for the drug. The therapeutic range should be considered as an initial guideline for drug concentrations in a specific patient; drug dose and steady-state concentrations should then be titrated and individualized based on therapeutic response. For example, the therapeutic range for theophylline is generally accepted as 10–20 μg/mL for the treatment of asthma with concentrations of 8–12 μg/mL considered as a reasonable starting point. If it were known that the theophylline clearance for a patient equaled 3 L/h and the desired steady-state theophylline serum concentration was 10 μg/mL, the theophylline maintenance dose to achieve this concentration would be 30 mg/h (10 μg/mL = 10 mg/L; MD = Css · Cl; MD = 10 mg/L · 3 L/h = 30 mg/h).

The definition of clearance is the volume of serum or blood completely cleared of the drug per unit time. Thus, the dimension of clearance is volume per unit time, such as L/h or mL/min. The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination. The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile. Drug metabolism is characterized as Phase I reactions, which oxidize drug molecules, and Phase II reactions, which form glucuronide or sulfate esters with drug molecules. In either case, the resulting metabolite is more water soluble than the parent drug, and is more likely to be eliminated in the urine.

The majority of drug metabolism is catalyzed by enzymes contained in the microsomes of hepatocytes known as the cytochrome P-450 (CYP) enzyme system. This family of enzymes is very important to understand because specific enzymes are responsible for the metabolism of each drug entity. Once it is known that a patient is deficient in one of the enzymes, usually because the clearance of a known drug substrate is very low resulting in high steady-state serum concentrations for a low to moderate dose, it can be inferred that all drugs metabolized by that enzyme will have a low clearance, and doses of other drugs that are substrates of the enzyme may be empirically reduced. If a metabolic drug interaction occurs between one medication and another known to be a substrate for a specific enzyme, it can be assumed that a drug interaction will occur between that drug and other substrates of the same enzyme. The enzymes are classified using a series of numbers and letters, and indicate how closely related the enzymes are to each other using amino acid sequencing. As an example of the classification scheme, the enzyme known as CYP3A4 is named because it is part of the cytochrome P-450 family, the major family group is "3," the subfamily group within the family is "A," and the specific, individual enzyme within the subfamily is "4." Thus, using this scheme, one can tell that CYP2C9 and CYP2E1 belong to the same family, and CYP2C9 and CYP2C19 belong to the same subfamily and are closely related, but are different enzymes. Table 1-1

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[7, 8]

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Acetaminophen Caffeine Clomipramine Imipramine Nortriptyline Ondansetron Phenacetin Tacrine	Atazanavir Cimetidine Ciprofloxacin Enoxacin Erythromycin Fluvoxamine Interferon Mexiletine	Barbiturates Carbamazepine Charcoal-broiled meat Omeprazole Phenobarbital Primidone Rifampin Tobacco/Marijuana
Smoke	Theophylline (R)-Warfarin Zileuton	Tacrine Zileuton	
CYP2B6 PM: ~4% Caucasians	Bupropion Cyclophosphamide Ifosfamide	Thiotepa Ticlopidine	Phenobarbital Rifampin
CYP2C9 PM: ~7% Caucasians	Candesartan Celecoxib Chlorpropamide Diclofenac Dronabinol Glipizide Glyburide Ibuprofen Losartan Naproxen Phenytoin Piroxicam Sulfamethoxazole Tolbutamide Torsemide Valsartan (S)-Warfarin	Amiodarone Atazanavir Clopidogrel Cotrimoxazole Delavirdine Disulfiram Efavirenz Fluconazole Fluvastatin Fluvoxamine Imatinib Isoniazid Leflunomide Metronidazole Miconazole Sulfamethoxazone Sulfinpyrazole Voriconazole Zafirlukast	Aminoglutethimide Barbiturates Carbamazepine Phenobarbital Phenytoin Primidone Rifampin
CYP2C19 PM: ~4% Caucasians ~20% Japanese & Chinese	Amitriptyline Carisoprodol Citalopram Clomipramine Desmethyldiazepam Diazepam Hexobarbital Imipramine Lansoprazole (S)-Mephenytoin Nelfinavir Omeprazole Pantoprazole Phenytoin	Chloramphenicol Cimetidine Clopidogrel Delavirdine Efavirenz Felbamate Fluconazole Felbamate Fluoxetine Fluvoxamine Isoniazid Modafinil Omeprazole Oxcarbazepine	Barbiturates Phenytoin Rifampin St. John's Wort

(*Continued*)

TABLE 1-1 (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP2C19 *(continued)*	Primidone Propranolol Sertraline Voriconazole (R)-Warfarin	Ticlopidine Voriconazole	
CYP2D6 PM: ~8% Caucasians ~3% African-Americans ~1% Japanese & Chinese	Amitriptyline Carvedilol Chlorpromazine Clomipramine Codeine Debrisoquin Desipramine Dextromethorphan Encainide Flecainide Fluoxetine Fluvoxamine Haloperidol Hydrocodone Imipramine Maprotiline Methamphetamine (S)-Metoprolol Mexiletine Nortriptyline Oxycodone Paroxetine Perhexiline Perphenazine Propafenone Propranolol Risperidone Sertraline Sparteine Thioridazine Timolol Tramadol Trazodone Venlafaxine	Amiodarone Bupropion Chloroquine Chlorpheniramine Chlorpromazine Cimetidine Cinacalcet Clemastine Diphenhydramine Duloxetine Fluoxetine Haloperidol Hydroxyzine Imatinib Paroxetine Perphenazine Promethazine Propafenone Propoxyphene Quinidine Ritonavir Sertraline Terbinafine Thioridazine Tripelennamine	
CYP2E1	Acetaminophen Chlorzoxazone Enflurane Ethanol Halothane Isoflurane Theophylline	Disulfiram	Ethanol Isoniazid

(*Continued*)

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[7, 8] (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP3A family (includes 3A4, 3A5, 3A7)	Alfentanil Alprazolam Amiodarone Amlodipine Astemizole Atorvastatin Bepridil Bromocriptine Buspirone Carbamazepine Cerivastatin Chlorpheniramine Cilostazol Cisapride Clarithromycin Clonazepam Clopidogrel Cyclosporine Delavirdine Dexamethasone Diazepam Diltiazem Disopyramide Donepezil Doxorubicin Erythromycin Ethinyl Estradiol Etoposide Felodipine Fentanyl Finasteride Flurazepam Hydrocortisone Indinavir Isradipine Itraconazole Ketoconazole Lansoprazole Lidocaine Loratadine Losartan Lovastatin Methylprednisolone Midazolam Nefazodone Nelfinavir Nicardipine Nifedipine Nimodipine	Amiodarone Amprenavir Aprepitant Atazanavir Clarithromycin Danazole Darunavir Delavirdine Diltiazem Erythromycin Fluconazole Fluvoxamine Grapefruit Juice Imatinib Indinavir Isoniazid Itraconazole Ketoconazole Mifepristone Miconazole Nefazodone Nelfinavir Norfloxacin Quinupristin Ritonavir Saquinavir Tamoxifen Telithromycin Troleandomycin Verapamil Voriconazole Zafirlukast	Aminoglutethimide Barbiturates Bexarotene Bosetan Carbamazepine Dexamethasone Efavirenz Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin Primidone Rifabutin Rifampin St. John's Wort Troglitazone

(*Continued*)

TABLE 1-1 (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP3A family (includes 3A4, 3A5, 3A7) *(continued)*	Nisoldipine Nitrendipine Oxycodone Pioglitazone Prednisolone Prednisone Progesterone Quinidine Quinine Rifabutin Ritonavir Salmeterol Saquinavir Sildenafil Simvastatin Sirolimus Sufentanil Tacrolimus Telithromycin Teniposide Terfenadine Testosterone Theophylline Topiramate Triazolam Troleandomycin Vardenafil Verapamil Vinblastine Vincristine Voriconazole Zalepion Ziprasidone Zolpidem Zonisamide		

lists the cytochrome P-450 enzymes responsible for the majority of drug oxidative metabolism in humans along with examples of known substrates, inhibitors, and inducers.[7, 8] Some ethnic groups are deficient in certain enzyme families to a varying extent, and this information is included. P-glycoprotein (PGP) is a transport protein responsible for the active secretion of drugs into the bile, urine, and gastrointestinal tract. Table 1-2 lists PGP substrates, inhibitors, and inducers.[8]

The kidney eliminates drugs by glomerular filtration and tubular secretion in the nephron. Once drug molecules have entered the urine by either of these processes, it is possible that the molecules may reenter the blood via a process known as *tubular reabsorption.* Glomerular filtration and, usually, tubular reabsorption are passive processes. *Tubular secretion* is an active process usually mediated by a transport molecule which

TABLE 1-2 P-Glycoprotein Substrates, Inhibitors, and Inducers[8]

SUBSTRATES	INHIBITORS	INDUCERS
Atorvastatin	Amiodarone	Carbamazepine
Azithromycin	Clarithromycin	St. John's Wart
Cetirizine	Cyclosporine	Rifampin
Cyclosporine	Diltiazem	
Daunorubicin	Erythromycin	
Desloratadine	Grapefruit juice	
Digoxin	Indinavir	
Diltiazem	Itraconazole	
Doxorubicin	Ketoconazole	
Erythromycin	Nicardipine	
Etoposide	Nelfinavir	
Fexofenadine	Propafenone	
Indinavir	Quinidine	
Loperamide	Ritonavir	
Nelfinavir	Saquinavir	
Ondansetron	Tacrolimus	
Paclitaxel	Tamoxifen	
Quinidine	Testosterone	
Rifampin	Verapamil	
Ritonavir		
Saquinavir		
Tacrolimus		
Verapamil		
Vinblastine		
Vincristine		

facilitates the transfer of drug across the kidney tubule. The majority of drug tubular secretion takes place in the proximal tubule of the nephron while tubular reabsorption usually takes place in the distal tubule of the nephron.

The clearance for an organ, such as the liver or kidney, that metabolizes or eliminates drugs is determined by the blood flow to the organ and the ability of the organ to metabolize or eliminate the drug.[9] Liver blood flow (LBF) and renal blood flow (RBF) are each ~ 1–1.5 L/min in adults with normal cardiovascular function. The ability of an organ to remove or extract the drug from the blood or serum is usually measured by determining the extraction ratio (ER), which is the fraction of drug removed by the organ, and is computed by measuring the concentrations of the drug entering (C_{in}) and leaving (C_{out}) the organ: $ER = (C_{in} - C_{out})/C_{in}$. Liver or renal blood flow and the extraction ratio for a drug are rarely measured in patients. However, the extraction ratio is oftentimes determined during the drug development process, and knowledge of this parameter can be extremely useful in determining how the pharmacokinetics of a drug will change during a drug interaction or if a patient develops hepatic, renal, or cardiac failure.

The drug clearance for an organ is equal to the product of the blood flow to the organ and the extraction ratio of the drug. Therefore, hepatic clearance (Cl_H) for a drug would be determined by taking the product of liver blood flow and the hepatic extraction ratio (ER_H) for the drug ($Cl_H = LBF \cdot ER_H$), and renal clearance (Cl_R) for a medication would be determined by multiplying renal blood flow and the renal extraction ratio for the agent ($Cl_R = RBF \cdot ER_R$). For example, verapamil has a hepatic extraction ratio of 90% ($ER_H = 0.90$).

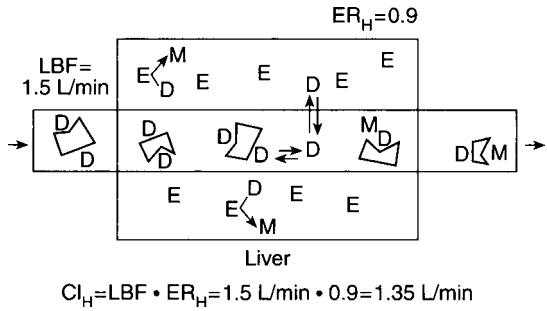

FIGURE 1-4 This schematic depicts the liver (*large box*) with the blood vessel supplying blood to it. When drug molecules (*D*) enter an organ (blood flows from left to right) that clears the drug, they may be bound to plasma proteins (*trapezoid shapes*) or exist in the unbound state. The unbound or "free" drug molecules are in equilibrium with the bound drug in the blood and unbound drug in the tissue. Drug-protein complexes are usually too big to diffuse across biologic membranes into tissues. Drug molecules that have entered hepatic tissue may encounter an enzyme (*E*) that metabolizes the drug. When this occurs the drug is chemically converted to a metabolite (*M*) which can diffuse back into the blood and leave the liver along with drug molecules that were not metabolized. The clearance of drug is equal to the blood flow to the organ (*LBF*) times the extraction ratio (ER_H) for the organ.

For patients with normal liver blood flow (LBF = 1.5 L/min), hepatic clearance would be expected to equal 1.35 L/min ($Cl_H = LBF \cdot ER_H$, $Cl_H = 1.5$ L/min $\cdot$ 0.90 = 1.35 L/min; Figure 1-4). The total clearance for a drug is the sum of the individual clearances for each organ that extracts the medication. For example, the total clearance (Cl) for a drug that is metabolized by the liver and eliminated by the kidney is the sum of hepatic and renal clearance for the agent: $Cl = Cl_H + Cl_R$.

Hepatic Clearance

The physiologic determinates of hepatic clearance have been extensively studied.[9–11] Another way to think of hepatic clearance is to recognize that its value is a function of the intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance); the fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α_1-acid glycoprotein, or lipoproteins, but is present in the unbound, or "free," state (unbound fraction of drug); and liver blood flow. The *intrinsic clearance* (Cl'_{int}) is the inherent ability of the enzyme to metabolize the drug and is the quotient of the Michaelis-Menten constants V_{max} (maximum rate of drug metabolism) and Km (drug concentration at which the metabolic rate equals $V_{max}/2$; $Cl'_{int} = V_{max}/Km$) for the unbound drug. The unbound fraction of drug in the blood or serum (f_B) is the unbound drug concentration divided by the total (bound + unbound) drug concentration. The relationship between the three physiological factors and hepatic drug clearance is:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Fortunately, most drugs have a large hepatic extraction ratio ($ER_H \geq 0.7$) or a small hepatic extraction ratio ($ER_H \leq 0.3$), and the relationship is simplified in these situations.

For drugs with a low hepatic extraction ratio, hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance: $Cl_H = f_B \cdot Cl'_{int}$. In this case, drug interactions that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood ($\uparrow f_B$); more unbound drug molecules will be able to leave the vascular system (drug-protein complexes are far too big to exit the vascular system) and enter hepatocytes where the additional unbound drug will be metabolized and hepatic drug clearance will increase. Additionally, drug interactions that inhibit or induce the cytochrome P-450 enzyme system (decreasing or increasing Cl'_{int}, respectively) will change the hepatic clearance of the medication accordingly. The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease. Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

For drugs with high hepatic extraction ratios, hepatic clearance is mainly a function of liver blood flow: $Cl_H = LBF$. The rate limiting step for drug metabolism in this case is how much drug can be delivered to the liver because the capacity to metabolize drug is very large. In this case, hepatic clearance is very sensitive to changes in liver blood flow due to congestive heart failure or liver disease. However, the hepatic clearance of drugs with high extraction ratios does not change much when protein binding displacement or enzyme induction or inhibition occurs due to drug interactions. Examples of drugs with high hepatic extraction ratios are lidocaine, morphine, and most tricyclic antidepressants.

Renal Clearance

The physiological determinants of renal clearance are glomerular filtration rate (GFR), the free fraction of drug in the blood or serum (f_B), the clearance of drug via renal tubular secretion (Cl_{sec}), and the fraction of drug reabsorbed in the kidney (FR): $Cl_R = [(f_B \cdot GFR) + Cl_{sec}](1 - FR)$.[12,13] Average glomerular filtration rates in adults with normal renal function are 100–120 mL/min. Since tubular secretion is an active process, it has been described by an equation similar to that used to explain liver metabolism:

$$Cl_{sec} = [RBF \cdot (f_B Cl'_{sec})] / [RBF + (f_B Cl'_{sec})],$$

where Cl'_{sec} is the intrinsic clearance due to active tubular secretion. Thus, the entire equation is:

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

If the renal clearance of a drug is greater than glomerular filtration rate, it is likely that the drug was eliminated, in part, by active tubular secretion. The aminoglycoside antibiotics and vancomycin are eliminated primarily by glomerular filtration. Digoxin, procainamide, ranitidine, and ciprofloxacin are eliminated by both glomerular filtration and active tubular secretion.

In some cases, glomerular filtration rate and renal tubular secretion function may be measured in patients with renal disease. However, for the purposes of drug dosing, glomerular filtration rate is approximated by measuring or estimating creatinine clearance for a patient. Creatinine is a by-product of muscle metabolism that is eliminated primarily by glomerular filtration.

VOLUME OF DISTRIBUTION

Volume of distribution (V) is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered: LD = Css · V (Figure 1-5). However, it is rare to know the exact volume of distribution for a patient because it is necessary to administer a dose on a previous occasion in order to have computed the volume of distribution. Thus, usually an average volume of distribution measured in other patients with similar demographics (age, weight, gender, etc.) and medical conditions (renal failure, liver failure, heart failure, etc.) is used to estimate a loading dose (Figure 1-6). Because of this, most patients will not actually attain steady state after a loading dose, but, hopefully, serum drug concentrations will be high enough so that the patient will experience the pharmacological effect of the drug.

The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body. Thus, the dimension of volume of distribution is in volume units, such as L or mL. At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is equal to the quotient of the amount of drug in the body (A_B) and the volume of distribution: $C = A_B/V$. The volume of distribution can be

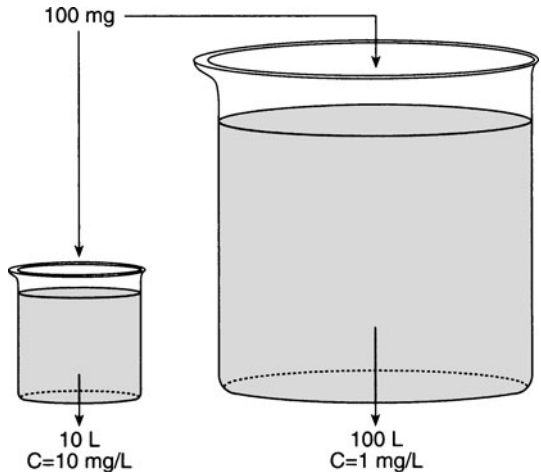

FIGURE 1-5 The volume of distribution (*V*) is a hypothetical volume that is the proportionality constant which relates the concentration of drug in the blood or serum (*C*) and the amount of drug in the body (A_B): $A_B = C \cdot V$. It can be thought of as a beaker of fluid representing the entire space that drug distributes into. In this case, one beaker, representing a patient with a small volume of distribution, contains 10 L while the other beaker, representing a patient with a large volume of distribution, contains 100 L. If 100 mg of drug is given to each patient, the resulting concentration will be 10 mg/L in the patient with the smaller volume of distribution, but 1 mg/L in the patient with the larger volume of distribution. If the minimum concentration needed to exert the pharmacological effect of the drug is 5 mg/L, one patient will receive a benefit from the drug while the other will have a subtherapeutic concentration.

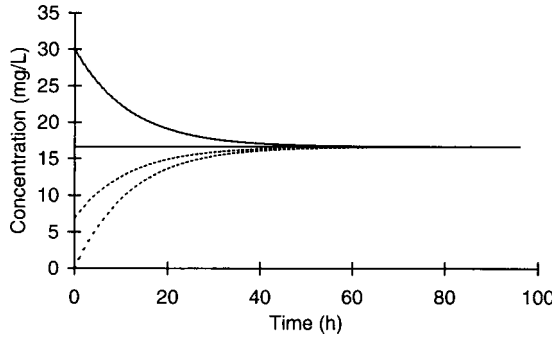

FIGURE 1-6 If the volume of distribution (*V*) is known for a patient, it is possible to administer a loading dose (*LD*) that will attain a specified steady-state drug concentration (*Css*): LD = Css · V. This example depicts the ideal loading dose given as an intravenous bolus dose followed by a continuous intravenous infusion (*solid line* starting at 16 mg/L) so steady state is achieved immediately and maintained. If a loading dose was not given and a continuous infusion started (*dashed line* starting at 0 mg/L), it would take time to reach steady-state concentrations, and the patient may not experience an effect from the drug until a minimum effect concentration is achieved. This situation would not be acceptable for many clinical situations where a quick onset of action is needed. Since the volume of distribution is not known for a patient before a dose is given, clinicians use an average volume of distribution previously measured in patients with similar demographics and disease states to compute loading doses. When this is done, the patient's volume of distribution may be smaller than average and result in higher than expected concentrations (*solid line* starting at 30 mg/L) or larger than average and result in lower than expected concentrations (*dotted line* starting at 7 mg/L). In these cases, it still takes 3–5 half-lives to reach steady-state, but therapeutic drug concentrations are achieved much sooner than giving the drug by intravenous infusion only.

very small if the drug is primarily contained in the blood (warfarin V = 5–7 L), or very large if the drug distributes widely in the body and is mostly bound to bodily tissues (digoxin V = 500 L).

The physiologic determinates of volume of distribution are the actual volume of blood (V_B) and size (measured as a volume) of the various tissues and organs of the body (V_T). Therefore, a larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother. How the drug binds in the blood or serum compared to the binding in tissues is also an important determinate of the volume of distribution for a drug. For example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so that the free fraction of drug in the blood (f_B) is very small. Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small. The equation that relates all of these physiologic determinates to the volume of distribution is:[14]

$$V = V_B + \frac{f_B}{f_T} V_T$$

This equation can help clinicians understand why a drug has a large or small volume of distribution, or why the volume of distribution might change under various circumstances. An example is how the volume of distribution changes when plasma protein binding drug interactions occur. If a drug that is highly bound to plasma proteins is given to a patient, and then a second drug that is also highly bound to the same plasma protein is given concurrently, the second drug will compete for plasma protein binding sites and displace the first drug from the protein. In this case, the free fraction in the serum of the first drug will increase ($\uparrow f_B$), resulting in an increased volume of distribution: $\uparrow V = V_B + (\uparrow f_B/f_T)V_T$.

HALF-LIFE AND ELIMINATION RATE CONSTANT

When drugs that follow linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion (Figure 1-7). When the same data is plotted on a semilogarithmic axis, serum concentrations decrease in a linear fashion after drug absorption and distribution phases are complete (Figure 1-8). This part of the curve is known as the *elimination phase.* The time that it takes for serum concentrations to decrease by $^1/_2$ in the elimination phase is a constant and is called the *half-life* ($t_{1/2}$). The half-life describes how quickly drug serum concentrations decrease in a patient after a medication is administered, and the dimension of half-life is time (hour, minute, day, etc.). Another common measurement used to denote how quickly drug serum concentrations decline in a patient is the elimination rate constant (k_e). The dimension for the elimination rate constant is reciprocal time ($hour^{-1}$, $minute^{-1}$, day^{-1}, etc.). If the amount of drug in the body is known, the elimination rate for the drug can be computed by taking the product of the elimination rate constant and the amount of drug in the body (A_B): elimination rate = $A_B \cdot k_e$. The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known: $t_{1/2} = 0.693/k_e$. The elimination rate constant can also be measured graphically by computing the slope of the log concentration

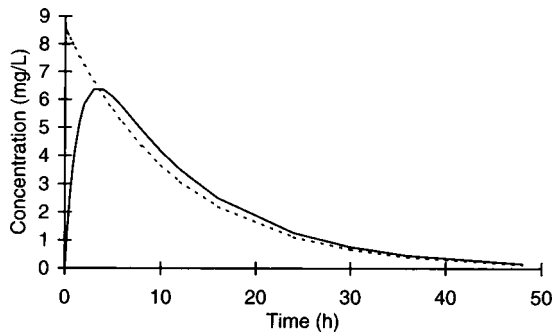

FIGURE 1-7 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on rectilinear axes, serum concentrations decline in a curvilinear fashion in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete.

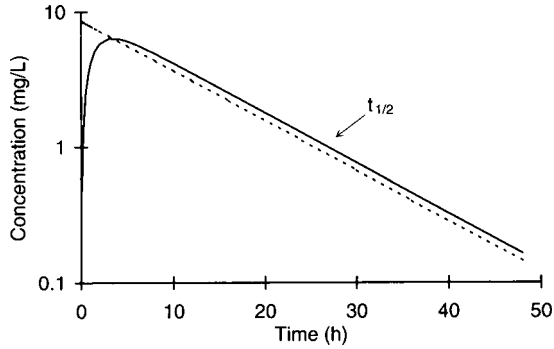

FIGURE 1-8 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on semilogarithmic axes, serum concentrations decline in a straight line in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete. This same data set is plotted in Figure 1-7 on rectilinear axes.

versus time graph during the elimination phase: using $\log_{10}$, $k_e/2.303 = -(\log C_1 - \log C_2)/(t_1 - t_2)$; or, using natural logarithms, $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$.

The half-life is important because it determines the time to steady state during the continuous dosing of a drug and the dosage interval. The approach to steady-state serum concentrations is an exponential function. If a drug is administered on a continuous basis for 3 half-lives, serum concentrations are ~90% of steady-state values; on a continuous basis for 5 half-lives, serum concentrations equal ~95% of steady-state values; or on a continuous basis for 7 half-lives, serum concentrations achieve ~99% of steady-state values (Figure 1-9). Generally, drug serum concentrations used for pharmacokinetic monitoring can be safely measured after 3–5 estimated half-lives because most drug assays

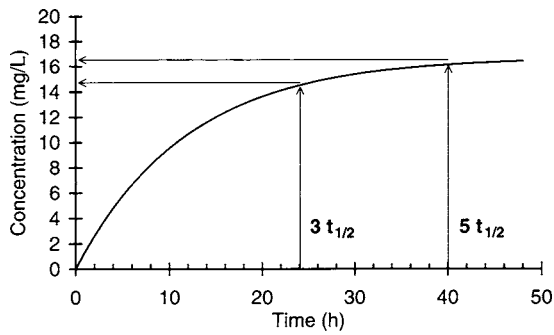

FIGURE 1-9 Serum concentration/time graph for a drug that has a half-life equal to 8 hours. The arrows indicate concentrations at 3 half-lives (24 hours, ~90% of Css) and at 5 half-lives (40 hours, ~95% of Css). Since most drug assays have 5–10% measurement error, serum concentrations obtained between 3–5 half-lives after dosing commenced can be considered to be at steady state for clinical purposes and used to adjust drug doses.

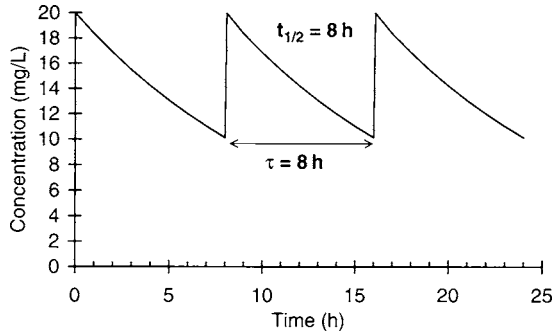

FIGURE 1-10 The dosage interval for a drug is determined by the half-life of the agent. In this case, the half-life of the drug is 8 hours, and the therapeutic range of the drug is 10–20 mg/L. In order to ensure that maximum serum concentrations never go above and minimum serum concentrations never go below the therapeutic range, it is necessary to give the drug every 8 hours (τ = dosage interval).

have 5–10% measurement error. It should be noted that the half-life for a drug in a patient is not usually known, but is estimated using values previously measured during pharmacokinetic studies conducted in similar patients.

The dosage interval for a drug is also determined by the half-life of the medication. For example, if the therapeutic range of a drug is 10–20 mg/L, the ideal dosage interval would not let maximum serum concentrations exceed 20 mg/L or allow the minimum serum concentration to go below 10 mg/L (Figure 1-10). In this case, the dosage interval that would produce this steady-state concentration/time profile would be every half-life. After a dose is given, the maximum serum concentration would be 20 mg/L. In 1 half-life the serum concentration would be 10 mg/L, and the next dose would be administered to the patient. At steady state this serum concentration/time profile would be repeated after each dose. During drug development, it is very common to use the drug half-life as the initial dosage interval for the new drug compound until the pharmacodynamics of the agent can be determined.

The half-life and elimination rate constant are known as *dependent parameters* because their values depend on the clearance (Cl) and volume of distribution (V) of the agent: $t_{1/2} = (0.693 \cdot V)/Cl$, $k_e = Cl/V$. The half-life and elimination rate constant for a drug can change either because of a change in clearance or a change in the volume of distribution. Because the values for clearance and volume of distribution depend solely on physiological parameters and can vary independently of each other, they are known as *independent parameters*.

MICHAELIS-MENTEN OR SATURABLE PHARMACOKINETICS

Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or

saturates the enzyme's ability to metabolize the drug.[2,3] When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase (Figure 1-3). In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems: rate of metabolism = $(V_{max} \cdot C)/(Km + C)$, where V_{max} is the maximum rate of metabolism, C is the substrate concentration, and Km is the substrate concentration where the rate of metabolism = $V_{max}/2$.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent. As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions: $Cl = V_{max}/(Km + C)$. This is the reason concentrations increase disproportionately after a dosage increase. For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of V_{max} = 500 mg/d and Km = 4 mg/L. The therapeutic range of phenytoin is 10–20 mg/L. As the steady-state concentration of phenytoin increases from 10 mg/L to 20 mg/L, clearance decreases from 36 L/d to 21 L/d [$Cl = V_{max}/(Km + C)$; Cl = (500 mg/d) / (4 mg/L + 10 mg/L) = 36 L/d; Cl = (500 mg/d)/(4 mg/L + 20 mg/L) = 21 L/d]. Unfortunately, there is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for a drug (typically V_{max} = 100–1000 mg/d and Km = 1–10 mg/L for phenytoin) that dosing drugs which follow saturable metabolism is extremely difficult.

The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T): $V = V_B + (f_B/f_T)V_T$. Also, half-life ($t_{1/2}$) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t_{1/2} = (0.693 \cdot V)/Cl$. However, since clearance is dose- or concentration-dependent, half-life also changes with dosage or concentration changes. As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug: $\uparrow t_{1/2} = (0.693 \cdot V)/\downarrow Cl$. The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.

Under steady-state conditions the rate of drug administration equals the rate of drug removal. Therefore, for a drug that is solely removed by metabolism via one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{V_{max} \cdot Css}{Km + Css}$$

When the therapeutic range for a drug is far below the Km value for the enzymes that metabolize the drug Css, this equation simplifies to: $MD = (V_{max}/Km)Css$ or, since V_{max}/Km is a constant, $MD = Cl \cdot Css$. Therefore, when $Km >> Css$, drugs that are metabolized follow linear pharmacokinetics. When the therapeutic range for a drug is far above the Km value for the enzyme system that metabolizes the drug, the rate of metabolism becomes a constant equal to V_{max}. Under these conditions only a fixed amount of drug is metabolized because the enzyme system is completely saturated and cannot increase its

metabolic capacity. This situation is also known as *zero-order pharmacokinetics*. *First-order pharmacokinetics* is another name for linear pharmacokinetics.

Based on these facts, it can be seen that any drug that is metabolized by enzymes undergoes Michaelis-Menten pharmacokinetics. But, the therapeutic ranges of most drugs are far below the Km for the enzymes that metabolize the agent. Because of this, most medications that are metabolized follow linear pharmacokinetics. However, even in these cases saturable drug metabolism can occur in drug overdose cases where the drug concentration far exceeds the therapeutic range for the medication.

BIOAVAILABILITY

When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. For example, an orally administered tablet may not completely dissolve so that part of the dose is eliminated in the stool, or a transdermal patch may not release the entire dose before it is removed from the skin. The fraction of the administered dose that is delivered to the systemic circulation is known as the *bioavailability* for the drug and dosage form. When medications are given orally, intramuscularly, subcutaneously, or by other extravascular routes, the drug must be absorbed across several biologic membranes before entering the vascular system. In these cases, drug serum concentrations rise while the drug is being absorbed into the bloodstream, reach a maximum concentration (C_{max}) when the rate of drug absorption equals the rate of drug elimination, and eventually decrease according to the half-life of the drug. The phase of the curve over which absorption takes place is known as the *absorption phase*, and the time that the maximum concentration occurs is called T_{max} (Figure 1-11).

If a medication is given orally, drug molecules must pass through several organs before entering the systemic circulation. During absorption from the gastrointestinal tract, the drug molecules will encounter enzymes that may metabolize the agent (primarily

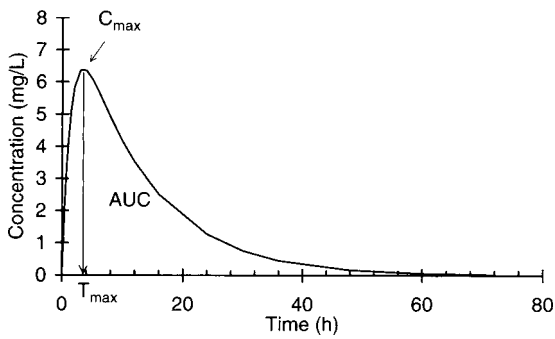

FIGURE 1-11 Area under the serum concentration/time curve (*AUC*), the maximum concentration (C_{max}), and the time that the maximum concentration occurs (T_{max}) are considered primary bioavailability parameters. When the AUC, C_{max}, and T_{max} are the same within statistical limits for two dosage forms of the same drug, the dosage forms are considered to be bioequivalent.

CYP3A4 substrates since ~90% of cytochrome P-450 contained in the gut wall is CYP3A4) or even pump the drug back into the lumen and prevent absorption from taking place (primarily P-glycoprotein substrates). Once drug molecules are absorbed from the gastrointestinal tract, they enter the portal vein. The portal vein and hepatic artery together supply blood to the liver, and the sum of portal vein (~$^2/_3$ total LBF) and hepatic artery (~$^1/_3$ total LBF) blood flows make up liver blood flow (LBF) which equals ~1–1.5 L/min. If the drug is hepatically metabolized, part of the drug may be metabolized by the liver even though the majority of the drug was absorbed from the gastrointestinal tract. Drugs that are substrates for CYP3A4 and CYP2D6 are particularly susceptible to presystemic metabolism by the liver. Blood leaving the liver via the hepatic vein enters the inferior vena cava, and will eventually be pumped through the lung by the right side of the heart before entering the left side of the heart and being pumped into the arterial system. To a lesser extent, some drugs are metabolized by the lung or irreversibly eliminated into expired air.

The loss of drug from these combined processes is known as presystemic metabolism or the first-pass effect. Since the entire oral dose that was absorbed must take this route before entering the systemic vascular system, large amounts of drug can be lost via these processes. For example, the oral bioavailability of both propranolol (a substrate for CYP2D6 and CYP2C19) and verapamil (a substrate for CYP3A4 and P-glycoprotein) is about ~10% even though the oral dosage forms for each agent release 100% of the drug into the gastrointestinal tract.

For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing serum concentrations achieved after extravascular and intravenous doses in the same individual. Rather than compare drug concentrations at each time point, a composite of drug concentrations over time is derived by measuring the total area under the serum concentration time curve (AUC) for each route of administration (Figure 1-11). If the extravascular and intravenous doses are the same, the bioavailability for a drug can be calculated by taking the ratio of the AUCs for each route of administration. For example, if 10 mg of a drug were administered to a subject on two separate occasions by intravenous (IV) and oral (PO) routes of administration, the bioavailabilty (F) would be computed by dividing the AUC after oral administration (AUC_{PO}) by the AUC after intravenous administration (AUC_{IV}): $F = AUC_{PO}/AUC_{IV}$. If it is not possible to administer the same dose intravenously and extravascularly because poor absorption or presystemic metabolism yields serum concentrations that are too low to measure, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration: $F = (AUC_{PO}/AUC_{IV})(D_{IV}/D_{PO})$, where D_{IV} is the intravenous dose and D_{PO} is the oral dose.

Bioequivalence

When the patent expires for drug entities, generic drugs are manufactured that are less expensive than brand name products. This is because the drug company manufacturing the generic drug does not have to prove that the drug is safe and effective since those studies were done by the pharmaceutical company producing the brand name drug. Although it is not a requirement for generic drug products to be marketed by a pharmaceutical company, a desirable attribute of a generic drug dosage form is that it produce the same serum concentration/time profile as its brand name counterpart. When it meets

this requirement, the generic drug product is said to be *bioequivalent* to the brand name drug. In theory, it should be possible to substitute a bioequivalent generic drug dosage form for a brand name product without a change in steady-state drug serum concentrations or therapeutic efficacy.

Bioequivalence is achieved when the serum concentration/time curve for the generic and brand name drug dosage forms are deemed indistinguishable from each other using statistical tests. Concentration/time curves are superimposable when the area under the total serum concentration/time curve (AUC), maximum concentration (C_{max}), and time that the maximum concentration occurs (T_{max}) are identical within statistical limits. In order to achieve the Food and Drug Administration's (FDA) definition of oral bioequivalance and be awarded an "AB" rating in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as *The Orange Book*), the pharmaceutical company producing a generic drug product must administer single doses or multiple doses of the drug until steady state is achieved using both the generic and brand name drug dosage forms to a group of 18–24 humans and prove that the AUC (from time = 0 to infinity after a single dose, or over the dosage interval at steady state), C_{max}, and T_{max} values are statistically identical for the two dosage forms. The ratio of the area under the serum concentration/time curves for the generic ($AUC_{generic}$) and brand name (AUC_{brand}) drug dosage forms is known as the *relative bioavailability* ($F_{relative}$) since the reference AUC is derived from the brand name drug dosage form: $F_{relative} = AUC_{generic}/AUC_{brand}$. Many states allow the substitution of generic drugs for brand name drugs if the prescriber notes on the prescription order that generic substitution is acceptable, and the generic drug dosage form has an AB rating.

PROBLEMS

1. Define the following terms:
- **a.** absorption
- **b.** distribution
- **c.** metabolism
- **d.** elimination
- **e.** steady state
- **f.** linear or first-order pharmacokinetics
- **g.** nonlinear pharmacokinetics
- **h.** saturable or Michaelis-Menten pharmacokinetics
- **i.** autoinduction
- **j.** therapeutic range
- **k.** zero-order pharmacokinetics
- **l.** bioavailability
- **m.** bioequivalent
- **n.** clearance
- **o.** volume of distribution
- **p.** half-life
- **q.** elimination rate constant

2. Two new antibiotics are marketed by a pharmaceutical manufacture. Reading the package insert, you find the following information:

DOSE	CURACILLIN STEADY-STATE CONCENTRATIONS (mg/L)	BETTERMYCIN STEADY-STATE CONCENTRATIONS (mg/L)
0	0	0
100	15	25
250	37.5	62.5
500	75	190
1000	150	510

What type of pharmacokinetics do each of these drugs follow?

3. A patient with liver failure and a patient with heart failure need to be treated with a new antiarrhythmic drug. You find a research study that contains the following information for Stopabeat in patients similar to the ones you need to treat: normal subjects: clearance = 45 L/h, volume of distribution = 175 L; liver failure: clearance = 15 L/h, volume of distribution = 300 L; heart failure: clearance = 30 L/h, volume of distribution = 100 L. Recommend an intravenous loading dose (LD) and continuous intravenous infusion maintenance dose (MD) to achieve a steady-state concentration of 10 mg/L for your two patients based on this data and estimate the time it will take to achieve steady-state conditions.

4. After the first dose of gentamicin is given to a patient with renal failure, the following serum concentrations are obtained:

TIME AFTER DOSAGE ADMINISTRATION (HOUR)	CONCENTRATION (μg/mL)
1	7.7
24	5.6
48	4.0

Compute the half-life and the elimination rate constant for this patient.

5. Average values of Michaelis-Menten pharmacokinetic parameters for phenytoin in adults are V_{max} = 500 mg/d and Km = 4 mg/L. What are the expected average doses of phenytoin that would produce steady-state concentrations at the lower and upper limits of the therapeutic range (10–20 mg/L)?

6. A new immunosuppresant, Noreject, is being studied in the renal transplant clinic where you work. Based on previous studies, the following area under the serum concentration/time curves (AUC) were measured after single doses of 10 mg in renal transplant patients: intravenous bolus AUC = 1530 mg · h/L, oral capsule AUC = 1220 mg · h/L, oral liquid AUC = 1420 mg · h/L. What is the bioavailability of the oral capsule and oral liquid? What is the relative bioavailability of the oral capsule compared to the oral liquid?

ANSWERS TO PROBLEMS

1. The following are definitions for terms in question 1:

- **a.** Passage of drug molecules through physiological/biological barriers before reaching the vascular system
- **b.** Passage of drug molecules from the bloodstream into tissues and organs
- **c.** Chemical conversion of a drug molecule into a metabolite
- **d.** Irreversible removal of drug from the body
- **e.** Rate of drug administration equals the rate of drug removal so that serum concentrations and amount of drug in the body are constant
- **f.** Situation where steady-state serum concentration or area under the serum concentration/time curve (AUC) changes proportionally with dosage changes
- **g.** Situation where steady-state serum concentration or area under the serum concentration/time curve (AUC) changes disproportionally with dosage changes
- **h.** Type of nonlinear pharmacokinetics where an increase in dose results in a disproportionally large increase in steady-state serum concentration or area under the serum concentration/time curve. Results from overwhelming or "saturating" the enzymes' ability to metabolize the drug
- **i.** Situation where a drug increases its own rate of metabolism by inducing more drug metabolizing enzyme to be produced
- **j.** Minimum and maximum serum or blood concentrations that produce the desired pharmacological effect without producing unwanted adverse effects
- **k.** A constant amount of drug is eliminated per unit time usually due to complete saturation of the enzyme system responsible for the metabolism of the drug
- **l.** Fraction of administered dose that is delivered to the systemic circulation
- **m.** A dosage form for a drug that produces the same serum concentration/time profile as another dosage form of the same drug. Usually measured by showing that the two dosage forms have the same area under the serum concentration/time curve (AUC), maximum serum concentration (C_{max}), and time that maximum serum concentration occurs (T_{max}) values within statistical limits
- **n.** Volume of serum or blood completely cleared of drug per unit time
- **o.** Proportionality constant that relates serum concentrations to amount of drug in the body
- **p.** Time required for serum concentrations to decrease by one-half after absorption and distribution phases are complete
- **q.** Terminal slope (using an ln C versus time plot) of the serum concentration/time curve after absorption and distribution phases are complete

2. A plot of steady-state concentration versus doses is a straight line for Curacillin, but a curved line for Bettermycin (see Table for problem 2). Since this relationship is a straight line for Curacillin, it follows linear or first-order pharmacokinetics. Because the steady-state concentration versus dose plot is curved upward indicating disproportionally large increases in concentration after a dosage increase, Bettermycin follows nonlinear pharmacokinetics. The type of nonlinear pharmacokinetics is Michaelis-Menten or saturable pharmacokinetics.

3. The liver failure patient would likely have pharmacokinetic parameters similar to the liver failure patients in the research study (Cl = 15 L/h, V = 300 L): LD = V · Css, LD = (300 L)(10 mg/L) = 3000 mg intravenous bolus; MD = Cl · Css, MD = (15 L/h) (10 mg/L) = 150 mg/h intravenous infusion. The half-life would be estimated using the clearance and volume of distribution: $t_{1/2}$ = (0.693 V)/Cl, $t_{1/2}$ = [(0.693)(300 L)] / (15 L/h) = 13.9 h. Steady state would be achieved in 3–5 $t_{1/2}$ equal to 42–70 hours.

The heart failure patient would likely have pharmacokinetic parameters similar to the heart failure patients in the research study (Cl = 30 L/h, V = 100 L): LD = V · Css, LD = (100 L)(10 mg/L) = 1000 mg intravenous bolus; MD = Cl · Css, MD = (30 L/h) (10 mg/L) = 300 mg/h intravenous infusion. The half-life would be estimated using the clearance and volume of distribution: $t_{1/2}$ = (0.693 V)/Cl, $t_{1/2}$ = [(0.693)(100 L)]/ (30 L/h) = 2.3 h. Steady state would be achieved in 3–5 $t_{1/2}$ equal to 7–12 hours.

4. The serum concentration/time profile is plotted on semilogarithmic paper (see Table for problem 4), and the best straight line is drawn through the points. Since all of the concentrations fall on the straight line, any two concentration/time pairs can be used to compute the elimination rate constant (k_e): $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, $k_e = -(\ln 7.7 - \ln 4)/(1\text{ h} - 48\text{ h}) = 0.0139\text{ h}^{-1}$. The elimination rate constant can be used to calculate the half-life for the patient: $t_{1/2} = 0.693/k_e$, $t_{1/2} = 0.693/0.0139\text{ h}^{-1} = 50$ h.

5. Since phenytoin follows saturable pharmacokinetics, the Michaelis-Menten equation can be used for concentrations of 10 mg/L and 20 mg/L: MD = (V_{max} · Css)/(Km + Css); MD = [(500 mg/d)(10 mg/L)]/(4 mg/L + 10 mg/L) = 357 mg/d for Css = 10 mg/L; MD = [(500 mg/d)(20 mg/L)]/(4 mg/L + 20 mg/L) = 417 mg/d for Css = 20 mg/L.

6. The bioavailability for the capsule and liquid are: F = AUC_{PO}/AUC_{IV}; for capsule, F = (1220 mg · h/L)/(1530 mg · h/L) = 0.80 or 80%; for liquid, F = (1420 mg · h/L)/ (1530 mg · h/L) = 0.93 or 93%. The relative bioavailability is: $F_{relative} = AUC_{CAPSULE}/AUC_{LIQUID}$; $F_{relative}$ = (1220 mg · h/L)/(1420 mg · h/L) = 0.86 or 86%.

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2

CLINICAL PHARMACOKINETIC EQUATIONS AND CALCULATIONS

INTRODUCTION

Clinical pharmacokinetic dosage calculations are conducted using the easiest possible equations and methods. This is because there are usually only a few (sometimes as little as 1–2) drug serum concentrations on which to base the calculations. Drug serum concentrations are expensive (typically $25–75 each), and obtaining them can cause minor discomfort and trauma to the patient. This situation is much different than that found in pharmacokinetic research studies where there may be 10–15 drug serum concentrations used to calculate pharmacokinetic parameters, and more complex equations can be used to describe the pharmacokinetics of the drug. Since the goal of therapeutic drug monitoring in patients is to individualize the drug dose and serum concentrations in order to produce the desired pharmacological effect and avoid adverse effects, it may not be possible, or even necessary, to compute pharmacokinetic parameters for every patient or clinical situation.

ONE-COMPARTMENT MODEL EQUATIONS FOR LINEAR PHARMACOKINETICS

When medications are administered to humans, the body acts as if it is a series of compartments[1] (Figure 2-1). In many cases, the drug distributes from the blood into the tissues quickly, and a pseudoequilibrium of drug movement between blood and tissues is established rapidly. When this occurs, a one-compartment model can be used to describe the serum concentrations of a drug.[2,3] In some clinical situations, it is possible to use a one-compartment model to compute doses for a drug even if drug distribution takes time

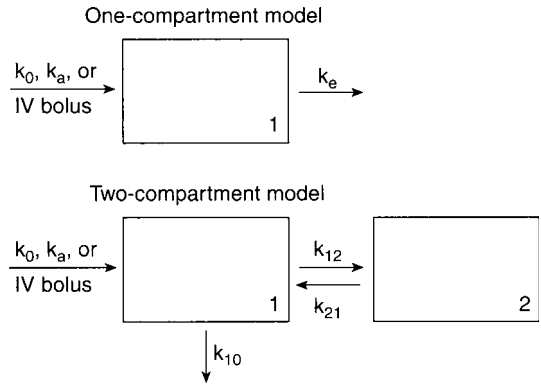


FIGURE 2-1 Using ~~compartment~~ models, the body can be represented as a series of discrete sections. The simplest model is the one-compartment model which depicts the body as one large container where drug distribution between blood and tissues occurs instantaneously. Drug is introduced into the compartment by infusion (k_o), absorption (k_a), or IV bolus; distributes immediately into a volume of distribution *(V)*; and is removed from the body via metabolism and elimination via the elimination rate constant *(k_e)*. The simplest multicompartment model is a two-compartment model which represents the body as a central compartment into which drug is administered and a peripheral compartment into which drug distributes. The central compartment (1) is composed of blood and tissues which equilibrate rapidly with blood. The peripheral compartment (2) represents tissues that equilibrate slowly with blood. Rate constants (k_{12}, k_{21}) represent the transfer between compartments and elimination from the body (k_{10}).

to complete.[4,5] In this case, drug serum concentrations are not obtained in a patient until after the distribution phase is over.

Intravenous Bolus Equation

When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line when plotted on semilogarithmic axes (Figure 2-2). In this case, a one-compartment model intravenous bolus equation can be used: $C = (D/V)e^{-k_e t}$, where t is the time after the intravenous bolus was given (t = 0 at the time the dose was administered), C is the concentration at time = t, V is the volume of distribution, and k_e is the elimination rate constant. Most drugs given intravenously cannot be given as an actual intravenous bolus because of side effects related to rapid injection. A short infusion of 5–30 minutes can avoid these types of adverse effects, and if the intravenous infusion time is very short compared to the half-life of the drug so that a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is 30 L, the elimination rate constant equals 0.116 h^{-1}, and the half-life ($t_{1/2}$) is 6 hours ($t_{1/2} = 0.693/k_e = 0.693/0.115\ h^{-1} = 6$ h). To compute the expected theophylline concentration 4 hours after the dose was given, a one-compartment model intravenous bolus equation can be used: $C = (D/V)e^{-k_e t} = (400\ mg/30\ L)e^{-(0.115\ h^{-1})(4\ h)} = 8.4$ mg/L.

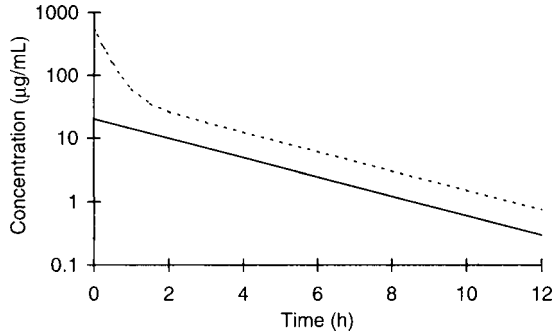


FIGURE 2-2 The *solid line* shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics after intravenous bolus administration. Drug distribution occurs instantaneously, and serum concentrations decline in a straight line on semilogarithmic axes. The *dashed line* represents the serum concentration/time plot for a drug that follows two-compartment model pharmacokinetics after an intravenous bolus is given. Immediately after the dose is given, serum concentrations decline rapidly. This portion of the curve is known as the distribution phase. During the distribution phase, drug is distributing between blood and tissues and is removed from the body via hepatic metabolism and renal elimination. Later, serum concentrations decline more slowly during the elimination phase. During the elimination phase, drug is primarily being removed from the body.

If drug distribution is not rapid, it is still possible to use a one compartment model intravenous bolus equation if the duration of the distribution phase and infusion time is small compared to the half-life of the drug and only a small amount of drug is eliminated during the infusion and distribution phases.[6] The strategy used in this situation is to infuse the medication and wait for the distribution phase to be over before obtaining serum concentrations in the patient. For instance, vancomycin must be infused slowly over 1 hour in order to avoid hypotension and red flushing around the head and neck areas. Additionally, vancomycin distributes slowly to tissues with a $^1/_2$–1 hour distribution phase. Because the half-life of vancomycin in patients with normal renal function is approximately 8 hours, a one compartment model intravenous bolus equation can be used to compute concentrations in the postinfusion, postdistribution phase without a large amount of error. As an example of this approach, a patient is given an intravenous dose of vancomycin 1000 mg. Since the patient has received this drug before, it is known that the volume of distribution equals 50 L, the elimination rate constant is 0.077 h^{-1}, and the half-life equals 9 h ($t_{1/2}$ = $0.693/k_e$ = $0.693/0.077\ h^{-1}$ = 9 h). To calculate the expected vancomycin concentration 12 hours after the dose was given, a one compartment model intravenous bolus equation can be used: $C = (D/V)e^{-k_e t} = (1000\ mg/50\ L)e^{-(0.077\ h^{-1})(12\ h)} = 7.9\ mg/L$.

Pharmacokinetic parameters for patients can also be computed for use in the equations. If two or more serum concentrations are obtained after an intravenous bolus dose, the elimination rate constant, half-life and volume of distribution can be calculated (Figure 2-3). For example, a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour. One day and four days after the dose was administered phenobarbital serum concentrations were 12.6 mg/L and 7.5 mg/L, respectively. By plotting the serum concentration/time data on semilogarithmic axes, the time it takes for serum concentrations to decrease by one-half can be determined and is equal to

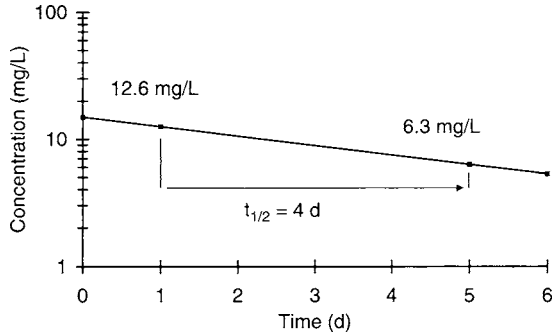


FIGURE 2-3 Phenobarbital concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life *($t_{1/2}$)* is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 12.6 mg/L to 6.3 mg/L), and is converted to the elimination rate constant ($k_e = 0.693/t_{1/2} = 0.693/4d = 0.173d^{-1}$). The concentration/time line can be extrapolated to the concentration axis to derive the concentration at time zero (C_0 = 15 mg/L) and used to compute the volume of distribution ($V = D/C_0$).

4 days. The elimination rate constant can be computed using the following relationship: $k_e = 0.693/t_{1/2} = 0.693/4$ d = 0.173 d^{-1}. The concentration/time line can be extrapolated to the y-axis where time = 0. Since this was the first dose of phenobarbital and the predose concentration was zero, the extrapolated concentration at time = 0 (C_0 = 15 mg/L in this case) can be used to calculate the volume of distribution (Figure 2-4): $V = D/C_0$ = 600 mg/(15 mg/L) = 40 L.

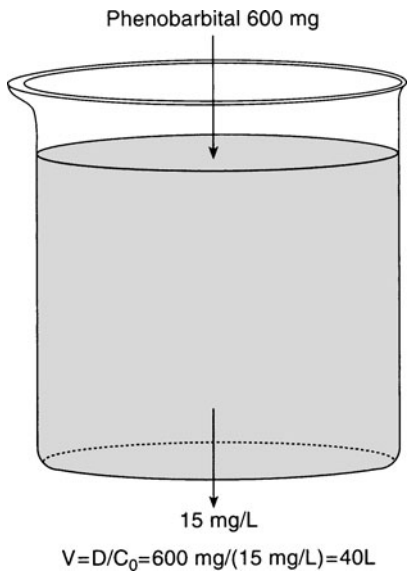


FIGURE 2-4 For a one-compartment model, the body can be thought of as a beaker containing fluid. If 600 mg of phenobarbital is added to a beaker of unknown volume and the resulting concentration is 15 mg/L, the volume can be computed by taking the quotient of the amount placed into the beaker and the concentration: $V = D/C_0$ = 600 mg/(15 mg/L) = 40 L.

Alternatively, these parameters could be obtained by calculation without plotting the concentrations. The elimination rate constant can be computed using the following equation: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, where t_1 and C_1 are the first time/concentration pair and t_2 and C_2 are the second time/concentration pair; $k_e = -[\ln (12.6 \text{ mg/L}) - \ln (7.5 \text{ mg/L})]/(1 \text{ d} - 4 \text{ d}) = 0.173 \text{ d}^{-1}$. The elimination rate constant can be converted into the half-life using the following equation: $t_{1/2} = 0.693/k_e = 0.693/0.173 \text{ d}^{-1} = 4$ d. The volume of distribution can be calculated by dividing the dose by the serum concentration at time = 0. The serum concentration at time = zero (C_0) can be computed using a variation of the intravenous bolus equation: $C_0 = C/e^{-k_e t}$, where t and C are a time/concentration pair that occur after the intravenous bolus dose. Either phenobarbital concentration can be used to compute C_0. In this case, the time/concentration pair on day 1 will be used (time = 1 d, concentration = 12.6 mg/L): $C_0 = C/e^{-k_e t} = (12.6 \text{ mg/L})/e^{-(0.173 \text{ d}^{-1})(1 \text{ d})} = 15.0$ mg/L. The volume of distribution (V) is then computed: $V = D/C_0 = 600 \text{ mg}/(15 \text{ mg/L}) = 40$ L.

Continuous and Intermittent Intravenous Infusion Equations

Some drugs are administered using a continuous intravenous infusion, and if the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on a semilogarithmic axes (Figure 2-5). In this case, a one compartment model intravenous infusion equation can be used to compute concentrations (C) while the infusion is running: $C = (k_0/Cl)(1 - e^{-k_e t}) = [k_0/(k_e V)](1 - e^{-k_e t})$, where k_0 is the drug infusion rate (in amount per unit time, such as mg/h or μg/min), Cl is the drug clearance (since $Cl = k_e V$, this substitution was made in the second version of the equation), k_e is the elimination rate constant, and t is the time that the infusion has been running. If the infusion is allowed to continue until steady state is achieved, the steady-state concentration (Css) can be calculated easily: $Css = k_0/Cl = k_0/(k_e V)$.

If the infusion is stopped, postinfusion serum concentrations ($C_{postinfusion}$) can be computed by calculating the concentration when the infusion ended (C_{end}) using the appropriate

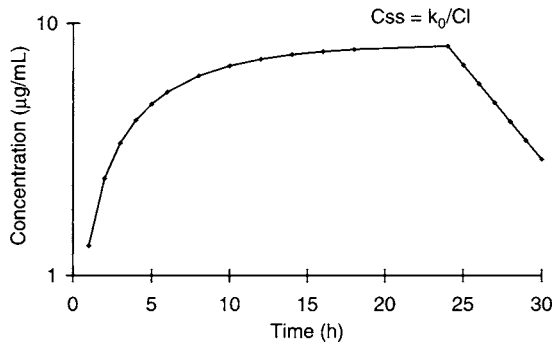


FIGURE 2-5 If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration *(Css)* is achieved in 5–7 half-lives. The steady-state concentration is determined by the quotient of the infusion rate *(k_0)* and drug clearance *(Cl):* $Css = k_0/Cl$. When the infusion is discontinued, serum concentrations decline in a straight line if the graph is plotted on semilogarithmic axes. When using $\log_{10}$ graph paper, the elimination rate constant (k_e) can be computed using the following formula: slope = $-k_e/2.303$.

equation in the preceding paragraph, and the following equation: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}}$, where k_e is the elimination rate constant and $t_{postinfusion}$ is the postinfusion time ($t_{postinfusion} = 0$ at end of infusion and increases from that point).

For example, a patient is administered 60 mg/h of theophylline. It is known from previous hospital admissions that the patient has the following pharmacokinetic parameters for theophylline: V = 40 L and $k_e = 0.139\ h^{-1}$. The serum concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state can be calculated: $C = [k_0/(k_eV)](1 - e^{-k_e t}) = [(60\ mg/h)/(0.139\ h^{-1} \cdot 40\ L)](1 - e^{-(0.139\ h^{-1})(8\ h)}) = 7.2$ mg/L; $Css = k_0/(k_eV) = (60\ mg/h)/(0.139\ h^{-1} \cdot 40\ L) = 10.8$ mg/L. It is possible to compute the theophylline serum concentration 6 hours after the infusion stopped in either circumstance. If the infusion only ran for 8 hours, the serum concentration 6 hours after the infusion stopped would be: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}} = (7.2\ mg/L)e^{-(0.139\ h^{-1})(6\ h)} = 3.1$ mg/L. If the infusion ran until steady state was achieved, the serum concentration 6 hours after the infusion ended would be: $C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}} = (10.8\ mg/L)e^{-(0.139\ h^{-1})(6\ h)} = 4.7$ mg/L.

Even if serum concentrations exhibit a distribution phase after the drug infusion has ended, it is still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.[4, 5] The strategy used in this instance is to infuse the medication and wait for the distribution phase to be over before measuring serum drug concentrations in the patient. For example, gentamicin, tobramycin, and amikacin are usually infused over one-half hour. When administered this way, these aminoglycoside antibiotics have distribution phases that last about one-half hour. Using this strategy, aminoglycoside serum concentrations are obtained no sooner than one-half hour after a 30-minute infusion in order to avoid the distribution phase. If aminoglycosides are infused over 1 hour, the distribution phase is very short and serum concentrations can be obtained immediately. For example, a patient is given an intravenous infusion of gentamicin 100 mg over 60 minutes. Because the patient received gentamicin before, it is known that the volume of distribution is 20 L, the elimination rate constant equals $0.231\ h^{-1}$, and the half-life equals 3 h ($t_{1/2} = 0.693/k_e = 0.693/0.231\ h^{-1} = 3$ h). To compute the gentamicin concentration at the end of infusion, a one compartment model intravenous infusion equation can be employed: $C = [k_0/(k_eV)](1 - e^{-k_e t}) = [(100\ mg/1\ h)/(0.231\ h^{-1} \cdot 20\ L)](1 - e^{-(0.231\ h^{-1})(1\ h)}) = 4.5$ mg/L.

Pharmacokinetic constants can also be calculated for use in the equations. If a steady-state concentration is obtained after a continuous intravenous infusion has been running uninterrupted for 3–5 half-lives, the drug clearance (Cl) can be calculated by rearranging the steady-state infusion formula: $Cl = k_0/Css$. For example, a patient receiving procainamide via intravenous infusion ($k_0 = 5$ mg/min) has a steady-state procainamide concentration measured as 8 mg/L. Procainamide clearance can be computed using the following expression: $Cl = k_0/Css = (5\ mg/min)/(8\ mg/L) = 0.625$ L/min.

If the infusion did not run until steady state was achieved, it is still possible to compute pharmacokinetic parameters from postinfusion concentrations. In the following example, a patient was given a single 120-mg dose of tobramycin as a 60-minute infusion, and concentrations at the end of infusion (6.2 mg/L) and 4 hours after the infusion ended (1.6 mg/L) were obtained. By plotting the serum concentration/time information on semilogarithmic axes, the half-life can be determined by measuring the time it takes for serum concentrations to decline by one-half (Figure 2-6), and equals 2 hours in this case. The elimination rate constant (k_e) can be calculated using the following formula:

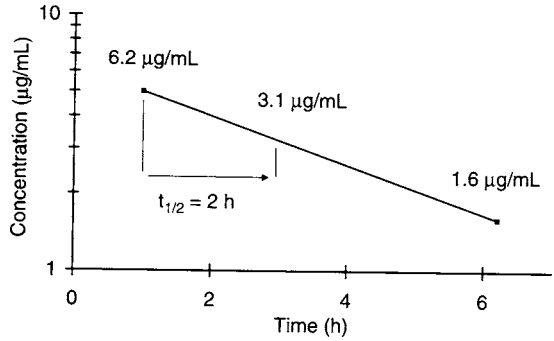


FIGURE 2-6 Tobramycin concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ($t_{1/2}$) is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 6.2 mg/L to 3.1 mg/L), and is converted to the elimination rate constant ($k_e = 0.693/t_{1/2} = 0.693/2$ h $= 0.347$ h^{-1}). Volume of distribution is computed using the equation given in the text.

$k_e = 0.693/t_{1/2} = 0.693/2$ h $= 0.347$ h^{-1}. Alternatively, the elimination rate constant can be calculated without plotting the concentrations using the following equation: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, where t_1 and C_1 are the first time/concentration pair and t_2 and C_2 are the second time/concentration pair; $k_e = -[\ln (6.2 \text{ mg/L}) - \ln (1.6 \text{ mg/L})]/(1 \text{ h} - 5 \text{ h}) = 0.339$ h^{-1} (note the slight difference in k_e is due to rounding errors). The elimination rate constant can be converted into the half-life using the following equation: $t_{1/2} = 0.693/k_e = 0.693/0.339$ h$^{-1} = 2$ h.

The volume of distribution (V) can be computed using the following equation[4]:

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

where k_0 is the infusion rate, k_e is the elimination rate constant, t' = infusion time, C_{max} is the maximum concentration at the end of infusion, and $C_{predose}$ is the predose concentration. In this example, the volume of distribution is:

$$V = \frac{(120 \text{ mg/1 h})(1 - e^{-(0.339 \text{h}^{-1})(1 \text{ h})})}{0.339 \text{ h}^{-1}[(6.2 \text{ mg/L}) - (0 \text{ mg/L} \cdot e^{-(0.339 \text{h}^{-1})(1 \text{ h})})]} = 16.4 \text{ L}$$

Extravascular Equation

When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place (Figure 2-7). If serum concentrations decrease in a straight line when plotted on semilogarithmic axes after drug absorption is complete, a one compartment model extravascular equation can be used to describe the serum concentration/time curve: $C = \{(Fk_aD)/[V(k_a - k_e)]\}(e^{-k_e t} - e^{-k_a t})$, where t is the time after the extravascular dose was given (t = 0 at the time the dose was administered), C is the concentration at time = t, F is the bioavailability fraction, k_a is the absorption rate constant, D is the dose, V is the

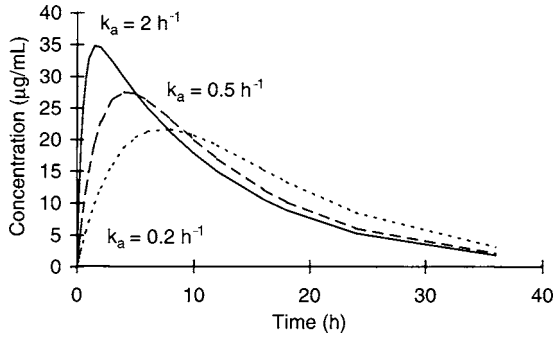


FIGURE 2-7 Serum concentration/time curves for extravascular drug administration for agents following a one-compartment pharmacokinetics. The absorption rate constant *(k_a)* controls how quickly the drug enters the body. A large absorption rate constant allows drug to enter the body quickly while a small elimination rate constant permits drug to enter the body more slowly. The *solid line* shows the concentration/time curve on semilogarithmic axes for an elimination rate constant equal to 2 h^{-1}. The *dashed* and *dotted lines* depict serum concentration/time plots for elimination rate constants of 0.5 h^{-1} and 0.2 h^{-1}, respectively.

volume of distribution, and k_e is the elimination rate constant. The absorption rate constant describes how quickly drug is absorbed with a large number indicating fast absorption and a small number indicating slow absorption (Figure 2-7).

An example of the use of this equation would be a patient that is administered 500 mg of oral procainamide as a capsule. It is known from prior clinic visits that the patient has a half-life equal to 4 hours, an elimination rate constant of 0.173 h^{-1} ($k_e = 0.693/t_{1/2} = 0.693/4$ h = 0.173 h^{-1}), and a volume of distribution of 175 L. The capsule that is administered to the patient has an absorption rate constant equal to 2 h^{-1}, and an oral bioavailability fraction of 0.85. The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \frac{Fk_aD}{V(k_a - k_e)}(e^{-k_et} - e^{-k_at})$$

$$C = \frac{(0.85)(2\ h^{-1})(500\ mg)}{(175\ L)(2\,h^{-1} - 0.173\ h^{-1})}(e^{-(0.173\ h^{-1})(4\ h)} - e^{-(2\ h^{-1})(4\ h)})$$

$$C = 1.3\ mg/L$$

If the serum concentration/time curve displays a distribution phase, it is still possible to use one compartment model equations after an extravascular dose is administered. In order to do this, serum concentrations are obtained only in the postdistribution phase. Since the absorption rate constant is also hard to measure in patients, it is also desirable to avoid drawing drug serum concentrations during the absorption phase in clinical situations. When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, the equation simplifies to: $C = [(FD)/V]e^{-k_et}$, where C is the concentration at any postabsorption, postdistribution time; F is the

bioavailability fraction; D is the dose; V is the volume of distribution; k_e is the elimination rate constant; and t is any postabsorption, postdistribution time. This approach works very well when the extravascular dose is rapidly absorbed and not a sustained- or extended-release dosage form. An example would be a patient receiving 24 mEq of lithium ion as lithium carbonate capsules. From previous clinic visits, it is known that the patient has a volume of distribution of 60 L and an elimination rate constant equal to 0.058 h^{-1}. The bioavailability of the capsule is known to be 0.90. The serum lithium concentration 12 hours after a single dose would be: $C = [(FD)/V]e^{-k_e t} = [(0.90 \cdot 24 \text{ mEq})/60 \text{ L}]$ $e^{-(0.058 \text{ h}^{-1})(12 \text{ h})} = 0.18$ mEq/L.

Pharmacokinetic constants can also be calculated and used in these equations. If two or more postabsorption, postdistribution serum concentrations are obtained after an extravascular dose, the volume of distribution, elimination rate constant, and half-life can be computed (Figure 2-8). For example, a patient is given an oral dose of valproic acid 750 mg as capsules. Six and twenty-four hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively. After graphing the serum concentration/time data on semilogarithmic axes, the time it takes for serum concentrations to decrease by one-half can be measured and equals 14 hours. The elimination rate constant is calculated using the following equation: $k_e = 0.693 / t_{1/2} = 0.693/14 \text{ h} = 0.0495 \text{ h}^{-1}$. The concentration/time line can be extrapolated to the y-axis where time = 0. Since this was the first dose of valproic acid, the extrapolated concentration at time = 0 ($C_0 = 70$ mg/L) is used to estimate the hybrid volume of distribution/bioavailability (V/F) parameter: $V/F = D/C_0 = 750 \text{ mg}/70 \text{ L} = 10.7$ L. Even though the absolute volume of distribution and bioavailability cannot be computed without the administration of intravenous drug, the hybrid constant can be used in extravascular equations in place of V/F.

An alternative approach is to directly calculate the parameters without plotting the concentrations. The elimination rate constant (k_e) is computed using the following

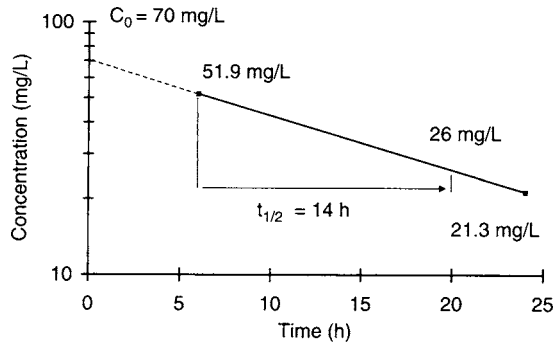


FIGURE 2-8 Valproic acid concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life *($t_{1/2}$)* is determined by measuring the time needed for serum concentrations to decline by $^1/_2$ (i.e., from 51.9 mg/L to 26 mg/L), and is converted to the elimination rate constant ($k_e = 0.693/t_{1/2} = 0.693/14 \text{ h} = 0.0495 \text{ h}^{-1}$). The concentration/time line can be extrapolated to the concentration axis to derive the concentration at time zero (C_0 = 70 mg/L) and used to compute the hybrid constant volume of distribution/bioavailability fraction ($V/F = D/C_0$).

relationship: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, where C_1 is the first concentration at time = t_1, and C_2 is the second concentration at time = t_2; $k_e = -[\ln (51.9 \text{ mg/L}) - \ln (21.3 \text{ mg/L})]/(6 \text{ h} - 24 \text{ h}) = 0.0495 \text{ h}^{-1}$. The elimination rate constant can be translated into the half-life using the following equation: $t_{1/2} = 0.693/k_e = 0.693/0.0495 \text{ h}^{-1} = 14$ h. The hybrid constant volume of distribution/bioavailability (V/F) is computed by taking the quotient of the dose and the extrapolated serum concentration at time = 0. The extrapolated serum concentration at time = zero (C_0) is calculated using a variation of the intravenous bolus equation: $C_0 = C/e^{-k_e t}$, where t and C are a time/concentration pair that occur after administration of the extravascular dose in the postabsorption and postdistribution phases. Either valproic acid concentration can be used to compute C_0. In this situation, the time/concentration pair at 24 hours will be used (time = 24 hours, concentration = 21.3 mg/L): $C_0 = C/e^{-k_e t} = (21.3 \text{ mg/L})/e^{-(0.0495 \text{ h}^{-1})(24 \text{ h})} = 70$ mg/L. The hybrid volume of distribution/bioavailability constant (V/F) is then computed: $V/F = D/C_0 = 750 \text{ mg}/(70 \text{ mg/L}) = 10.7$ L.

Multiple-Dose and Steady-State Equations

In most cases, medications are administered to patients as multiple doses, and drug serum concentrations for therapeutic drug monitoring are not obtained until steady state is achieved. For these reasons, multiple dose equations that reflect steady-state conditions are usually more useful in clinical settings than single dose equations. Fortunately, it is simple to convert single dose compartment model equations to their multiple dose and steady-state counterparts.[7] In order to change a single dose equation to the multiple dose version, it is necessary to multiply each exponential term in the equation by the multiple dosing factor: $(1 - e^{-nk_i\tau})/(1 - e^{-k_i\tau})$, where n is the number of doses administered, k_i is the rate constant found in the exponential of the single dose equation, and τ is the dosage interval. At steady state, the number of doses (n) is large, the exponential term in the numerator of the multiple dosing factor ($-nk_i\tau$) becomes a large negative number, and the exponent approaches zero. Therefore, the steady-state version of the multiple dosing factor becomes the following: $1/(1 - e^{-k_i\tau})$ where k_i is the rate constant found in the exponential of the single dose equation and τ is the dosage interval. Whenever the multiple dosing factor is used to change a single dose equation to the multiple dose or steady-state versions, the time variable in the equation resets to zero at the beginning of each dosage interval.

As an example of the conversion of a single dose equation to the steady-state variant, the one compartment model intravenous bolus equation is: $C = (D/V)e^{-k_e t}$, where C is the concentration at time = t, D is the dose, V is the volume of distribution, k_e is the elimination rate constant, and t is time after the dose is administered. Since there is only one exponential in the equation, the multiple dosing factor at steady state is multiplied into the expression at only one place, substituting the elimination rate constant (k_e) for the rate constant in the multiple dosing factor: $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$, where C is the steady-state concentration at any postdose time (t) after the dose (D) is given, V is the volume of distribution, k_e is the elimination rate constant, and τ is the dosage interval. Table 2-1 lists the one compartment model equations for the different routes of administration under single dose, multiple dose, and steady-state conditions.

The following are examples of steady-state one compartment model equations for intravenous, intermittent intravenous infusions, and extravascular routes of administration:

TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}\,[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$	$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$
Continuous intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t})$	N/A	$Css = k_0/Cl = k_0/(k_e V)$
Intermittent intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t'})$	$C = [k_0/(k_e V)](1 - e^{-k_e t'})\,[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$	$C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e \tau})]$
Extravascular (postabsorption, postdistribution)	$C = [(FD)/V]e^{-k_e t}$	$C = [(FD)/V]e^{-k_e t}\,[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$	$C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$
Average steady-state concentration (any route of administration)	N/A	N/A	$Css = [F(D/\tau)]/Cl$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, k_0 is the infusion rate, Cl is clearance, t' is infusion time, N/A is not applicable.

Intravenous bolus. A patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. Pharmacokinetic constants for phenobarbital in the patient are: $k_e = 0.116\ d^{-1}$, V = 75 L. The steady-state concentration 23 hours [(23 h)/(24 h/d) = 0.96 d] after the last dose equals: $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})] = (100\ mg/75\ L)[e^{-(0.116\ d^{-1})(0.96\ d)}/(1 - e^{-(0.116\ d^{-1})(1\ d)})] = 10.9$ mg/L.

Intermittent intravenous infusion. A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. Pharmacokinetic parameters for tobramycin in the patient are: V = 16 L, $k_e = 0.30\ h^{-1}$. The steady-state concentration immediately after a 1 hour infusion equals: $C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e \tau})] = [(140\ mg/h)/(0.30\ h^{-1} \cdot 16\ L)][(1 - e^{(-0.30\ h^{-1} \cdot 1\ h)})/(1 - e^{(-0.30\ h^{-1} \cdot 8\ h)})] = 8.3$ mg/L.

Extravascular. A patient with an arrhythmia is administered 250 mg of quinidine orally (as 300 mg quinidine sulfate tablets) every six hours until steady state occurs. Pharmacokinetic constants for quinidine in the patient are: V = 180 L, $k_e = 0.0693\ h^{-1}$, F = 0.7. The postabsorption, postdistribution steady-state concentration just before the next dose (t = 6 h) equals: $C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})] = [(0.7 \cdot 250\ mg)/180\ L][e^{(-0.0693\ h^{-1} \cdot 6\ h)}/(1 - e^{(-0.0693\ h^{-1} \cdot 6\ h)})] = 1.9$ mg/L.

It is also possible to compute pharmacokinetic parameters under multiple dose and steady-state conditions. Table 2-2 lists the methods to compute pharmacokinetic constants using a one compartment model for different routes of administration under single-dose, multiple-dose, and steady-state conditions. The main difference between single-dose and multiple-dose calculations is in the computation of the volume of distribution. When a single dose of medication is given, the predose concentration is assumed to be zero. However, when multiple doses are given, the predose concentration is not usually zero, and the volume of distribution equation (V) needs to have the baseline, predose concentration ($C_{predose}$) subtracted from the extrapolated drug concentration at time = 0 (C_0) for the intravenous bolus ($V = D/[C_0 - C_{predose}]$, where D is dose) and extravascular ($V/F = D/[C_0 - C_{predose}]$, where F is the bioavailability fraction and D is dose) cases. In the case of intermittent intravenous infusions, the volume of distribution equation already has a parameter for the predose concentration in it[4]:

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

where k_0 is the infusion rate, k_e is the elimination rate constant, t' = infusion time, C_{max} is the maximum concentration at the end of infusion, and $C_{predose}$ is the predose concentration. For each route of administration, the elimination rate constant (k_e) is computed using the same equation as the single dose situation: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$, where C_1 is the first concentration at time = t_1, and C_2 is the second concentration at time = t_2.

The following are examples of multiple dose and steady-state computations of pharmacokinetic parameters using a one compartment model for intravenous, intermittent intravenous infusions, and extravascular routes of administration:

Intravenous bolus. A patient receiving theophylline 300 mg intravenously every 6 hours has a predose concentration equal to 2.5 mg/L and postdose concentrations of 9.2 mg/L one hour and 4.5 mg/L five hours after the second dose is given. The patient has an elimination rate constant (k_e) equal to: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 9.2\ mg/L) - (\ln 4.5\ mg/L)]/(1\ h - 5\ h) = 0.179\ h^{-1}$. The volume of distribution (V) of theophylline for

TABLE 2-2 Single-Dose, Multiple-Dose, and Steady-State Pharmacokinetic Constant Computations Utilizing a One Compartment Model

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_0$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_e V$
Continuous intravenous infusion	N/A	N/A	$Cl = k_0/Css$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$
Extravascular (postabsorption, postdistribution)	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/C_0$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$
Average steady-state concentration (any route of administration)	N/A	N/A	$Cl/F = (D/\tau)/Css$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, k_0 is the continuous infusion rate, t′ is the infusion time, V/F is the hybrid constant volume of distribution/bioavailability fraction, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, Cl/F is the hybrid constant clearance/bioavailability fraction, $C_{predose}$ is the predose concentration, Css is the steady-state concentration, N/A is not applicable.

the patient is: $C_0 = C/e^{-k_e t} = (9.2 \text{ mg/L})/e^{(-0.179 \text{ h}^{-1})(1 \text{ h})} = 11.0$ mg/L and $V = D/[C_0 - C_{predose}] = (300 \text{ mg})/(11.0 \text{ mg/L} - 2.5 \text{ mg/L}) = 35.3$ L.

Intermittent intravenous infusion. A patient is prescribed gentamicin 100 mg infused over 60 minutes every 12 hours. A predose steady-state concentration ($C_{predose}$) is drawn and equals 2.5 mg/L. After the 1-hour infusion, a steady-state maximum concentration (C_{max}) is obtained and equals 7.9 mg/L. Since the patient is at steady state, it can be assumed that all predose steady-state concentrations are equal. Because of this the predose steady-state concentration 12 hours after the dose can also be considered equal to 2.5 mg/L and used to compute the elimination rate constant (k_e) of gentamicin for the patient: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 7.9 \text{ mg/L}) - (\ln 2.5 \text{ mg/L})]/(1 \text{ h} - 12 \text{ h}) = 0.105 \text{ h}^{-1}$. The volume of distribution (V) of gentamicin for the patient is:

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

where k_0 is the infusion rate, k_e is the elimination rate constant, t' = infusion time, C_{max} is the maximum concentration at the end of infusion, and $C_{predose}$ is the predose concentration. In this example, volume of distribution is:

$$V = \frac{(100 \text{ mg/1 h})(1 - e^{-(0.105 \text{h}^{-1})(1 \text{ h})})}{0.105 \text{h}^{-1}[(7.9 \text{ mg/L}) - (2.5 \text{ mg/L} \cdot e^{-(0.105 \text{ h}^{-1})(1 \text{ h})})]} = 16.8 \text{ L}$$

Extravascular. A patient is given procainamide capsules 750 mg every 6 hours. The following concentrations are obtained before and after the second dose: $C_{predose} = 1.1$ mg/L, concentrations 2 hours and 6 hours postdose equal 4.6 mg/L and 2.9 mg/L. The patient has an elimination rate constant (k_e) equal to: $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 4.6 \text{ mg/L}) - (\ln 2.9 \text{ mg/L})]/(2 \text{ h} - 6 \text{ h}) = 0.115 \text{ h}^{-1}$. The hybrid volume of distribution/bioavailability constant (V/F) of procainamide for the patient is: $C_0 = C/e^{-k_e t} = (2.9 \text{ mg/L})/e^{(-0.115 \text{ h}^{-1})(6 \text{ h})} = 5.8$ mg/L and $V/F = D/[C_0 - C_{predose}] = (750 \text{ mg})/(5.8 \text{ mg/L} - 1.1 \text{ mg/L}) = 160$ L.

Average Steady-State Concentration Equation

A very useful and easy equation can be used to compute the average steady-state concentration (Css) of a drug: $Css = [F(D/\tau)]/Cl$, where F is the bioavailability fraction, D is the dose, τ is the dosage interval, and Cl is the drug clearance.[8] This equation works for any single or multiple compartment model, and because of this it is deemed a model-independent equation. The steady-state concentration computed by this equation is the concentration that would have occurred if the dose, adjusted for bioavailability, was given as a continuous intravenous infusion. For example, 600 mg of theophylline tablets given orally every 12 hours (F = 1.0) would be equivalent to a 50 mg/h (600 mg/12 h = 50 mg/h) continuous intravenous infusion of theophylline. The average steady-state concentration equation is very useful when the half-life of the drug is long compared to the dosage interval or if a sustained-release dosage form is used. Examples of both situations follow:

Long half-life compared to dosage interval. A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d. The average steady-state concentration would equal: $Css = [F(D/\tau)]/Cl = [0.7(250 \text{ µg/d})]/(120 \text{ L/d}) = 1.5$ µg/L.

Sustained-release dosage form. A patient is given 1500 mg of procainamide sustained-release tablets every 12 hours until steady state for the treatment of an arrhythmia. The pharmacokinetic parameters for procainamide in the patient are: F = 0.85, Cl = 30 L/h. The average steady-state concentration would be: Css = [F(D/τ)]/Cl = [0.85(1500 mg/12 h)] / (30 L/h) = 3.5 mg/L.

If an average steady-state concentration (Css) is known for a drug, the hybrid pharmacokinetic constant clearance/bioavailability (Cl/F) can be computed: Cl/F = (D/τ)/Css, where D is dose and τ is the dosage interval. For example, a patient receiving 600 mg of sustained-release theophylline every 12 hours has a steady-state concentration equal to 11.2 mg/L. The clearance/bioavailability constant for theophylline in this patient would equal: Cl/F = (D/τ) / Css = (600 mg/12 h) / 11.2 mg/L = 4.5 L/h.

DESIGNING INDIVIDUALIZED DOSAGE REGIMENS USING ONE COMPARTMENT MODEL EQUATIONS

The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions. One compartment model equations can be used to compute initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient.[4, 5, 9] The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured. At that time, individualized dosage regimens at steady state can be designed for a patient. Table 2-3 lists the equations used to customize doses for the various routes of administration.

TABLE 2-3 Equations to Compute Individualized Dosage Regimens for Various Routes of Administration

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR k_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$
Continuous intravenous infusion	$k_0 = Css\ Cl = Css\ k_eV$ $LD = CssV$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau}) / (1 - e^{-k_et'})]$ $LD = k_0/(1 - e^{-k_e\tau})$
Extravascular (postabsorption, postdistribution)	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$ $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}]$ $LD = (Css_{max}V)/F$
Average steady-state concentration (any route of administration)	$D = (Css\ Cl\ \tau)/F = (Css\ k_eV\tau)/F$ $LD = (CssV)/F$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, Css is the steady-state concentration, k_0 is the continuous infusion rate, t' is the infusion time, T_{max} is the time that Css_{max} occurs, F is the bioavailability fraction.

Intravenous Bolus

If the volume of distribution and elimination rate constant can be estimated for a patient, a loading dose and initial maintenance dose can be computed. To design these doses, estimates of pharmacokinetic constants are obtained using patient characteristics such as weight, age, gender, renal and liver function, and other disease states and conditions that are known to effect the disposition and elimination of the drug. When the actual elimination rate constant and volume of distribution are measured for the medication, a maintenance dose to achieve any target steady-state concentrations can be designed.

Desired maximum and minimum steady-state concentrations are chosen for the patient. If the patient has never received the drug before, the therapeutic range can be used to choose starting concentrations. If the patient has taken the drug on previous occasions, safe and effective concentrations may be known. The dosage interval (τ) can be computed using the desired maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations: $\tau = (\ln Css_{max} - \ln Css_{min})/k_e$, where k_e is the elimination rate constant. The maintenance dose is then computed using the one compartment model equation for intravenous bolus administration at the time Css_{max} occurs (t = 0 hour after the bolus is given) solved for dose: $D = [Css_{max}\ V(1 - e^{-k_e\tau})] / e^{-k_e(0\ h)} = Css_{max}\ V(1 - e^{-k_e\tau})$. If a loading dose (LD) is necessary, it is computed using the following equation: $LD = Css_{max}\ V$.

An example of this approach is a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. An initial dosage regimen is designed using population pharmacokinetic parameters ($k_e = 0.139\ d^{-1}$, V = 50 L) to achieve maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations equal to 30 mg/L and 25 mg/L, respectively: $\tau = (\ln Css_{max} - \ln Css_{min})/k_e = [\ln (30\ mg/L) - \ln (25\ mg/L)] / 0.139\ d^{-1} = 1.3$ d, round to a practical dosage interval of 1 d; $D = Css_{max}\ V(1 - e^{-k_e\tau}) = (30\ mg/L \cdot 50\ L)(1 - e^{(-0.139\ d^{-1})(1\ d)}) = 195$ mg, round to a practical dose of 200 mg. The patient would be prescribed intravenous phenobarbital 200 mg daily.

Continuous and Intermittent Intravenous Infusion

The dosage regimen for a continuous intravenous infusion is computed using the following equation: $k_0 = Css\ Cl = Css\ k_eV$, where k_0 is the infusion rate, Css is the steady-state drug concentration, Cl is the drug clearance, k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) is computed using the following expression: LD = CssV. An example using this method is a patient with a ventricular arrhythmia after a myocardial infarction needing treatment with lidocaine at a Css of 3.0 mg/L (population pharmacokinetic parameters used: V = 50 L, Cl = 1.0 L/min) : LD = CssV = (3 mg/L)(50 L) = 150 mg; k_0 = CssCl = (3 mg/L)(1.0 L/min) = 3 mg/min. The patient would be prescribed lidocaine 150 mg intravenously followed by a 3 mg/min continuous infusion.

For intermittent intravenous infusions, the dosage interval (τ) is computed by choosing minimum (Css_{min}) and maximum (Css_{max}) steady-state concentrations: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$, where k_e is the elimination rate constant, and t' is the infusion time. The maintenance dose is calculated using the one compartment model equation for intermittent intravenous infusions at the time Css_{max} occurs solved for infusion rate (k_0): $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau}) / (1 - e^{-k_et'})]$, where k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) can be calculated using the following

formula which takes into account the amount of drug eliminated during the infusion time: $LD = k_0/(1 - e^{-k_e\tau})$.

An example using these techniques is a patient receiving tobramycin for the treatment of intraabdominal sepsis. Using pharmacokinetic parameters (V = 20 L, $k_e = 0.087\ h^{-1}$) previously measured in the patient using serum concentrations, compute a tobramycin dose (infused over 1 hour) that would provide maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations of 6 mg/L and 1 mg/L, respectively: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 6\ mg/L - \ln 1\ mg/L)/0.087\ h^{-1}] + 1\ h = 22$ h, round to practical dosage interval of 24 h; $k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau})/(1 - e^{-k_et'})] = [(6\ mg/L)(0.087\ h^{-1})(20\ L)]\ [(1 - e^{(-0.087\ h^{-1})(24\ h)})/(1 - e^{(-0.087\ h^{-1})(1\ h)})] = 110$ mg. The patient would be prescribed tobramycin 110 mg infused over 1 hour every 24 hours.

Extravascular

The dosage regimen for extravascular doses is determined by choosing maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$, where k_e is the elimination rate constant and T_{max} is the time that the maximum concentration occurs. The maintenance dose is computed employing the one compartment model equation for extravascular doses at the time Css_{max} occurs ($t = T_{max}$) solved for dose (D): $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}]$ where V is the volume of distribution and F is the bioavailability fraction. A loading dose (LD) can be computed using the following equation: $LD = (Css_{max}V)/F$.

An example of these computations is a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, $k_e = 0.05\ h^{-1}$, $T_{max} = 3$ h, F = 1.0) and maintain steady-state maximum (Css_{max}) and minimum (Css_{min}) concentrations of 80 mg/L and 50 mg/L, respectively: $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max} = [(\ln 80\ mg/L - \ln 50\ mg/L)/0.05\ h^{-1}] + 3\ h = 12.4$ h, round to practical dosage interval of 12 h; $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_eT_{max}}] = [(80\ mg/L \cdot 12\ L)/1.0)][(1 - e^{(-0.05\ h^{-1})(12\ h)})/e^{(-0.05\ h^{-1})(3\ h)}] = 503$ mg, round to practical dose of 500 mg. The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.

Average Steady-State Concentration

If the drug is administered as a sustained-release dosage form or the half-life is long compared to the dosage interval, it is possible to use the average steady-state concentration equation to individualize doses. The dosage regimen is computed using the following equation: $D = (Css\ Cl\ \tau)/F = (Css\ k_eV\tau)/F$, where D is the dose, Css is the steady-state drug concentration, Cl is the drug clearance, τ is the dosage interval, k_e is the elimination rate constant, and V is the volume of distribution. A loading dose (LD) is computed using the following expression: $LD = (CssV)/F$.

An example of this technique is a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h based on current procainamide continuous infusion; F = 0.85, $\tau = 12$ h for sustained-release tablet) and an average steady-state procainamide concentration equal to 5 mg/L: $D = (Css\ Cl\ \tau)/F = (5\ mg/L \cdot 24\ L/h \cdot 12\ h)/0.85 = 1694$ mg, round to a practical dose of 1500 mg. The patient would be prescribed procainamide sustained-release tablets 1500 mg orally every 12 hours.

MULTICOMPARTMENT MODELS

When serum concentrations decrease in a rapid fashion initially and then decline at a slower rate later (Figure 2-2), a multicompartment model can be used to describe the serum concentration/time curve[1] (Figure 2-1). The reason serum concentrations drop so rapidly after the dose is given is that all of the drug is in the bloodstream initially, and drug is leaving the vascular system by distribution to tissues and by hepatic metabolism and/or renal elimination. This portion of the curve is called the *distribution phase*. After this phase of the curve is finished, drug distribution is nearly complete and a psuedoequilibrium is established between the blood and tissues. During the final part of the curve, serum concentrations drop more slowly since only metabolism and/or elimination are taking place. This portion of the curve is called the *elimination phase*, and the elimination half-life of the drug is measured in this part of the serum concentration/time graph. Digoxin, vancomycin, and lidocaine are examples of drugs that follow multicompartment pharmacokinetics.

A two compartment model is the simplest of the multicompartment models. The equation that describes a two compartment model after an intravenous bolus is: $C = \{[D(\alpha - k_{21})]/[V_1(\alpha - \beta)]\}e^{-\alpha t} + \{[D(k_{21} - \beta)]/[V_1(\alpha - \beta)]\}e^{-\beta t}$, where C is the drug serum concentration, D is the intravenous bolus dose, k_{21} is the rate constant that describes the transfer of drug from compartment 2 to compartment 1, α is the distribution rate constant, β is the elimination rate constant, V_1 is the volume of distribution for compartment 1, and t is the time after the dose was administered. Similar equations for a two compartment model are available for intravenous infusions and extravascular doses. In order to get accurate values for the pharmacokinetic constants in the equation, 3–5 serum concentrations for each phase of the curve need to be obtained after a dose is given to a patient. Because of the cost and time involved to collect 6–10 serum concentrations after a dose, multicompartment models are rarely used in patient care situations. If a drug follows multicompartment pharmacokinetics, serum concentrations are usually not drawn for clinical use until the distribution phase is over and the elimination phase has been established. In these cases, it is possible to use simpler one compartment model equations to compute doses with an acceptable degree of accuracy.

MICHAELIS-MENTEN EQUATIONS FOR SATURABLE PHARMACOKINETICS

When the dose of a drug is increased and steady-state serum concentrations do not increase in a proportional fashion, but instead increase more than expected, Michaelis-Menten or saturable pharmacokinetics may be taking place. This situation occurs when the serum concentration of the drug approaches or exceeds the Km value for the enzyme system that is responsible for its metabolism. The Michaelis-Menten expression describes the dose required to attain a given steady-state drug concentration: $D = (V_{max} \cdot Css)/(Km + Css)$, where D is the dose, Css is the steady-state drug concentration, V_{max} is the maximum rate of drug metabolism, and Km is the concentration where the rate of metabolism equals $V_{max}/2$. Phenytoin is an example of a drug that follows saturable pharmacokinetics.[10]

Computing the Michaelis-Menten constants for a drug is not as straightforward as the calculation of pharmacokinetic parameters for a one-compartment linear pharmacokinetic model. The calculation of V_{max} and Km requires a graphical solution.[10]

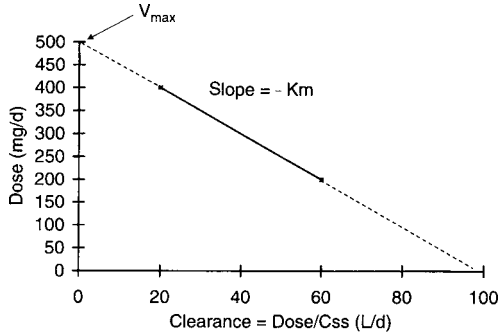


FIGURE 2-9 Michaelis-Menten plot for phenytoin. Dose (D) is plotted versus the ratio of dose and steady-state concentration *(D/Css)* for 2 or more different doses, and a straight line is drawn connecting the points. The slope of the line is –Km , and the y-intercept is V_{max}. The Michaelis-Menten constants are then used to compute the dose needed to achieve a new desired steady-state concentration.

The Michaelis-Menten equation is rearranged to the following formula: $D = V_{max} - [Km (D/Css)]$. This version of the function takes the form of the equation of a straight line: y = y-intercept + [(slope)*x*]. A plot of dose (D) versus dose divided by the steady-state concentration (D/Css) will yield a straight line with a slope equal to –Km and a y-intercept of V_{max}. In order to use this approach, a patient is placed on an initial dose (D_1) of the medication, a steady-state concentration is obtained (Css_1), and the dose/steady-state concentration ratio determined (D_1/Css_1). The dose of the medication is changed (D_2), a second steady-state concentration is measured (Css_2), and the new dose/steady-state concentration ratio is computed (D_2/Css_2). The dose and dose/steady-state concentration pairs are plotted on a graph so that V_{max} (the y-intercept) and Km (the -slope) can be determined (Figure 2-9). If additional doses are administered until steady state has been achieved, they can also be added to the same plot and the best straight line computed using linear regression. Once V_{max} and Km are known, the Michaelis-Menten expression can be used to compute a dose to reach any steady-state concentration.

An example is a patient receiving phenytoin for the treatment of tonic-clonic seizures. The patient received a dose of 300 mg/d with a steady-state concentration of 8 mg/L and a dose of 500 mg/d with a steady-state concentration equal to 22 mg/L. The dose/steady-state concentration ratios are 37.5 L/d and 22.7 L/d for the first and second doses, respectively ([300 mg/d] / 8 mg/L = 37.5 L/d; [500 mg/d] / 22 mg/L = 22.7 L/d). A plot of this data yields a V_{max} = 807 mg/d and a Km = 13.5 mg/L (Figure 2-9). The phenytoin dose to reach a steady-state concentration equal to 13 mg/L is: $D = (V_{max} \cdot Css) / (Km + Css)$ = (807 mg/d · 13 mg/L) / (13.5 mg/L + 13 mg/L) = 396 mg/d, rounded to a practical dose of 400 mg/d.

CALCULATION OF CLEARANCE, VOLUME OF DISTRIBUTION, AND HALF-LIFE IN PHARMACOKINETIC RESEARCH STUDIES

It is important to understand the methods used to compute the three principle pharmacokinetic parameters in research studies since these will be used by clinicians to determine population pharmacokinetic parameters for initial dosage regimen design.[11] The typical

pharmacokinetic research study administers a single dose of the medication and measures 10–15 serum concentrations for an estimated 3–5 half-lives or gives the drug until steady state is achieved and obtains 10–15 serum concentrations over a dosage interval. In either case, the serum concentration/time plot is used to compute the area under the serum concentration/ time curve (AUC). For drugs that follow linear pharmacokinetics, the AUC extrapolated to infinity after a single dose equals the AUC over the dosage interval at steady state for a dose of the same size so either can be used to compute pharmacokinetic constants.

Clearance (Cl) is computed by taking the ratio of the dose (D) and area under the serum concentration/time curve (AUC) for a drug that is administered intravenously: $Cl = D/AUC$. If the dose is administered extravascularly, the bioavailability fraction (F) must be included to compensate for drug that does not reach the systemic vascular system: $Cl = (FD)/AUC$.

Of the three volumes of distribution typically computed in a pharmacokinetic experiment, the one most useful in clinical situations is the volume of distribution (V) calculated using the area under the serum concentration/time curve (AUC): $V = D/(k_eAUC)$, where k_e is the elimination rate constant. For doses administered extravascularly, the bioavailability fraction (F) must be included to compensate for drug that does not reach the systemic vascular system: $V = (FD)/(k_eAUC)$.

Half-life is determined by plotting the serum concentration/time curve and computing the time it takes for serum concentrations to decrease by one-half in the postabsorption, postdistribution phase of the graph. In order to get the most accurate measurement of half-life, 5–7 serum concentrations are usually measured during the terminal portion of the curve, and nonlinear regression is used to compute the best value for the parameter. Alternatively, the data can be plotted on semilogarithmic axes and linear regression utilized to compute the terminal half-life.

PROBLEMS

1. PZ is a 35-year-old, 60-kg female with a *Staphylococcus aureus* wound infection. While receiving vancomycin 1 g every 12 hours (infused over one hour), the steady-state peak concentration (obtained one-half hour after the end of infusion) was 35 mg/L, and the steady-state trough concentration (obtained immediately predose) was 15 mg/L. (A) Using one compartment IV bolus equations, compute the pharmacokinetic parameters for this patient. (B) Using the patient-specific pharmacokinetic parameters calculated in part A, compute a new vancomycin dose that would achieve $Css_{max} = 30$ mg/L and $Css_{min} = 7.5$ mg/L.

2. Negamycin is a new antibiotic with an average volume of distribution of 0.35 L/kg and a half-life of 2 hours in patients with cystic fibrosis. Compute a dosage regimen for JM, a 22-year-old, 45-kg female cystic fibrosis patient with *Pseudomonas aeruginosa* in her sputum, that will achieve steady-state peak concentrations of 10 mg/L and trough concentrations of 0.6 mg/L using one-compartment model IV bolus equations (assume that the drug is given as an IV bolus).

3. KL is a 65-year-old, 60-kg female being treated for septic shock. Among other antibiotics, she is being treated with tobramycin 60 mg every 8 hours (infused over 1 hour). Steady-state serum concentrations are: Css_{max} = 7.1 mg/L, Css_{min} = 3.1 mg/L. Using one compartment intermittent intravenous infusion equations, compute the pharmacokinetic parameters for this patient and use them to individualize the tobramycin dose to achieve Css_{max} = 8 mg/L and Css_{min} = 1.0 mg/L.

4. JB is a 52-year-old, 72-kg male being treated for gram-negative pneumonia. Assuming a V = 18 L and a $t_{1/2}$ = 8 h, design a gentamicin dosage (infused over 1 hour) to achieve Css_{max} = 10 mg/L and Css_{min} = 1.2 mg/L using one compartment intermittent intravenous infusion equations.

5. EV is a 42-year-old, 84-kg male suffering from an acute asthmatic attack. Using one-compartment model equations, compute a theophylline IV bolus loading dose (to be administered over 20 minutes) and continuous infusion to achieve a Css = 12 mg/L. Assume a V = 40 L and $t_{1/2}$ = 5 h.

6. BJ is a 62-year-old, 70-kg female with a ventricular arrhythmia. Assuming a V = 33 L and Cl = 0.5 L/min, use one-compartment model equations to compute a lidocaine IV bolus loading dose (to be administered over 1–2 minutes) and continuous infusion to achieve a Css = 3 mg/L.

7. MM is a 54-year-old, 68-kg male being treated with procainamide 750-mg regular release capsules every 6 hours for an arrhythmia. The following steady-state concentration is available: Css_{min} = 1.5 mg/L (obtained immediately predose). Calculate a dose that will achieve a Css_{min} = 2.5 mg/L.

8. LM is a 59-year-old, 85-kg male needing treatment with oral quinidine for an arrhythmia. Assuming F = 0.7, T_{max} = 2 h, V = 200 L, and $t_{1/2}$ = 8 h, compute Css_{min} for a dose of oral quinidine 400 mg every 6 hours.

9. JB is a 78-year-old, 100-kg male being treated with digoxin for heart failure. While receiving digoxin tablets 125 μg daily, a steady-state digoxin concentration equal to 0.6 μg/L is obtained. (A) Assuming F = 0.7, compute digoxin clearance for the patient using the average steady-state concentration equation. (B) Compute a new digoxin tablet dose for the patient that will achieve Css = 1.2 μg/L.

10. QJ is a 67-year-old, 80-kg male being treated for chronic obstructive pulmonary disease. Sustained-release oral theophylline is being added to his drug regimen. Assuming F = 1.0, V = 40 L, and $t_{1/2}$ = 5 hours, compute an oral theophylline dose to be administered every 12 hours that would achieve a Css = 8 mg/L using the average steady-state concentration equation.

11. TD is a 32-year-old, 70-kg male with generalized tonic-clonic seizures. Assuming Michaelis-Menten parameters of V_{max} = 500 mg/d and Km = 4 mg/L, calculate a dose of phenytoin that will achieve Css = 15 mg/L.

12. OP is a 28-year-old, 55-kg female with complex partial seizures. She has the following information available: Css = 8 mg/L while receiving phenytoin 300 mg at bedtime and Css = 22 mg/L while receiving phenytoin 400 mg at bedtime. Compute the patient's Michaelis-Menten parameters for phenytoin, and the phenytoin dose that would achieve Css = 15 mg/L.

ANSWERS TO PROBLEMS

1. (A) $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 35\ mg/L) - (\ln 15\ mg/L)]/(1.5\ h - 12\ h) = 0.081\ h^{-1}$

$$t_{1/2} = 0.693/k_e = 0.693/0.081\ h^{-1} = 8.6\ h$$

$$C_0 = C/e^{-k_e t} = (35\ mg/L)/e^{(-0.081\ h^{-1})(1.5\ h)} = 39.5\ mg/L$$

$$V = D/[C_0 - C_{predose}] = (1000\ mg)/(39.5\ mg/L - 15\ mg/L) = 41\ L$$

(B) $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] = [\ln (30\ mg/L) - \ln (7.5\ mg/L)]/0.081\ h^{-1} = 17.1\ h$, round to a dosage interval of 18 hours.

$D = Css_{max}\ V(1 - e^{-k_e\tau}) = (30\ mg/L \cdot 41\ L)(1 - e^{(-0.081\ h^{-1})(18\ h)}) = 944\ mg$, round to a dose of 1000 mg.

Recommended dose: 1000 mg every 18 hours

2. Estimated $V = 0.35\ L/kg\ (45\ kg) = 15.8\ L$

Estimated $k_e = 0.693/t_{1/2} = 0.693/2\ h = 0.347\ h^{-1}$

$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] = [\ln (10\ mg/L) - \ln (0.6\ mg/L)]/0.347\ h^{-1} = 8.1\ h$, round to a dosage interval of 8 hours.

$D = Css_{max}\ V(1 - e^{-k_e\tau}) = (10\ mg/L \cdot 15.8\ L)(1 - e^{(-0.347\ h^{-1})(8\ h)}) = 148\ mg$, round to a dose of 150 mg.

Recommended dose: 150 mg every 8 hours.

If desired a loading dose can be calculated: $LD = Css_{max}\ V = (10\ mg/L)(15.8\ L) = 158\ mg$, round to a dose of 160 mg.

3. $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2) = -[(\ln 7.1\ mg/L) - (\ln 3.1\ mg/L)]/(1\ h - 8\ h) = 0.118\ h^{-1}$

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose}e^{-k_e t'})]}$$

$$V = \frac{(60\ mg/1\ h)(1 - e^{-(0.118\ h^{-1})(1\ h)})}{0.118\ h^{-1}[(7.1\ mg/L) - (3.1\ mg/L \cdot e^{-(0.118\ h^{-1})(1\ h)})]} = 13\ L$$

$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 8\ mg/L - \ln 1\ mg/L)/0.118\ h^{-1}] + 1\ h = 18.6\ h$, round to dosage interval of 18 h.

$k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau})/(1 - e^{-k_e t'})] = [(8\ mg/L)(0.118\ h^{-1})(13\ L)][(1 - e^{(-0.118\ h^{-1})(18\ h)})/(1 - e^{(-0.118\ h^{-1})(1\ h)})] = 97\ mg$, round to dose of 100 mg

Recommended dose: 100 mg every 18 hour.

4. $k_e = 0.693/t_{1/2} = 0.693/8\ h = 0.087\ h^{-1}$, V = 18 L

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 10\ mg/L - \ln 1.2\ mg/L)/0.087\ h^{-1}] + 1\ h = 25.4\ h, \text{ round to dosage interval of 24 h.}$$

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau})/(1 - e^{-k_e t'})] = [(10\ mg/L)(0.087\ h^{-1})(18\ L)][(1 - e^{(-0.087\ h^{-1})(24\ h)})/(1 - e^{(-0.087\ h^{-1})(1\ h)})] = 165\ mg$$

Recommended dose: 165 mg every 24 hour.

5. $k_e = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$

$$V = 40\ L,\ Cl = k_e V = (0.139\ h^{-1})(40\ L) = 5.56\ L/h$$

$$LD = Css\ V = (12\ mg/L)(40\ L) = 480\ mg, \text{ round to 500 mg IV over 20 minutes}$$

$$k_0 = Css\ Cl = (12\ mg/L)(5.56\ L/h) = 67\ mg/h, \text{ round to 70 mg/h}$$

6. $LD = Css\ V = (3\ mg/L)(33\ L) = 99\ mg$, round to 100 mg IV over 2 minutes

$$k_0 = Css\ Cl = (3\ mg/L)(0.5\ L/min) = 1.5\ mg/min$$

7. $D_{new}/D_{old} = Css_{new}/Css_{old}$

$$D_{new} = D_{old}(Css_{new}/Css_{old}) = 750\ mg\ [(2.5\ mg/L)/(1.5\ mg/L)] = 1250\ mg$$

Recommended dose: 1250 mg every 6 hour.

8. $k_e = 0.693/t_{1/2} = 0.693/8\ h = 0.087\ h^{-1}$

$$Css_{max} = [(FD)/V][e^{-k_e T_{max}}/(1 - e^{-k_e\tau})]$$

$$Css_{max} = [(0.7 \cdot 400\ mg)/200\ L][e^{(-0.087\ h^{-1})(2\ h)}/(1 - e^{(-0.087\ h^{-1})(6\ h)})] = 2.9\ mg/L$$

$$Css_{min} = Css_{max} e^{-k_e(\tau - T_{max})} = (2.9\ mg/L)e^{(-0.087\ h^{-1})(6\ h - 2\ h)} = 2.0\ mg/L$$

9. (A) $Css = F(D/\tau)/Cl$

$$Cl = F(D/\tau)/Css = [0.7(125\ \mu g/1\ d)]/(0.6\ \mu g/L) = 146\ L/d$$

(B) $D_{new} = D_{old}(Css_{new}/Css_{old}) = 125\ \mu g\ [(1.2\ \mu g/L)/(0.6\ \mu g/L)] = 250\ \mu g$

Recommended dose: 250 µg daily

10. $k_e = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$

$$Cl = k_e V = (0.139 h^{-1})(40\ L) = 5.56\ L/h$$

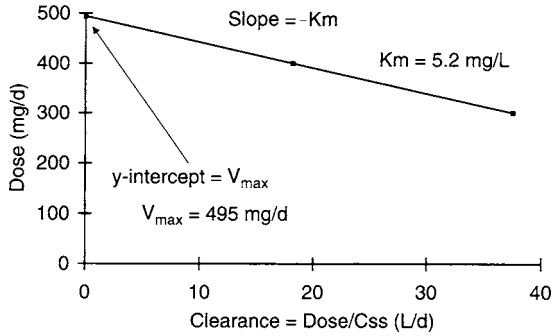
$$Css = F(D/\tau)/Cl$$

$D = (Css \cdot Cl \cdot \tau)/F = (8\ mg/L \cdot 5.56\ L/h \cdot 12\ h)/1.0 = 534\ mg$, round to 500 mg

Recommended dose: 500 mg every 12 hour.

11. $D = (V_{max} \cdot Css)/(Km + Css) = (500\ mg/d \cdot 15\ mg/L)/(4\ mg/L + 15\ mg/L) = 395\ mg$, round to 400 mg

Recommended dose: 400 mg daily at bedtime.



12. Graph data (see graph): Km = 5.2 mg/L, V_{max} = 495 mg/d

$D = (V_{max} \cdot Css)/(Km + Css) = (495\ mg/d \cdot 15\ mg/L)/(5.2\ mg/L + 15\ mg/L) = 367\ mg$, round to 375 mg

Recommended dose: 375 mg daily at bedtime.

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3

DRUG DOSING IN SPECIAL POPULATIONS: RENAL AND HEPATIC DISEASE, DIALYSIS, HEART FAILURE, OBESITY, AND DRUG INTERACTIONS

INTRODUCTION

All medications have specific disease states and conditions that change the pharmacokinetics of the drug and warrant dosage modification. However, the dosing of most drugs will be altered by one or more of the important factors discussed in this chapter. Renal or hepatic disease will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent. Dialysis procedures, conducted using artificial kidneys in patients with renal failure, removes some medications from the body while the pharmacokinetics of other drugs are not changed. Heart failure results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ blood flow. Obesity adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication. Finally, drug interactions can inhibit or induce drug metabolism, alter drug protein binding, or change blood flow to organs that eliminate or metabolize the drug.

RENAL DISEASE

Most water-soluble drugs are eliminated unchanged to some extent by the kidney. In addition to this, drug metabolites that were made more water soluble via oxidation or conjugation are typically removed by renal elimination. The nephron is the functional unit of the

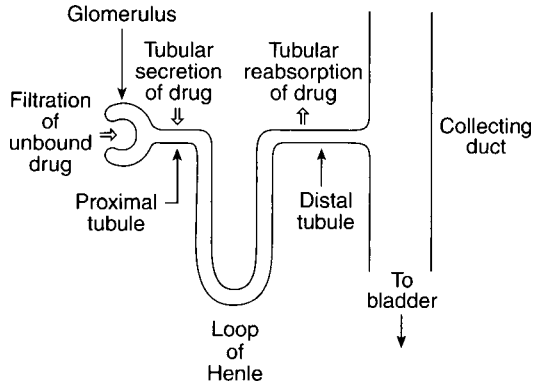

FIGURE 3-1 The nephron is the functional unit of the kidney responsible for drug elimination. Unbound drug is filtered freely at the glomerulus *(shown by arrow).* Active tubular secretion of drug *(denoted by arrow into nephron)* usually occurs in the proximal tubule of the nephron. Passive tubular reabsorption *(denoted by arrow out of nephron)* usually occurs in the distal tubule of the nephron. Tubular reabsorption requires un-ionized drug molecules so that the molecules can pass through the lipid membranes of the nephron and surrounding capillaries.

kidney that is responsible for waste product removal from the body and also eliminates drug molecules (Figure 3-1). Unbound drug molecules that are relatively small are filtered at the glomerulus. Glomerular filtration is the primary elimination route for many medications. Drugs can be actively secreted into the urine, and this process usually takes place in the proximal tubules. Tubular secretion is an active process conducted by relatively specific carriers or pumps that move the drug from blood vessels in close proximity to the nephron into the proximal tubule. Additionally, some medications may be reabsorbed from the urine back into the blood by the kidney. Reabsorption is usually a passive process and requires a degree of lipid solubility for the drug molecule. Thus, tubular reabsorption is influenced by the pH of the urine, the pKa of the drug molecule, and the resulting extent of molecular ionization. Compounds that are not ionized in the urine are more lipid soluble, better able to pass through lipid membranes, and more prone to renal tubular reabsorption. The equation that describes these various routes of renal elimination is:

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

where f_B is the free fraction of drug in the blood, GFR is glomerular filtration rate, RBF is renal blood flow, Cl'_{sec} is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed.[1]

When infants are born, renal function is not yet completely developed in full-term neonates (~40 weeks gestational age). Kidney development is complete and renal function stabilizes 3–6 months after birth. In premature infants (<35 weeks), kidney development may take even longer during the postpartum period. Kidney function, as measured by glomerular filtration rate, typically averages ~120–140 mL/min in young, healthy adults between the ages of 18–22 years. As humans age, there is a gradual decline in glomerular function so that by 65 years of age, the average glomerular filtration rate

is ~50–60 mL/min. The expected glomerular filtration rate for otherwise healthy, normal 80-year-old adults is ~30–40 mL/min. A glomerular filtration rate of 80–120 mL/min is usually considered the normal range by most clinical laboratories.

In patients with renal disease, there is a functional loss of nephrons. Depending on the etiology of the renal disease, patients with acute kidney failure may recoup their baseline renal function after a period of supportive care and dialysis long enough for their kidneys to recover. Patients with acute renal failure due to a sudden decrease in renal blood flow, such as that seen during hypotension, shock, or hypovolemia, or due to nephrotoxic drug therapy such as aminoglycoside antibiotics or vancomycin, often have their kidney function return to its preinsult level if they survive the underlying causes of their renal dysfunction. Patients with chronic renal failure sustain permanent loss of functional nephrons due to irreversible damage and do not recover lost kidney function.

Measurement and Estimation of Creatinine Clearance

Glomerular filtration rate can be determined by administration of special test compounds such as inulin or ^{125}I-iothalamate; this is sometimes done for patients by nephrologists when precise determination of renal function is needed. Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation: GFR (in mL/min / 1.73 m^2) = $186 \cdot S_{Cr}^{-1.154} \cdot Age^{-0.203} \cdot$ (0.742, if female) · (1.21, if African-American).[2,3] For example, the estimated GFR for a 53-year-old African-American male with a S_{Cr} = 2.7 mg/dL would be computed as follows: GFR = $186 \cdot (2.7 \text{ mg/dL})^{-1.154} \cdot (53 \text{ y})^{-0.203} \cdot 1.21 = 32$ mL/min / 1.73 m^2.

However, the method recommended by the Food and Drug Administration (FDA) and others to estimate renal function for the purposes of drug dosing is to measure or estimate creatinine clearance (CrCl).[4–9] Creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration. Because of this property, it is used as a surrogate measurement of glomerular filtration rate. Since creatinine is also eliminated by other routes, CrCl does not equal GFR, so the two parameters are not interchangeable.[3,5]

Creatinine clearance rates can be measured by collecting urine for a specified period and collecting a blood sample for determination of serum creatinine at the midpoint of the concurrent urine collection time: CrCl (in mL/min) = $(U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T)$, where U_{Cr} is the urine creatinine concentration in mg/dL, V_{urine} is the volume of urine collected in mL, S_{Cr} is the serum creatinine collected at the midpoint of the urine collection in mg/dL, and T is the time in minutes of the urine collection. Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24-hour urine collection period for the determination of creatinine clearance. For example, a 24-hour urine was collected for a patient with the following results: U_{Cr} = 55 mg/dL, V_{urine} = 1000 mL, S_{Cr} = 1.0 mg/dL, T = 24 h × 60 min/h = 1440 min, and CrCl (in mL/min) = $(U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T) = (55 \text{ mg/dL} \cdot 1000 \text{ mL}) / (1.0 \text{ mg/dL} \cdot 1440 \text{ min}) = 38$ mL/min. However, for the purpose of drug dosing, collection periods of 8–12 hours have been sufficient and provide a quicker turnaround time in emergent situations. Also, if renal function is stable, the blood sample for determination of serum creatinine may not need to be collected at the precise midpoint of the urine collection.

Routine measurement of creatinine clearances in patients has been fraught with problems. Incomplete urine collections, serum creatinine concentrations obtained at incorrect times, and collection time errors can produce erroneous measured creatinine clearance values. This realization has prompted investigators to derive methods which estimate

creatinine clearance from serum creatinine values and other patient characteristics in various populations. The most widely used of these formulas for adults aged 18 years and older is the method suggested by Cockcroft and Gault:[10] for males, $CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr})$; for females, $CrCl_{est} = [0.85(140 - age)BW]/(72 \cdot S_{Cr})$; where $CrCl_{est}$ is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and S_{Cr} is serum creatinine in mg/dL. The Cockcroft-Gault method should only be used in patients ≥18 years old, actual weight within 30% of their ideal body weight [IBW_{males} (in kg) = 50 + 2.3(Ht − 60) or $IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60), where Ht is height in inches], and stable serum creatinine concentrations. The 0.85 correction factor for females is present because women have smaller muscle mass than men and, therefore, produce less creatinine per day. For example, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be: $IBW_{males} = 50 + 2.3\ (Ht - 60) = 50 + 2.3(71 - 60) = 75$ kg, so the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used; $CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 55\ y)80\ kg]/(72 \cdot 1.9\ mg/dL) = 50$ mL/min.

Some patients have decreased muscle mass due to disease states and conditions that effect muscle or prevent exercise. Patients with spinal cord injury, cancer patients with muscle wasting, HIV-infected patients, cachectic patients, and patients with poor nutrition are examples of situations where muscle mass may be very small resulting in low creatinine production. In these cases, serum creatinine concentrations are low because of the low creatinine production rate and not due to high renal clearance of creatinine. In these cases, investigators have suggested that if serum creatinine values are <1.0 mg/dL for a patient an arbitrary value of 1 mg/dL be used in the Cockcroft-Gault formula to estimate creatinine clearance.[11–13] While it appears that the resulting estimate of creatinine clearance is closer to the actual creatinine clearance in these patients, it can still result in misestimates. It may be necessary to measure creatinine clearance in these types of patients if an accurate reflection of glomerular filtration rate is needed.

If serum creatinine values are not stable, but increasing or decreasing in a patient, the Cockcroft-Gault equation cannot be used to estimate creatinine clearance. In this case, an alternate method must be used which was suggested by Jelliffe and Jelliffe.[14] The first step in this method is to estimate creatinine production. The formula for this is different for males and females due to gender-dependent differences in muscle mass: $Ess_{male} = IBW[29.3 - (0.203 \cdot age)]$; $Ess_{female} = IBW[25.1 - (0.175 \cdot age)]$, where Ess is the excretion of creatinine, IBW is ideal body weight in kilograms, and age is in years. The remainder of the equations correct creatinine production for renal function, and adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse:

$$Ess_{corrected} = Ess[1.035 - (0.0337 \cdot Scr_{ave})]$$

$$E = Ess_{corrected} - \frac{[4IBW(Scr_2 - Scr_1)]}{\Delta t}$$

$$CrCl\ (in\ mL/min/1.73m^2) = E/(14.4 \cdot Scr_{ave})$$

where Scr_{ave} is the average of the two serum creatinine determinations in mg/dL, Scr_1 is the first serum creatinine and Scr_2 is the second serum creatinine both in mg/dL, and Δt is the time that expired between the measurement of Scr_1 and Scr_2 in minutes.

If patients are not within 30% of their ideal body weight, other methods to estimate creatinine clearance should be used.[15,16] It has been suggested that use of ideal body weight or adjusted body weight (ideal body weight plus 40% of obese weight) instead of actual body weight in the Cockcroft-Gault equation gives an adequate estimate of creatinine clearance for obese individuals. However, a specific method suggested by Salazar and Corcoran[17] for estimating creatinine clearance for obese patients has been shown to be generally superior:

$$\mathrm{CrCl}_{\mathrm{est(males)}} = \frac{(137 - \mathrm{age})[(0.285 \cdot \mathrm{Wt}) + (12.1 \cdot \mathrm{Ht}^2)]}{(51 \cdot \mathrm{S_{Cr}})}$$

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - \mathrm{age})[(0.287 \cdot \mathrm{Wt}) + (9.74 \cdot \mathrm{Ht}^2)]}{(60 \cdot \mathrm{S_{Cr}})}$$

where age is in years, Wt is weight in kg, Ht is height in m, and S_{Cr} is serum creatinine in mg/dL.

Methods to estimate creatinine clearance for children and young adults are also available according to their age:[18] age 0–1 year, $\mathrm{CrCl_{est}}$ (in mL/min / 1.73 $\mathrm{m^2}$) = (0.45 · Ht) / S_{Cr}; age 1–20 years, $\mathrm{CrCl_{est}}$ (in mL/min / 1.73 $\mathrm{m^2}$) = (0.55 · Ht)/S_{Cr}, where Ht is in cm and S_{Cr} is in mg/dL. Note that for these formulas, estimated creatinine clearance is normalized to 1.73 $\mathrm{m^2}$ which is the body surface area of an adult male with a height and weight of approximately 5 ft 10 in and 70 kg, respectively.

Estimation of Drug Dosing and Pharmacokinetic Parameters Using Creatinine Clearance

It is common to base initial doses of drugs that are renally eliminated on creatinine clearance. The basis for this is that renal clearance of the drug is smaller in patients with a reduced glomerular filtration rate, and measured or estimated creatinine clearance is a surrogate marker for glomerular filtration rate. An implicit assumption made in this approach is that all drug excreting processes of the kidney, including tubular section and reabsorption, decline in parallel with glomerular filtration. The basis of this assumption is the intact nephron theory. While tubular secretion and reabsorption may not always decline in proportion to glomerular filtration, this approach approximates the decline in tubular function and is a useful approach to initial drug dosing in patients with renal dysfunction. However, clinicians should bear in mind that the suggested doses for patients with renal impairment is an initial guideline only, and doses may need to be increased in patients that exhibit suboptimal drug response and decreased in patients with adverse effects.

Breakpoints to consider altering drug doses are useful for clinicians to keep in mind. Generally, one should consider a possible, modest decrease in drug doses when creatinine clearance is <50–60 mL/min, a moderate decrease in drug doses when creatinine clearance is <25–30 mL/min, and a substantial decrease in drug doses when creatinine clearance is ≤15 mL/min. In order to modify doses for patients with renal impairment, it is possible to decrease the drug dose and retain the usual dosage interval, retain the usual dose and increase the dosage interval, or simultaneously decrease the dosage and prolong the dosage interval. The approach used depends on the route of administration, the dosage forms available, and the pharmacodynamic response to the drug. For example, if the drug is prescribed orally and only a limited number of solid dosage forms are available, one

will usually administer the usual dose and increase the dosage interval. If the drug is given parenterally, a smaller dose can be administered, and it is more likely that the usual dosage interval will be retained. Finally, for drugs with narrow therapeutic ranges like aminoglycoside antibiotics and vancomycin where target serum concentrations for maximum and minimum steady-state concentrations are established, both the dose and dosage interval can be manipulated to achieve the targeted drug levels. If the drug dose is reduced and the dosage interval remains unaltered in patients with decreased renal function, maximum drug concentrations are usually lower and minimum drug concentrations higher than that encountered in patients with normal renal function receiving the typical drug dose (Figure 3-2). If the dosage interval is prolonged and the drug dosage remains the same, maximum and minimum drug concentrations are usually about the same as in patients with good renal function receiving the usual drug dose.

Since the mid-1980s, the FDA has required pharmacokinetic studies to be done for agents that are renally eliminated in patients with decreased creatinine clearance rates before receiving agency approval.[8] In these cases, the package insert for the drug probably contains reasonable initial dosage guidelines. For example, the manufacturer's suggested guidelines for the dosing of gabapentin in patients with renal dysfunction are listed in Table 3-1. Guidelines to change drug doses for patients with decreased renal function are available for older drugs as well as updated guidelines for newer drugs that may not be included in the package insert.[4,6,7,19–21] Also, the primary literature should be consulted to ensure that the newest guidelines are used for all drugs. If no specific information is available for a medication, it is possible to calculate modified initial drug doses using the method described by Dettli.[22]

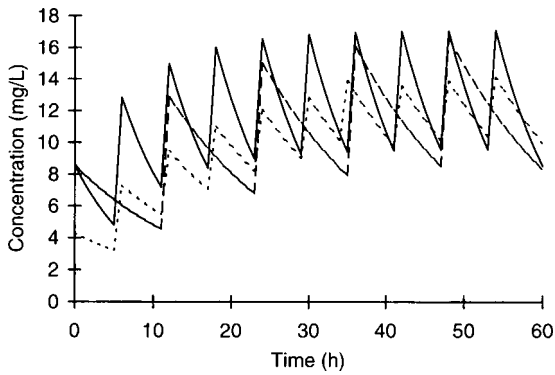

FIGURE 3-2 Serum concentration versus time profile for a patient with normal kidney function receiving a renally eliminated drug at the dose of 300 mg every 6 hours *(solid line).* In a patient with renal dysfunction, it is possible to give the same dose and prolong the dosage interval (300 mg every 12 hours, *dashed line),* or a reduced dose at the same dosage interval (150 mg every 6 hours, *dotted line).* Giving the same dose at a longer dosage interval in the patient with renal disease usually results in a concentration/time profile similar to that seen in a normal patient receiving the normal dose. However, giving a smaller dose and keeping the dosage interval the same usually produces a concentration/time profile with a lower peak steady-state concentration and a higher trough steady-state concentration. Note that since the total daily dose is the same for both renal disease dosage regimens (600 mg/d), the average steady-state concentration is identical for both dosage schemes. The same dosage options are available for liver-metabolized drugs for patients with hepatic dysfunction.

TABLE 3-1 Manufacturer's Recommended Dosing Schedule for Renal Dysfunction and Hemodialysis Patients Receiving Gabapentin[23]

CRCL (mL/min)	DAILY DOSE (mg/d)	DOSAGE (mg)				
≥60	900–3600	300 TID	400 TID	600 TID	800 TID	1200 TID
30–59	400–1400	200 BID	300 BID	400 BID	500 BID	700 BID
15–29	200–700	200 QD	300 QD	400 QD	500 QD	700 QD
15*	100–300	100 QD	125 QD	150 QD	200 QD	300 QD
Supplemental post-hemodialysis dose (mg)						
Hemodialysis		125**	150**	200**	250**	350**

Symbol key: TID is three times daily, BID is twice daily, QD is once daily
*For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).
**Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

For drugs with narrow therapeutic indexes, measured or estimated creatinine clearance may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction. Estimated pharmacokinetic parameters are then used in pharmacokinetic dosing equations to compute initial doses for patients. Clearance is the best pharmacokinetic parameter to estimate using creatinine clearance because it is an independent parameter that deals solely with drug elimination. The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the nonrenal clearance of the drug (Figure 3-3). For digoxin, an equation that describes the relationship between digoxin clearance (Cl) and creatinine

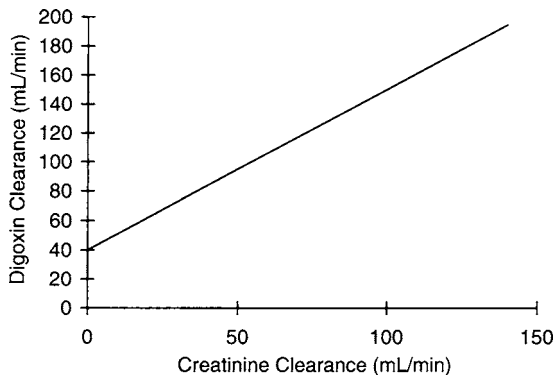

FIGURE 3-3 Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The y-axis intercept (40 mL/min) is nonrenal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, nonrenal clearance is set to a value of 20 mL/min.

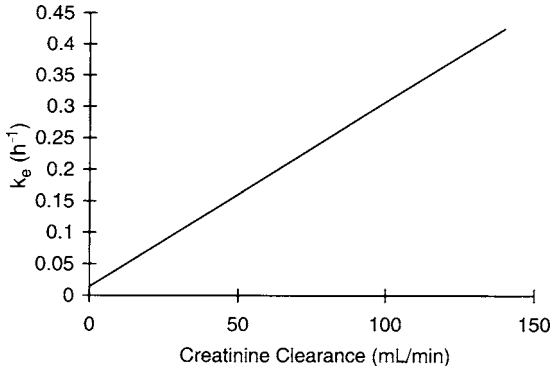

FIGURE 3-4 Relationship between creatinine clearance and aminoglycoside elimination rate constant *(k_e)* used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept (0.014 h^{-1}) is nonrenal elimination for aminoglycosides.

clearance (CrCl in mL/min) is: Cl (in mL/min) = 1.303 · CrCl + Cl_{NR}, where Cl_{NR} is nonrenal clearance and equals 20 mL/min in patients with moderate-severe heart failure and 40 mL/min in patients with no or mild heart failure.[24]

Elimination rate constant (k_e) can also be estimated using creatinine clearance, but it is a dependent pharmacokinetic parameter whose result is reliant on the relative values of clearance and volume of distribution (k_e = Cl/V). Because of this, changes in elimination rate constant may not always be due to changes in the renal elimination of the drug. The relationship between elimination rate constant and creatinine clearance is usually approximated by a straight line with a slope that is a function of renal elimination for the agent and an intercept that is related to the elimination of drug in functionally anephric patients (glomerular filtration rate ≈ 0; Figure 3-4). For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (k_e) and creatinine clearance (CrCl in mL/min) is: k_e (in h^{-1}) = 0.00293 · CrCl + 0.014.[25]

Volume of distribution can also change in patients with decreased renal function. Plasma protein binding displacement of drug by endogenous or exogenous substances that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function can increase the volume of distribution of drugs. Conversely, the volume of distribution of a drug can decrease if compounds normally excreted by the kidney accumulate to the extent that displacement of drug from tissue binding sites occurs. Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:[26] V (in L) = 226 + [(298 · CrCl)/(29.1 + CrCl)] where CrCl is in mL/min. The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

HEPATIC DISEASE

Most lipid-soluble drugs are metabolized to some degree by the liver. Phase I type reactions, such as oxidation, hydrolysis, and reduction, are often mediated by the cytochrome P-450 enzyme system (CYP) which is bound to the membrane of the endoplasmic

reticulum inside hepatocytes. Phase II type reactions, including conjugation to form glucuronides, acetates, or sulfates, may also be mediated in the liver by cytosolic enzymes contained in hepatocytes. Phase I and phase II drug metabolism generally results in metabolites that are more water soluble and prone to elimination by the kidney. Transport proteins, such as P-glycoprotein, actively secrete drug molecules into the bile.

The liver receives its blood supply via the hepatic artery, which contains oxygenated blood from the aorta via the superior mesenteric artery, and the portal vein, which drains the gastrointestinal tract (Figure 3-5). Liver blood flow averages 1–1.5 L/min in adults with about one-third coming from the hepatic artery and about two-thirds coming from the portal vein. Orally administered medications must pass through the liver before entering the systemic circulation, so if the drug is metabolized by the liver, a portion of the dose may be inactivated by the hepatic first-pass effect before having a chance to exert a pharmacologic effect. In addition to hepatic metabolism, drugs can be eliminated unchanged by liver in the bile. The equation that describes hepatic drug metabolism is[27]:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance.

Hepatic metabolism of drugs is not completely developed in neonates (~40-weeks gestational age), and continues to increase so that by age 3–6 months it is stable. In premature infants (<35 weeks), hepatic metabolism may take even longer to develop in the postpartum period. On a per kilogram basis, drug metabolism is more rapid in children until puberty. At that point, metabolic rate gradually decreases to adult values. The effect of advanced age on hepatic drug metabolism is quite variable. Patients over the age of 65 years may have decreased hepatic clearance of some drugs, but oftentimes concurrent disease states and conditions that effect drug pharmacokinetics obscure the influence of age in these older individuals. Elderly individuals have decreased liver mass, and it appears that hepatocytes which are still present have decreased ability to metabolize drugs.

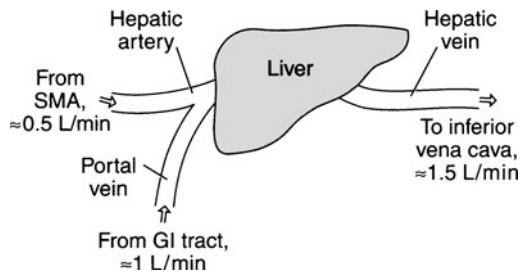

FIGURE 3-5 Schematic representation of the liver. Liver blood flow to the organ is supplied by the hepatic artery and the portal vein. The hepatic artery branches off of the superior mesenteric artery and provides oxygenated blood to the liver at the rate of ~0.5 L/min. The portal vein drains blood from the gastrointestinal tract at the rate of ~1 L/min and passes its contents to the liver. Any chemicals, including orally administered drugs, must pass through the liver before it enters the systemic circulation. The hepatic vein drains the liver of blood and empties into the inferior vena cava.

There are two major types of liver disease: hepatitis and cirrhosis. Patients with hepatitis experience an inflammation of the liver, and as a result, hepatocytes may experience decreased ability to function or die. Patients with acute hepatitis usually experience mild, transient decreases in drug metabolism that require no or minor changes in drug dosing. If the patient develops chronic hepatitis, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes will be required at some point. In patients with hepatic cirrhosis, there is a permanent loss of functional hepatocytes. Drug dosage schedules usually need to be modified in patients with severe cirrhosis. With sufficient long-term hepatocyte damage, patients with chronic hepatitis can progress to hepatic cirrhosis.

When hepatocytes are damaged they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduces the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase. A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely large increases in steady-state concentrations for orally administered drugs. Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by nonfunctional connective tissue which increases intraorgan pressure causing portal vein hypertension and shunting of blood flow around the liver. The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further. The liver produces albumin and, probably, α_1-acid glycoprotein, the two major proteins that bind acidic and basic drugs, respectively, in the blood. In patients with cirrhosis, the production of these proteins decline. When this is the case, the free fraction of drugs in the blood increases because of a lack of binding proteins. Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites. The increased free fraction in the blood will alter hepatic and renal drug clearance as well as the volume of distribution for drugs that are highly protein bound ($V = V_B + (f_B/f_T)V_T$, where V is the volume of distribution, V_B and V_T are the physiologic volume of blood and tissues, respectively, and f_B and f_T are the free fraction of drug in the blood and tissues, respectively). Since clearance typically decreases and volume of distribution usually increases or does not appreciably change for a drug in patients with liver disease, the elimination rate constant (k_e) almost always increases in patients with decreased liver function ($k_e = Cl/V$, where Cl is clearance and V is volume of distribution).

Determination of Child-Pugh Scores

Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that measured or estimated creatinine clearance is used to measure renal function. The most common way to estimate the ability of the liver to metabolize drug is to determine the Child-Pugh score for a patient.[28] The Child-Pugh score consists of five laboratory tests or clinical symptoms. The five areas are serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal)–3 (severely abnormal; Table 3-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15.

TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

A Child-Pugh score equal to 8–9 is grounds for a moderate decrease (~25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized, and a score of 10 or greater indicates that a significant decrease in initial daily dose (~50%) is required for drugs that are mostly liver metabolized. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects.

For example, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d. For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours. The patient would be closely monitored for pharmacologic and toxic effects due to the medication, and the dose would be modified as needed.

Estimation of Drug Dosing and Pharmacokinetic Parameters for Liver Metabolized Drugs

For drugs that are primarily liver metabolized, pharmacokinetic parameters are assigned to patients with liver disease by assessing values previously measured in patients with the same type of liver disease (e.g., hepatitis or cirrhosis) and a similar degree of liver dysfunction. Table 3-3 gives values for theophylline clearance in a variety of patients, including patients with cirrhosis.[29] The dose and dosing interval needed to achieve steady-state concentrations in the lower end of the therapeutic range using pharmacokinetic parameters measured in patients with liver disease are computed using pharmacokinetic equations. For example, the theophylline dosage rates listed in Table 3-3 are designed to produce steady-state theophylline concentrations between 8 and 12 mg/L. They were computed by multiplying theophylline clearance and the desired steady-state concentration ($MD = Css \cdot Cl$, where MD is the maintenance dose, Css is the steady-state concentration, and Cl is drug clearance). Average theophylline clearance is about 50% less in adults with liver cirrhosis compared to adults with normal hepatic function. Because of this, initial theophylline doses for patients with hepatic cirrhosis are one-half the usual dose for adult patients with normal liver function.

When prescribing medications that are principally eliminated by the liver in patients with liver dysfunction, it is possible to decrease the dose while retaining the normal

TABLE 3-3 Theophylline Clearance and Dosage Rates for Patients with Various Disease States and Conditions[28]

DISEASE STATE/CONDITION	MEAN CLEARANCE (mL/min/kg)	MEAN DOSE (mg/kg/h)
Children 1–9 years	1.4	0.8
Children 9–12 years or adult smokers	1.25	0.7
Adolescents 12–16 years or elderly smokers (>65 years)	0.9	0.5
Adult nonsmokers	0.7	0.4
Elderly nonsmokers (>65 years)	0.5	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.35	0.2

Mean volume of distribution = 0.5 L/kg.

dosage interval, retain the normal dose and prolong the dosage interval, or modify both the dose and dosage interval. Compared to individuals with normal liver function receiving a drug at the usual dose and dosage interval, patients with hepatic disease that receive a normal dose but a prolonged dosage interval will have similar maximum and minimum steady-state serum concentrations (Figure 3-2). However, if the dose is decreased but the dosage interval kept at the usual frequency, maximum steady-state concentrations will be lower and minimum steady-state concentrations will be higher for patients with liver disease than for patients with normal hepatic function. The actual method used to reduce the dose for patients with liver dysfunction will depend on the route of administration and the available dosage forms. For example, if the medication is only available as an oral capsule, it is likely that the usual dose will be given to a patient with liver disease but the dosage interval will be prolonged. However, if the drug is given parenterally, it may be possible to simultaneously modify the dose and dosage interval to attain the same maximum and minimum steady-state concentrations in patients with hepatic dysfunction as those encountered in patients with normal liver function.

Implications of Hepatic Disease on Serum Drug Concentration Monitoring and Drug Effects

The pharmacokinetic alterations that occur with hepatic disease result in complex changes for total and unbound steady-state concentrations and drug response. The changes that occur depend on whether the drug has a low or high hepatic extraction ratio. As previously discussed, hepatic drug metabolism is described by the following equation:[25]

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance. For drugs with a low hepatic extraction ratio (≤30%), the numeric

value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound ($LBF >> f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [$LBF \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

Similarly, for drugs with a high hepatic extraction ratio (≥70%), the numeric value of liver blood flow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent ($LBF << f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to the product of free fraction of drug in the blood and intrinsic clearance [$f_B \cdot Cl'_{int} \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to liver blood flow for a drug with a high hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{f_B \cdot Cl'_{int}} = LBF$$

For drugs with intermediate hepatic extraction ratios, the entire liver clearance equation must be used and all three factors, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account. An extremely important point for clinicians to understand is that the factors which are important determinants of hepatic clearance are different depending on the liver extraction ratio for the drug.

In order to illustrate the differences that may occur in steady-state drug concentrations and pharmacologic effects for patients with liver disease, a graphical technique will be used (Figure 3-6). The example assumes that a low hepatic extraction ratio drug (100% liver metabolized) is being given to a patient as a continuous intravenous infusion, and that all physiologic, pharmacokinetic, and drug effect parameters (shown on the y-axis) are initially stable. On the x-axis, an arrow indicates that intrinsic clearance decreases due to the development of hepatic cirrhosis in the patient; an assumption made for this illustration is that any changes in the parameters are instantaneous. An increase in the parameter is denoted as an uptick in the line while a decrease in the parameter is shown as a downtick in the line. The first three parameters are physiologic values (LBF, f_B, and Cl'_{int}) that will change in response to the development of hepatic dysfunction. In this case, only intrinsic clearance decreased due to the destruction of hepatocytes, and liver blood flow and free fraction of drug in the blood was not altered (Figure 3-6). This change will decrease the hepatic clearance of the drug, volume of distribution will not be modified because blood and tissue volume or plasma protein and tissue binding did not change, and half-life will increase because of the decrease in clearance [$t_{1/2} = (0.693 \cdot V)/Cl$, where $t_{1/2}$ is half-life, Cl is clearance, and V is volume of distribution]. Total and unbound steady-state drug concentrations will increase in tandem, and the pharmacologic response will increase because of the increase in unbound serum concentration.

Using the same baseline conditions as in the previous example, it is possible to examine what would happen if the major change in a similar patient receiving the same drug

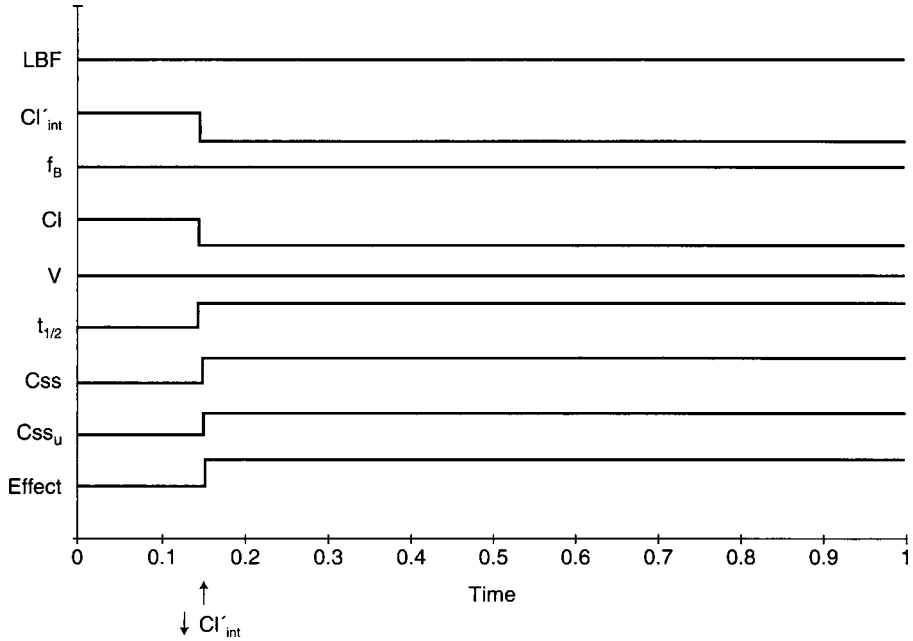

FIGURE 3-6 Changes in physiologic parameters *(LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

decreased plasma protein binding due to hypoalbuminemia and hyperbilirubinemia (Figure 3-7). Under these circumstances, liver blood flow and intrinsic clearance would not change, but free fraction of drug in the blood would increase. Because of the increased free fraction of drug in the blood, both clearance and volume of distribution would simultaneously increase. Clearance increases for a low hepatic extraction ratio drug because more is free to leave the bloodstream and enter hepatocytes where it can be metabolized. Volume of distribution increases because more drug is free to leave the vascular system and enter various tissues. Depending on the relative changes in clearance and volume of distribution, half-life could increase, decrease, or not change; for the purpose of this example the assumption is made that alterations in these independent parameters are similar so half-life does not change. The total steady-state concentration would decrease because total clearance increased, but the unbound steady-state concentration would remain unchanged because the decrease in total concentration is offset by the increase in free fraction of unbound drug. Finally, the pharmacologic effect of the drug is the same because free steady-state concentrations of the drug did not change. This can be an unexpected outcome for the decrease in protein binding, especially because the total

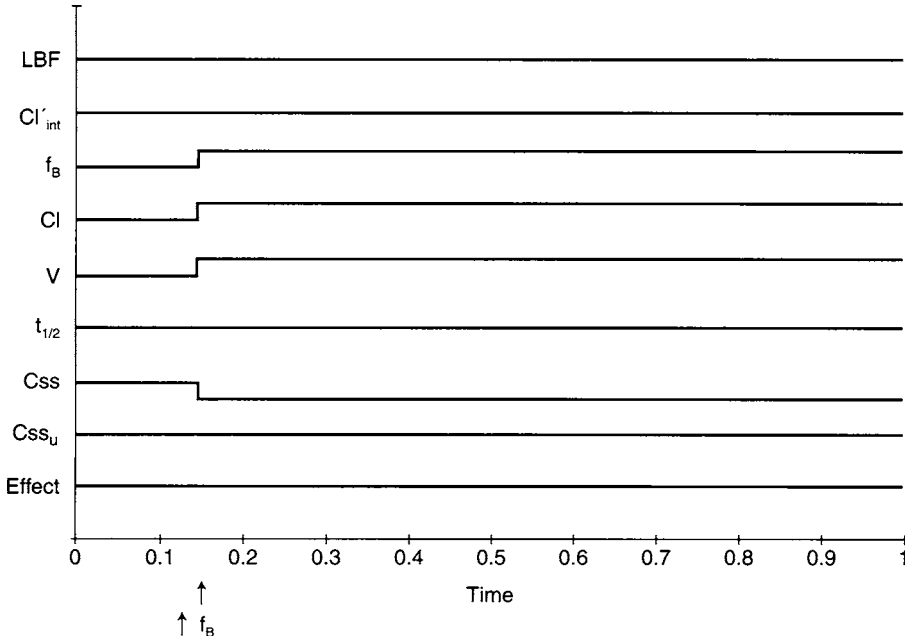

FIGURE 3-7 Changes in physiologic parameters *(LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if decreased protein binding occurred ($\uparrow f_B$, indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Increased free fraction of drug in the blood secondary to decreased plasma protein binding could happen during liver dysfunction because of hypoalbuminemia or hyperbilirubinemia. Increased free fraction of drug can occur in patients with normal liver function secondary to a plasma protein binding displacement drug interaction.

steady-state concentration of the drug decreased. Clinicians need to be on the outlook for situations like this because the total drug concentration (bound + unbound) can be misleading and cause an unwarranted increase in drug dosage. Unbound drug concentrations are available for several agents that are highly plasma protein bound, such as phenytoin, valproic acid, and carbamazepine, and are valuable tools to guide drug dosage in liver disease patients.

Finally, decreases in liver blood flow need to be considered for drugs with low hepatic extraction ratios. A decrease in liver blood flow will not change intrinsic clearance, plasma protein binding, clearance or volume of distribution under usual circumstances, and, thus, will not change total steady-state concentrations, unbound steady-state concentrations, or the pharmacologic effects of the drug. However, a drastic decrease in liver blood flow can effectively stop delivery of drug to the liver and change liver clearance even for compounds with a low hepatic extraction ratios.

For drugs with high hepatic extraction ratios, the pattern of changes using the above model is entirely different. If intrinsic clearance changes due to hepatocyte destruction for

a high hepatic extraction ratio drug, liver blood flow and unbound fraction of drug in the blood remain unaltered (Figure 3-8). Pharmacokinetic constants also do not change, because none are influenced by intrinsic clearance. Because of this, unbound and total steady-state drug concentrations and pharmacologic effect are unchanged. If the drug were administered orally, the hepatic first-pass effect would be decreased which would increase the bioavailability of the drug. Since this is effectively an increase in drug dosage, average total and unbound drug concentrations and pharmacologic effect would increase for this route of administration ($Css = [F(D/\tau)/Cl]$, where F is the bioavailability fraction, Css is the total steady-state drug concentration, D is dose, τ is the dosage interval, and Cl is clearance).

A decrease in plasma protein binding due to lack of binding protein or displacement from binding sites causes severe problems for high hepatic extraction ratio drugs (Figure 3-9). Decreased plasma protein binding results in an increased free fraction of drug in the blood, but no change in liver blood flow or intrinsic clearance. Since clearance is a function of liver blood flow, it does not change. However, a higher free fraction of drug in the blood increases the volume of distribution and this change causes a longer half-life for

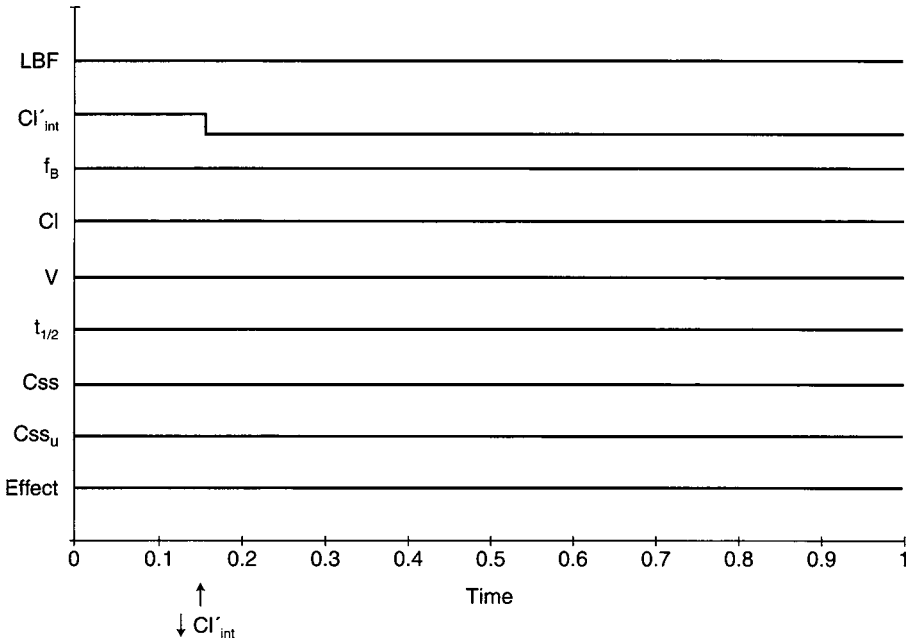

FIGURE 3-8 Changes in physiologic parameters *(LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance decreases (indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

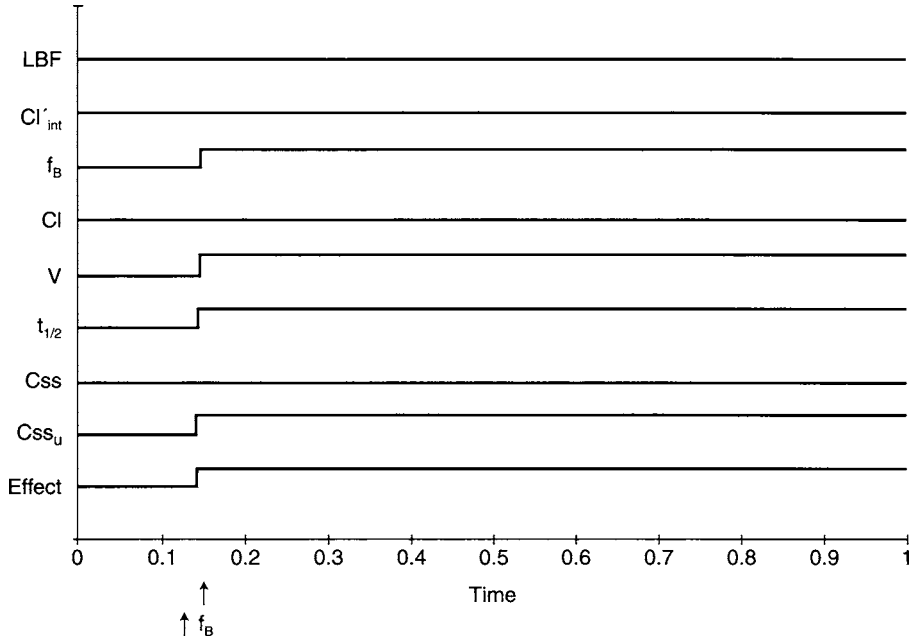

FIGURE 3-9 Changes in physiologic parameters *(LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if decreased protein binding occurred ($\uparrow f_B$, indicated by *arrow).* An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Increased free fraction of drug in the blood secondary to decreased plasma protein binding could happen during liver dysfunction because of hypoalbuminemia or hyperbilirubinemia. Increased free fraction of drug can occur in patients with normal liver function secondary to a plasma protein binding displacement drug interaction.

the drug. Total steady-state concentration does not change because clearance did not change. But, unbound steady-state concentration increases because of the increased free fraction of drug in the blood. Pharmacologic effect increases due to the increased unbound steady-state concentration. This is a very subtle change in drug metabolism, because total steady-state concentrations do not change, but the pharmacologic effect is augmented. Clinicians need to keep this possible change in mind and order unbound drug concentrations, if available, when they suspect that this phenomenon may be taking place. If unbound drug concentrations (or no drug concentrations) are available, a trial decrease in dose may be warranted. Orally administered drug would result in a similar pattern of change, but the increased free fraction of drug in the blood would result in a larger hepatic first-pass effect and an effective reduction in dose which would partially offset the increase in unbound steady-state concentration.

If liver blood flow decreases, the pharmacokinetic and pharmacologic changes are more straightforward for medications with large hepatic extraction ratios (Figure 3-10). Decreased liver blood flow does not change intrinsic clearance or the unbound fraction of

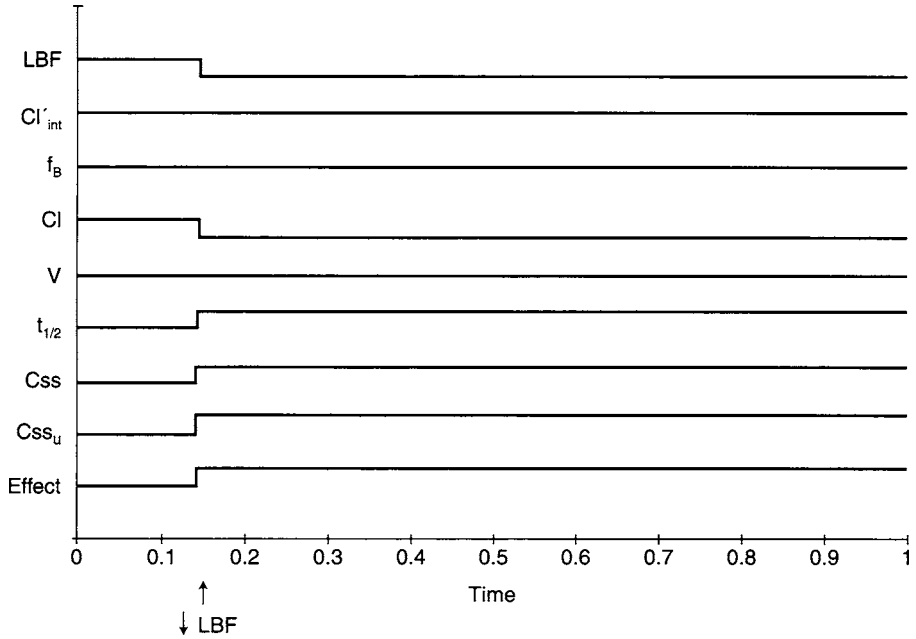

FIGURE 3-10 Changes in physiologic parameters *(LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters *(Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect *(Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if liver blood flow decreases (↓LBF, indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Decreased liver blood flow could happen because of portal hypertension secondary to hepatic cirrhosis. Decreased liver blood flow can occur in patients with normal liver function secondary to a drug interaction with an agent that decreases cardiac output such as β-blockers.

drug in the blood. Clearance decreases because it is dependent on liver blood flow for drugs with a high hepatic extraction ratio. Volume of distribution remains constant, but half-life increases because of the decrease in clearance. Total steady-state concentration increases because of the decrease in clearance, free steady-state concentration rises due to the increase in total steady-state concentration, and the increase in pharmacologic effect tracks the change in free concentration. If the drug is given orally, the first-pass effect would increase, and bioavailability would decrease, partially offsetting the increase in total and unbound steady-state concentrations.

HEART FAILURE

Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow. Changes in drug pharmacokinetics due to decreased renal blood flow are not widely reported. However, declines in hepatic clearance, especially for

compounds with moderate-to-high hepatic extraction ratios, are reported for many drugs. Additionally, decreased drug bioavailability has been reported in patients with heart failure. The proposed mechanisms for decreased bioavailability are collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract. The volume of distribution for some drugs decreases in patients with heart failure. Because clearance and volume of distribution may or may not simultaneously change, the alteration in half-life, if any, is difficult to predict in patients with heart failure.

DIALYSIS

Dialysis is a process whereby substances move via a concentration gradient across a semipermeable membrane (Figure 3-11). Artificial kidneys (also known as dialysis coils or filters) are available for use in hemodialysis that use a synthetic semipermeable membrane to remove waste products from the blood. Also, physiologic membranes, such as those present in the peritoneal cavity in the lower abdomen, can be used with peritoneal dialysis as an endogenous semipermeable membrane. Substances that are small enough to pass through the pores in the semipermeable membrane will pass out of the blood into the dialysis fluid. Once in the dialysis fluid, waste products and other compounds can be removed from the body. In some cases, dialysis is used to remove drugs from the bodies of patients that have taken drug overdoses or are experiencing severe adverse effects from the drug. However, in most cases drug molecules are removed from the blood coincidental to the removal of toxic waste products that would usually be eliminated by the kidney.

Because drugs can be removed by dialysis, it is important to understand when drug dosing needs to be modified in renal failure patients undergoing the procedure. Often,

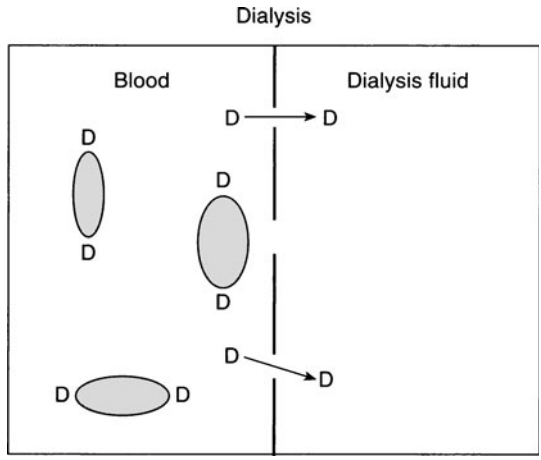

FIGURE 3-11 Dialysis removal of drug can occur when a patient's blood comes in contact with a semipermeable membrane that has drug-free dialysis fluid on the other side. In this schematic, the semipermeable membrane has pores in it large enough for unbound drug to pass through (represented by *D*), but not for protein-bound drug to pass through (denoted by *Ds attached to ovals* representing plasma proteins).

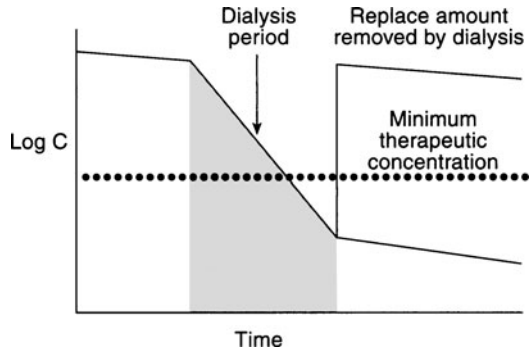

FIGURE 3-12 Concentration-time graph for a drug removed by dialysis. The *shaded area* indicates the time period that a dialysis procedure was conducted. Because extra drug was removed from the blood during dialysis, concentrations dropped much faster during that period. After dialysis is finished, the concentrations again drop at the predialysis rate. If drug concentrations drop below the minimum therapeutic concentration (shown by the *dark, dotted horizontal line)*, it may be necessary to give a supplemental dose to retain the pharmacologic effect of the drug (indicated by increase in drug concentration after dialysis).

dialysis removes enough drug from a patient's body that supplemental doses need to be given after dialysis has been completed (Figure 3-12). In a renal failure patient, the only clearance mechanism available to remove drugs from the body are nonrenal ($Cl = Cl_{NR}$, where Cl is total clearance and Cl_{NR} is nonrenal clearance). When the patient is receiving dialysis, clearance from both nonrenal routes and dialysis are present which will accelerate drug removal from the body during the dialysis procedure if the compound is significantly removed by dialysis ($Cl = Cl_{NR} + Cl_D$, where Cl_D is dialysis clearance). In order to determine if dialysis clearance is significant, one should consider the absolute value of dialysis clearance and the relative contribution of dialysis clearance to total clearance. Additionally, if dialysis clearance is ≥30% of total clearance or if the total amount of drug removed by the dialysis procedure is enough to warrant a postdialysis replacement dose, dialysis clearance is considered to be significant.

Drug Characteristics that Effect Dialysis Removal

MOLECULAR SIZE

Molecular size relative to pore size in the semipermeable membrane is a factor that influences dialysis clearance of a compound. Most hemodialysis procedures are conducted using "low-flux" artificial kidneys which have relatively small pores in the semipermeable membranes. However, "high-flux" filters are now available and widely used in some patients. The semipermeable membranes of these artificial kidneys have much larger pore sizes and larger surface areas so large drug molecules, such as vancomycin, that were previously considered unable to be removed by hemodialysis can be cleared by high-flux filters. It is important that clinicians know which type of artificial kidney is used for a patient before assessing its potential to remove drug molecules.

For low-flux filters, small drug molecules (molecular weight <500 Da, such as theophylline, lidocaine, procainamide) relative to the pore size of the semipermeable membrane

tend to be readily eliminated by dialysis and have high extraction ratios for the artificial kidney. In this case, dialyzability of the drug is influenced by blood flow to the artificial kidney, dialysis fluid flow rate to the artificial kidney, and the surface area of the semipermeable membrane inside the artificial kidney. Increased blood flow delivers more drug to the dialysis coil, increased dialysis fluid flow rate removes drug that entered the dialysis fluid more quickly from the artificial kidney and increases the concentration gradient across the semipermeable membrane, and increased semipermeable membrane surface area increases the number of pores that a drug molecule will encounter, making it easier for drug molecules to pass from the blood into the dialysis fluid.

Drug molecules with moderate molecular weights (molecular weight 500–1000 Da, such as aminoglycoside antibiotics [~400–500 Da] and digoxin) have a decreased ability to pass through the semipermeable membrane contained in low-flux filters. However, many drugs that fall in this intermediate category have sufficient dialysis clearances to require postdialysis replacement doses. Large drug molecules (molecular weight >1000 Da, such as vancomycin) are not removed to a significant extent when low-flux filters are used for dialysis because pore sizes in these artificial kidneys are too small for the molecules to fit through. However, many large molecular weight drugs can be removed by dialysis when high-flux filters are used, and, in some of these cases, supplemental postdialysis drug doses will be needed to maintain therapeutic amounts of drug in the body.

WATER/LIPID SOLUBILITY

Drugs that have a high degree of water solubility will tend to partition into the water-based dialysis fluid, while lipid-soluble drugs tend to remain in the blood.

PLASMA PROTEIN BINDING

Only unbound drug molecules are able to pass through the pores in the semipermeable membrane; drug–plasma protein complexes are too large to pass through the pores and gain access to the dialysis fluid side of the semipermeable membrane. Drugs that are not highly plasma protein bound have high free fractions of drug in the blood and are prone to better dialysis clearance. Drugs that are highly bound to plasma proteins have low free fractions of drug in the blood and poor dialysis clearance rates.

VOLUME OF DISTRIBUTION

The volume of distribution for a drug is a function of blood volume (V_B), organ size (V_T), drug plasma protein binding (f_B, free fraction of drug in the blood), and drug tissue binding [f_T, free fraction of drug in the tissues; $V = V_B + (f_B/f_T)V_T$]. Medications with large volumes of distribution are principally located at tissue binding sites and not in the blood where dialysis can remove the drug. Because of this, agents with large volumes of distribution are not easily removed from the body. In fact, some compounds such as digoxin, have good hemodialysis clearance rates, and drug contained in the bloodstream is very effectively eliminated. However, in this case the majority of the drug is present in the tissues and only a small amount of the total drug present in the body is removed. If serum concentrations of these types of drugs are followed closely during hemodialysis, the concentrations decrease by a substantial amount. But, when dialysis is completed, the blood and tissues have a chance to reequilibrate and serum concentrations increase, sometimes to their predialysis concentration. This “rebound” in serum concentration has been reported for several drugs.

Compounds with small volumes of distribution (<1 L/kg, such as the aminoglycoside antibiotics and theophylline) usually demonstrate high dialysis clearance rates. Drugs with moderate volumes of distribution (1–2 L/kg) have intermediate dialysis clearance values, while agents with large volumes of distribution (>2 L/kg, such as digoxin and tricyclic antidepressants) have poor dialysis characteristics.

HEMODIALYSIS

Hemodialysis is a very efficient procedure to remove toxic waste from the blood of renal failure patients (Figure 3-13). Blood is pumped out of the patient at the rate of 300–400 mL/min and through one side of the semipermeable membrane of the artificial kidney by the hemodialysis machine. Cleansed blood is then pumped back into the vascular system of the patient. In acute situations, vascular access can be obtained through centrally placed catheters. For patients with chronic renal failure, vascular shunts made of synthetic materials will be surgically placed between a high blood flow artery and vein in the arm or other site for the purpose of conducting hemodialysis. Dialysis fluid is pumped through the artificial kidney at a rate of 400–600 mL/min on the other side of the semipermeable membrane, in the opposite direction of blood flow. This "countercurrent" flow is more efficient in removing waste products than running the blood and dialysis fluid in parallel to each other. Dialysis fluid is electrolyte and osmotically balanced for the individual patient. It is possible to increase or decrease serum electrolytes by increasing or decreasing the concentration of the ion in the dialysis fluid compared to the concurrent serum value. Also, by adding solutes in order to increase the osmolality of the dialysis fluid relative to the blood, it is possible to remove fluid from the patient's body by osmotic pressure across the semipermeable membrane of the artificial kidney. This process is known as ultrafiltration. Using low-flux filters, hemodialysis is usually performed for 3–4 hours three times weekly.

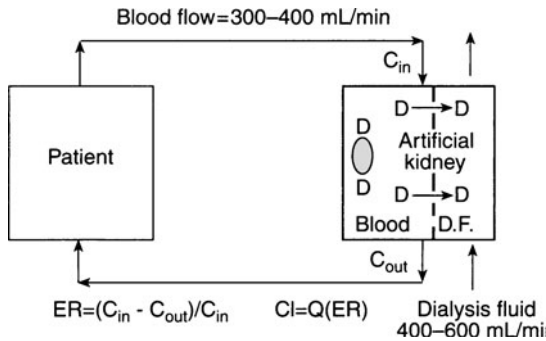

FIGURE 3-13 Hemodialysis removes blood from the patient's body (indicated by *arrows from patient to artificial kidney)* and passes it through an artificial kidney that contains a semipermeable membrane. Inside the artificial kidney, waste products pass into the dialysis fluid and are eliminated from the body. If drug molecules can pass through the pores in the semipermeable membrane, they will also be eliminated from the body. The extraction ratio of the artificial kidney can be computed using the concentration into (C_{in}) and out of (C_{out}) the device. Dialysis clearance can be calculated by taking the product of the dialysis extraction ratio and blood flow to the dialysis machine (Q). D = drug; D.F. = dialysis fluid.

The Food and Drug Administration has required pharmacokinetic studies to be done for renally eliminated drugs in patients receiving chronic hemodialysis since the mid-1980s. Because of this, the package insert for the drug may include manufacturer recommended doses to be administered to patients in the posthemodialysis period (Table 3-1). Guidelines for the administration of post-hemodialysis replacement doses are available for older drugs as well as updated guidelines for newer drugs that may not be included in the package insert.[4,6,7] Also, the primary literature should be consulted to ensure that the newest guidelines are used for all drugs. When assessing the hemodialysis removal characteristics of a drug and the need for postdialysis replacement doses, it should be recognized that the majority of information available is for low-flux artificial kidneys. If a high-flux dialysis coil is used, the primary literature is probably the best source of information, but in many cases studies have not been conducted using this technology.

Computation of Initial Doses and Modification of Doses Using Drug Serum Concentrations

Initial drug doses of patients with renal failure undergoing hemodialysis can be based on expected pharmacokinetic parameters for this population when published information for a drug is inadequate or the agent has a very narrow therapeutic index. For example, an initial dosage regimen for tobramycin needs to be computed for a patient to achieve peak concentrations of 6–7 mg/L and postdialysis concentrations 1–2 mg/L. The patient is a 62-year-old, 5-ft 8-in male who weighs 65 kg, has chronic renal failure, and receives hemodialysis three times weekly with a low-flux dialysis filter. Patients with renal failure are prone to having poor fluid balance because their kidneys are not able to provide this important function. Because of this, the patient should be assessed for overhydration (due to renal failure) or underhydration (due to renal failure and increased loss due to fever). Weight is a good indication of fluid status, and this patient's weight is less than his ideal weight [IBW_{male} = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(68 in − 60) = 68 kg]. Other indications of state of hydration (skin turgor, etc.) indicate that the patient has normal fluid balance at this time. Because of this, the average volume of distribution for aminoglycoside antibiotics equal to 0.26 L/kg can be used.

A loading dose of tobramycin would be appropriate for this patient because the expected half-life is long (~50 hours); administration of maintenance doses only might not result in therapeutic maximum concentrations for a considerable time period while drug accumulation is occurring. The loading dose is to be given after hemodialysis ends at 1300 H on Monday (hemodialysis conducted on Monday, Wednesday, and Friday from 0900–1300 H). Because the patient is expected to have a long half-life compared to the infusion time of the drug ($^1/_2$–1 hour), little drug will be eliminated during the infusion period, and IV bolus one-compartment model equations can be used. The loading dose for this patient would be based on the expected volume of distribution: V = 0.26 L/kg · 65 kg = 16.9 L; LD = C_{max} · V = 6 mg/L · 16.9 L = 101 mg, rounded to 100 mg (LD is loading dose, C_{max} is the maximum concentration after drug administration). This loading dose was given at 1400 H (Figure 3-14). Until the next dialysis period at 0900 H on Wednesday, tobramycin is cleared only by the patient's own body mechanisms. The expected elimination rate constant (k_e) for a patient with a creatinine clearance of approximately zero is: k_e (in h^{-1}) = 0.00293 · CrCl + 0.014 = 0.00293 (0 mL/min) + 0.014 = 0.014 h^{-1}. The expected concentration at 0900 H on Wednesday is: $C = C_0e^{-k_et}$,

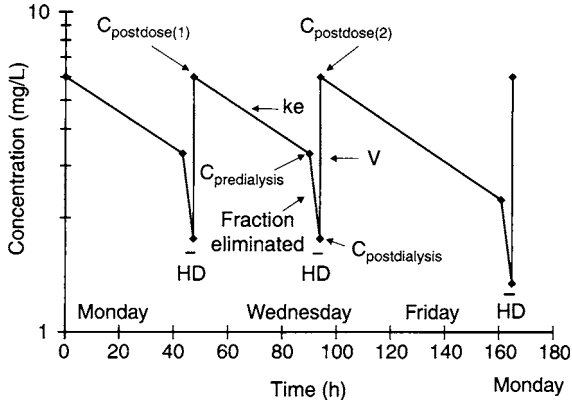

FIGURE 3-14 Concentration/time graph for tobramycin in a hemodialysis patient using estimated, population pharmacokinetic parameters. The initial dose was given postdialysis at 1400 H on Monday (time = 0 hour). Hemodialysis periods are shown by small horizontal bars labeled with HD, and days are indicated on the time line. In order to compute patient-specific pharmacokinetic parameters, four serum concentrations are measured. The elimination rate constant (k_e) is computed using two concentrations after dosage administration ($C_{postdose(1)}$ and $C_{predialysis}$), the fraction eliminated by dialysis by two concentrations ($C_{predialysis}$ and $C_{postdialysis}$) before and after dialysis, and the volume of distribution using two concentrations ($C_{postdialysis}$ and $C_{postdose(2)}$) after another dosage administration.

where C is the concentration at t hours after the initial concentration of C_0; $C = (6\ mg/L)e^{-(0.014\ h^{-1})(43\ h)} = 3.3\ mg/L$.

While the patient is receiving hemodialysis, tobramycin is eliminated by the patient's own mechanisms plus dialysis clearance. During hemodialysis with a low-flux filter, the average half-life for aminoglycosides is 4 hours. Because the patient is dialyzed for 4 hours, the tobramycin serum concentration should decrease by $^1/_2$ to a value of 1.7 mg/L, or using formal computations: $k_e = 0.693/(t_{1/2}) = 0.693/4\ h = 0.173\ h^{-1}$; $C = C_0e^{-k_et} = (3.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.7\ mg/L$. At this time, a postdialysis replacement dose could be given to increase the maximum concentration to its original value of 6 mg/L: Replacement dose = $(C_{max} - C_{baseline})V = (6\ mg/L - 1.7\ mg/L)16.9\ L = 73\ mg$, round to 75 mg (where C_{max} is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The postdialysis replacement dose of 75 mg was administered at 1400 H on Wednesday. Because all time frames and pharmacokinetic parameters are the same for Monday–Wednesday and Wednesday–Friday, the postdialysis replacement dose on Friday at 1400 H would also be 75 mg. However, more time elapses from Friday after drug administration to Monday before dialysis (67 hours), the next day for hemodialysis to be conducted in the patient, and this needs to be accounted for: $C = C_0e^{-k_et} = (6\ mg/L)e^{-(0.014\ h^{-1})(67\ h)} = 2.3\ mg/L$. Again, a 4-hour hemodialysis period would decrease serum concentrations by $^1/_2$ to a value of 1.2 mg/L: $C = C_0e^{-k_et} = (2.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.2\ mg/L$. At this time, a postdialysis replacement dose could be given to increase the maximum concentration to the original value of 6 mg/L: Replacement dose = $(C_{max} - C_{baseline})V = (6\ mg/L - 1.2\ mg/L)16.9\ L = 81\ mg$, round to 80 mg (where C_{max} is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The postdialysis replacement dose of 80 mg was administered at 1400 H on Monday. Because all time frames and

pharmacokinetic parameters subsequent weeks, the following postdialysis replacement doses would be prescribed postdialysis at 1400 H: Wednesday and Friday 75 mg, Monday 80 mg. In this particular example, recommended doses are within 5 mg of each other, and if the clinician wished, the same postdialysis dose could be given on each day. However, this will not be true in every case.

Since the initial dosage scheme outlined for this patient used average, estimated pharmacokinetic parameters, it is likely that the patient has different pharmacokinetic characteristics. It is possible to measure the patient's own unique pharmacokinetic parameters using four serum concentrations (Figure 3-14). The intradialysis elimination rate constant can be determined by obtaining postdose ($C_{postdose(1)}$) and predialysis ($C_{predialysis}$) concentrations [$k_e = (C_{postdose(1)} - C_{predialysis})/\Delta t$, where Δt is the time between the two concentrations], the fraction of drug eliminated by dialysis can be computed using predialysis and postdialysis ($C_{postdialysis}$) concentrations: Fraction eliminated = $[(C_{predialysis} - C_{postdialysis})/C_{predialysis}]$, and the volume of distribution can be calculated using postdialysis and postdose concentrations: $V = D/(C_{postdose(2)} - C_{postdialysis})$. Note that if the drug has a postdialysis "rebound" in drug concentrations, postdialysis serum samples should be obtained after blood and tissue have had the opportunity to reequilibrate. In the case of aminoglycosides, postdialysis samples should be collected no sooner than 3–4 hours after the end of dialysis. Once individualized pharmacokinetic parameters have been measured, they can be used in the same equations used to compute initial doses in the previous section in place of average population pharmacokinetic parameters, and used to calculate individualized doses for dialysis patients. It is also possible to use a mixture of measured and population-estimated pharmacokinetic parameters. For instance, a clinician may wish to measure the elimination rate constant or volume of distribution for a patient, but elect to use an average population estimate for fraction of drug removed by the artificial kidney.

Methods to Measure Hemodialysis Clearance

If needed, hemodialysis clearance can be measured in patients. The extraction ratio method measures the extraction of drug across the artificial kidney by obtaining simultaneous blood samples on input (C_{in}) and output (C_{out}) side of the dialysis coil (Figure 3-13). The tubing carrying blood to and from the patient usually has injection ports that can be used as access points to get the necessary blood samples. The artificial kidney extraction ratio (ER) can be computed using serum concentrations measured from the blood samples: $ER = (C_{in} - C_{out})/C_{in}$. Blood flow from the hemodialysis machine (HDBF) is available as a continuous readout on the pump, and hemodialysis clearance (Cl_{HD}) can be computed by taking the product of the extraction ratio and blood flow parameters: $Cl_{HD} = HDBF \cdot ER$. The advantage to this technique is that it is methodologically simple. The disadvantage is if the dialysis extraction ratio is low, serum concentration differences between C_{in} and C_{out} will be small and difficult for the drug assay to determine.

Another method is to collect the waste dialysis fluid used during the dialysis procedure, and measure several serum drug concentrations during the same time interval (Figure 3-15). The amount of drug eliminated in the dialysis fluid ($A_{Dialysis}$) is determined by multiplying the volume of dialysis fluid ($V_{Dialysis}$), and the concentration of drug in the dialysis fluid ($C_{Dialysis}$): $A_{Dialysis} = V_{Dialysis} \cdot C_{Dialysis}$. Hemodialysis clearance (Cl_{HD}) is computed by dividing the amount of drug eliminated in the dialysis fluid by the area under the serum concentration/time curve during the dialysis period ($AUC_{Dialysis}$, calculated using the serum concentrations obtained during hemodialysis): $Cl_{HD} = A_{Dialysis}/AUC_{Dialysis}$. An

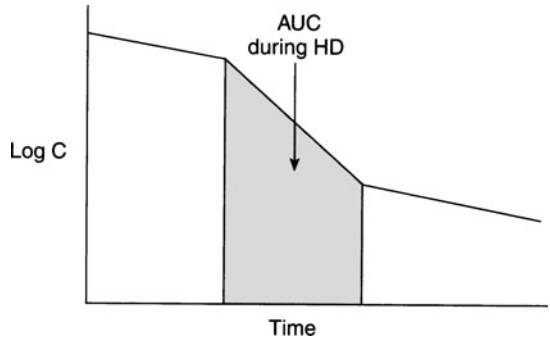

FIGURE 3-15 One method to measure hemodialysis clearance is to take the quotient of the amount of drug eliminated by the dialysis procedure ($A_{Dialysis}$) and the area under the concentration/time curve *(AUC)* during the dialysis time period *(HD,* indicated by the *shaded area).*

advantage of this method is that it is determined using multiple serum concentrations and may be more accurate. Disadvantages include collection of a large volume of dialysis fluid (~120 L) and the large number of serum concentrations needed to determine $AUC_{Dialysis}$.

The final method is to collect all the waste dialysis fluid used during the dialysis period, and measure a single serum drug concentration at the midpoint of the procedure. Using this information, hemodialysis clearance (Cl_{HD}) can be computed using the following equation: $Cl_{HD} = (C_{Dialysis} \cdot V_{Dialysis}) / (C_{Serum} \cdot T_{Dialysis})$, where $C_{Dialysis}$ is the drug concentration in the dialysis fluid, $V_{Dialysis}$ is the volume of dialysis fluid, C_{Serum} is the drug serum concentration, and $T_{Dialysis}$ is the duration of the hemodialysis procedure. An advantage of this technique is that it requires only one serum concentration. The chief disadvantage is that all dialysis fluid used during hemodialysis must be collected.

HEMOFILTRATION

Hemofiltration comprises a family of techniques that have some similarities and some differences compared to hemodialysis.[30] The hemofilter used in hemofiltration is similar to the artificial kidney used in hemodialysis. The pore size in hemofilters is large, which allows drug molecules up to 20,000 Da to cross its semipermeable membrane.

Continuous arteriovenous hemofiltration (CAVH) and continuous venovenous hemofiltration (CVVH) use an extracorporeal circuit that runs from an artery to a vein or from a vein to a vein, respectively. These processes do not use a dialysis fluid, so plasma water that passes through the hemofilter is collected and discarded. Continuous arteriovenous hemodialysis with filtration (CAVHD) and continuous venovenous hemodialysis with filtration (CVVHD) is a hybrid of conventional hemodialysis and CAVH or CVVH, respectively. The hemofilter has hemodialysis fluid on the other side of the semipermeable membrane containing the patient's blood. For CVVH and CVVHD, a mechanical pump is used to propel blood through the hemofilter. For CAVH and CAVHD, the patient's own blood pressure usually provides the propulsion of blood through the hemofilter.

The sieving coefficient is the ratio of the drug concentration in the hemofiltrate to the drug concentration in the serum. Table 3-4 lists sieving coefficients for a variety of

TABLE 3-4 Hemofiltration Sieving Coefficients for Selected Drugs[30,31]

DRUG	SIEVING COEFFICIENT
Antibiotics	
Amikacin	0.95
Amphotericin B	0.35
Amphotericin B (liposomal)	0.10
Ampicillin	0.69
Cefepime	0.72
Cefoperazone	0.27
Cefotaxime	1.06
Cefoxitin	0.83
Ceftazidime	0.90
Ceftriaxone	0.20
Cephapirin	1.48
Cilastatin	0.75
Ciprofloxacin	0.58
Clavulanic acid	1.69
Clindamycin	0.49
Doxycycline	0.40
Erythromycin	0.37
Fluconazole	1.00
Flucytosine	0.80
Ganciclovir	0.84
Gentamicin	0.81
Imipenem	0.90
Meropenem	1.00
Metronidazole	0.84
Mezlocillin	0.71
Nafcillin	0.55
Netilmicin	0.93
Oxacillin	0.02
Pefloxacin	0.80
Penicillin	0.68
Piperacillin	0.82
Streptomycin	0.30
Sulfamethoxazole	0.30
Teichoplanin	0.05
Ticarcillin	0.83
Tobramycin	0.90
Vancomycin	0.80
Other drugs	
Amrinone	0.80
Chlordiazepoxide	0.05
Cisplatin	0.10
Clofibrate	0.06
Cyclosporine	0.58
Diazepam	0.02
Digoxin	0.70
Digitoxin	0.15
Famotidine	0.73
Glyburide	0.60
Glutethimide	0.02

(*Continued*)

TABLE 3-4 (*Continued*)

DRUG	SIEVING COEFFICIENT
Lidocaine	0.14
Lithium	0.90
Metamizole	0.40
N-acetylprocainamide	0.92
Nizatidine	0.59
Nitrazepam	0.08
Nomifensin	0.70
Oxazepam	0.10
Phenobarbital	0.80
Phenytoin	0.45
Procainamide	0.86
Ranitidine	0.78
Tacrolimus	0.26
Theophylline	0.80

drugs.[31,32] The ultrafiltration rate (UFR) is the filtration provided by the specific hemofiltration technique. Typical ranges for UFR are 10–16 mL/min for procedures that do not use extracorporeal blood pumps, and 20–30 mL/min for procedures that use extracorporeal blood pumps. When hemofiltration procedures that incorporate dialysis fluid are used, an additional 15–20 mL/min is added to these values.[31,32]

Several different methods of calculating additional doses during hemofiltration have been suggested:[31,32]

1. Based on the expected ultrafiltration rates noted above, hemofiltration is usually equivalent to a glomerular filtration rate (GFR) of 10–50 mL/min. In lieu of specific recommendations for a drug, clinicians can use this GFR rate with FDA or renal drug dosing guidelines to suggest an adjusted dose.[4,6,7]

2. A supplemental dose (SD) can be estimated using a measured or estimated steady-state drug concentration (Css), unbound fraction in the serum (f_B), ultrafiltration rate (UFR), and drug dosing interval (τ): $SD = Css \cdot f_B \cdot UFR \cdot \tau$. Supplemental doses are given in addition to maintenance doses of the drug.

3. A booster dose (BD) can be computed using an actual measured concentration (C_{actual}), a desired concentration ($C_{desired}$), and an estimated or actual volume of distribution (V): $BD = (C_{desired} - C_{actual})V$. Booster doses are given in addition to maintenance doses of the drug.

PERITONEAL DIALYSIS

Peritoneal dialysis involves the surgical insertion of a catheter in the lower abdomen into the peritoneal cavity (Figure 3-16). The peritoneal membrane covering the internal organs is highly vascularized, so when dialysis fluid (1–3 L) is introduced into the peritoneal cavity using the catheter, waste products move from the blood vessels of the peritoneal membrane (a semipermeable membrane) into the dialysis fluid along a concentration gradient. The dialysis fluid is periodically removed from the peritoneal cavity and discarded.

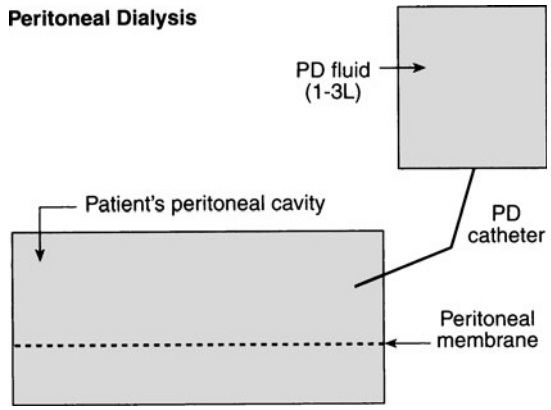

FIGURE 3-16 Schematic of peritoneal dialysis procedure. A catheter (labeled *PD Catheter)* is surgically inserted into the patient's peritoneal cavity and used to introduce 1–3 L of dialysis fluid (labeled *PD Fluid).* The dialysis fluid comes into contact with capillaries in the peritoneal membrane where waste products and drugs pass from the blood into the fluid. After the dwell time has concluded, the dialysis fluid is removed from the peritoneal cavity via the catheter and discarded.

Outpatients undergoing chronic ambulatory peritoneal dialysis have dialysis fluid present in their peritoneal cavities all day or most hours of a day.

Compared to hemodialysis, peritoneal dialysis removes drug much less efficiently. So, it is less likely that replacement drug doses will need to be given during intermittent peritoneal dialysis, and that drug dosages will need to be increased while patients receive chronic peritoneal dialysis. For instance, in patients with end-stage renal disease, the half-life of aminoglycoside antibiotics is ~50 hours. During hemodialysis, the half-life reduces to ~4 hours, but, during peritoneal dialysis in patients without peritonitis, the half-life only decreases to ~36 hours. In patients receiving chronic peritoneal dialysis, dialysis removal of drug is simply another clearance mechanism taking place in the patient body, so the usual methods of measuring serum concentrations and dosage adjustment require little or no modification. For patients undergoing peritoneal dialysis, clinicians should consult the manufacturer's package insert for drugs recently marketed (mid-1980s or later), reviews listing the peritoneal dialysis removal of older drugs and updated information on newer agents,[4,6,7] and the primary literature for the newest guidelines for all compounds.

Drugs can also be added to peritoneal dialysis fluid. If the agent is absorbed from the dialysis fluid into the body, systemic effects due to the drug may occur. Epoetin and insulin have been administered in this fashion to patients receiving peritoneal dialysis. Because the development of peritonitis is a common problem in patients receiving peritoneal dialysis, antibiotics have been administered intraperitoneally for local treatment of the infection using dialysis fluid as the delivery vehicle.[33] In most cases, antibiotics are absorbed into the body when given this way, but therapeutic serum concentrations may not be achieved for all agents making systemically administered doses necessary. Clinicians should pay particular attention to whether studies measuring peritoneal dialysis removal or absorption of drugs were conducted in patients with peritonitis. Peritonitis involves inflammation of the peritoneal membrane and increases its permeability.

Increased permeability allows for greater flux of drug across the membrane which allows more drug removal during dialysis or more drug absorption if the drug is added to the peritoneal dialysis fluid.

Methods to Measure Peritoneal Dialysis Clearance

If necessary, peritoneal dialysis clearance can be measured in patients. One method is to collect the waste dialysis fluid used during a peritoneal dialysis period, and measure several serum drug concentrations during the same time interval (Figure 3-15). The amount of drug eliminated in the dialysis fluid ($A_{Dialysis}$) is calculated by multiplying the volume of dialysis fluid ($V_{Dialysis}$), and the concentration of drug in the dialysis fluid ($C_{Dialysis}$): $A_{Dialysis} = V_{Dialysis} \cdot C_{Dialysis}$. Peritoneal clearance ($Cl_{PD}$) is computed by dividing the amount of drug eliminated in the dialysis fluid by the area under the serum concentration/time curve during the dialysis period ($AUC_{Dialysis}$, calculated using the serum concentrations obtained during peritoneal dialysis): $Cl_{PD} = A_{Dialysis} / AUC_{Dialysis}$. An advantage of this method is that the dialysate volume is relatively small. Disadvantages are the large number of serum concentrations needed to determine $AUC_{Dialysis}$, and if only a small amount of drug is removed via dialysis, the drug assay may not be sensitive enough to measure a small concentration.

Another method is to collect all the waste dialysis fluid used during a dialysis period, and measure a single serum drug concentration at the midpoint of the procedure. Using this information, peritoneal clearance (Cl_{PD}) can be computed using the following equation: $Cl_{PD} = (C_{Dialysis} \cdot V_{Dialysis}) / (C_{Serum} \cdot T_{Dialysis})$, where $C_{Dialysis}$ is the drug concentration in the dialysis fluid, $V_{Dialysis}$ is the volume of dialysis fluid, C_{Serum} is the drug serum concentration, and $T_{Dialysis}$ is the duration that dialysis fluid remained in the peritoneal cavity. Advantages of this technique are that it requires only one serum concentration and the volume of dialysis fluid is relatively small. A disadvantage is if only a small amount of drug is removed via dialysis, the drug assay may not be sensitive enough to measure a low concentration.

OBESITY

The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution. The general physiologic equation for volume of distribution can be broken down into separate parameters for individual tissue types:

$$V = V_B + \frac{f_B}{f_T} V_T = V_B + \frac{f_B}{f_{heart}} V_{heart} + \frac{f_B}{f_{muscle}} V_{muscle} + \frac{f_B}{f_{fat}} V_{fat} + \cdots + \frac{f_B}{f_n} V_n$$

Because of this, the sheer amount of adipose tissue will be a primary determinant of how much obesity will effect the volume of distribution of the drug. Also, the magnitude of effect that adipose tissue has on the volume of distribution for a drug is dependent on the binding of drug in the tissue itself. If the drug has a large affinity for adipose tissue and is highly bound there, the free fraction in adipose tissue will be small ($\downarrow f_{fat}$), and a large amount of drug will accumulate in that tissue. Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients. Examples of

lipophilic drugs with larger volume of distribution values in obese individuals are diazepam[34], carbamazepine[35], and trazodone[36]. However, hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients. The volumes of distribution for digoxin,[37] cimetidine,[38] and ranitidine[39] are similar in overweight- and normal-weight subjects.

Although the presence of excessive adipose tissue is the most obvious change that occurs in obese individuals, other physiologic changes are present. While adipose cells contain >90% fat, there are additional supportive tissues, extracellular fluid, and blood present in adipose tissue. Also, some lean tissues hypertrophy in obese individuals. The net result of these changes is that hydrophilic drugs with small volumes of distribution may experience distribution alterations in obese patients. For example, the aminoglycoside antibiotics are water-soluble molecules that have relatively small volumes of distribution similar to the value of extracellular fluid (V = 0.26 L/kg). Since the volume of distribution is so small (~18 L in a 70-kg person), the addition of just a few liters of extracellular fluid can alter the pharmacokinetics of these antibiotics. The additional extracellular fluid contained in excessive adipose tissue and other organs that hypertrophy in obese individuals causes larger volumes of distribution for the aminoglycoside antibiotics in overweight patients. Formulas that correct aminoglycoside volume of distribution for obese individuals are available.[40–43] However, if the volume of distribution for a hydrophilic drug is intermediate or large, the additional extracellular fluid contained in adipose tissue and other sources in obese individuals may not significantly alter the distribution of the agent. Examples of medications with larger and intermediate volumes of distribution are digoxin (V = 500 L) and vancomycin (V = 50 L); the addition of a few extra liters of extracellular fluid due to obesity will not substantially change the volume of distribution for these agents.[37,44]

Another change that is found in obese individuals is increased glomerular filtration rates. This alteration primarily affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent. Vancomycin,[44] the aminoglycosides,[40–42] and cimetidine[38] all have higher clearance rates in obese patients compared to normal weight individuals. Special methods are used to estimate creatinine clearance for obese patients, as previously noted in the Measurement and Estimation of Creatinine Clearance section of this chapter.[15–17]

Obesity has variable effects on the metabolism of drugs. For many agents, such as carbamazepine[35] and cyclosporine,[45] obesity does not significantly effect hepatic clearance. While for other drugs, obesity increases hepatic clearance, as with diazepam,[34] or decreases metabolic clearance, as with methylprednisolone.[46] Clinicians should be aware of this variability and dose hepatically metabolized drugs cautiously in obese individuals in the absence of specific recommendations.

Half-life changes vary according to the relative alterations in clearance (Cl) and volume of distribution (V): $t_{1/2} = (0.693 \cdot V)/Cl$, where $t_{1/2}$ is half-life. In the case of the aminoglycoside antibiotics, clearance and volume of distribution increases are about the same magnitude in obese patients, so half-life does not change.[40–42] If the volume of distribution increases with obesity, but clearance is unaffected, half-life can increase dramatically as with carbamazepine.[35] Finally, if clearance changes and volume of distribution remains constant, obesity may also cause a change in the half-life of a drug as is the case for methylprednisolone.[46]

DRUG INTERACTIONS

Pharmacokinetic drug interactions occur between drugs when one agent changes the clearance or volume of distribution of another medication. There are several drug interaction mechanisms that result in altered drug clearance. A drug can inhibit or induce the enzymes responsible for the metabolism of other drugs. Enzyme inhibition decreases intrinsic clearance, and enzyme induction increases intrinsic clearance. If two drugs are eliminated by the same enzyme, they may compete for the metabolic pathway and decrease the clearance of one or both compounds. Two drugs eliminated by the same active renal tubular secretion mechanism can compete for the pathway and decrease the renal clearance of one or both agents. Another type of drug interaction displaces a drug from plasma protein binding sites because the two compounds share the same binding site, and the two compete for the same area on plasma proteins. By virtue of its pharmacologic effect, a drug may increase or decrease blood flow to an organ that eliminates or metabolizes another medication and thereby decrease the clearance of the medication.

Changes in plasma protein binding also cause alterations in volume of distribution. If two drugs share the same tissue binding sites, it is possible for tissue-binding displacement drug interactions to occur and change the volume of distribution for one of the medications. Half-life may change as a result of drug interactions, or, if clearance and volume of distribution alterations are about equal, half-life may remain constant even though a major drug interaction has occurred.

The same graphical scheme introduced in the hepatic disease section of this chapter can be used to understand the clinical impact of drug interactions (Figures 3-6–3-10). To use these charts it is necessary to know if the drug under discussion has a low extraction ratio or high extraction ratio. The hepatic clearance of drugs with low hepatic extraction ratios equals the product of free fraction in the blood and intrinsic clearance ($Cl_H = f_B Cl'_{int}$), while the hepatic clearance of drugs with high hepatic extraction ratios equals liver blood flow ($Cl_H = LBF$). Whether a drug has a high or low extraction ratio, the volume of distribution ($V = V_B + [f_B/f_T]V_T$) and half-life ($t_{1/2} = [0.693 \cdot V]/Cl$) relationships are the same. The unbound steady-state concentration of drug in the blood equals the product of the total steady-state concentration and the unbound fraction of drug in the blood: $Css_u = f_B Css$. The effect of the drug increases when the unbound steady-state concentration increases and decreases when Css_u declines.

Plasma Protein Binding Displacement Drug Interactions

For a drug with a low hepatic extraction ratio, plasma protein binding displacement drug interactions cause major pharmacokinetic alterations but are not clinically significant because the pharmacologic effect of the drug does not change (Figure 3-7). Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent, addition of a plasma protein binding displacing compound will increase clearance ($\uparrow Cl = \uparrow f_B Cl'_{int}$) and volume of distribution [$\uparrow V = V_B + (\uparrow f_B/f_T)V_T$]. Since half-life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change ($t_{1/2} = [0.693 \cdot \uparrow V]/\uparrow Cl$). However, it is possible that if either clearance or volume of distribution changes disproportionately, half-life will change. The total steady-state concentration will decline because of the increase in clearance ($\downarrow Css = k_0/\uparrow Cl$, where k_0 is the infusion

rate of drug). But, the unbound steady-state concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the drug interaction occurred ($Css_u = \uparrow f_B \downarrow Css$). The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged. An example of this drug interaction is the addition of diflunisal to patients stabilized on warfarin therapy.[47] Diflunisal displaces warfarin from plasma protein binding sites, but does not augment the anticoagulant effect of warfarin. If drug concentrations are available for the medication, it can be difficult to convince clinicians that a drug dosage increase is not needed even though total concentrations decline as a result of this interaction. When available, unbound drug concentrations can be used to document that no change in drug dosing is needed.

For drugs with high hepatic extraction ratios given intravenously, plasma protein binding displacement drug interactions cause both major pharmacokinetic and pharmacodynamic changes (Figure 3-9). Because the clearance of the drug is dependent solely on liver blood flow for an agent of this type, total clearance does not change. However, both volume of distribution [$\uparrow V = V_B + (\uparrow f_B/f_T)V_T$] and half-life [$\uparrow t_{1/2} = (0.693 \cdot \uparrow V)/Cl$] will increase because of plasma protein binding displacement of the drug. Since total clearance did not change, the total steady-state concentration remains unaltered. However, the free concentration ($\uparrow Css_u = \uparrow f_B Css$) and pharmacologic effect ($\uparrow effect \propto \uparrow Css_u$) of the drug will both increase. Currently, there are no clinically significant drug interactions of this type. But, clinicians should be on the outlook for this profile for highly protein-bound drugs with high hepatic extraction ratios given intravenously because the interaction is very subtle. Most noteworthy is the fact that although total concentrations remain unchanged, the pharmacologic effect of the drug is augmented. If available, unbound drug concentration could be used to document the drug interaction.

If a drug with a high hepatic extraction ratio is given orally, a plasma protein binding displacement drug interaction will cause a simultaneous increase in the unbound fraction of drug in the blood ($\uparrow f_B$) and the hepatic presystemic metabolism of the drug. Hepatic presystemic metabolism increases because the higher unbound fraction of drug in the blood allows more drug molecules to enter the liver where they are ultimately metabolized. The increase in hepatic presystemic metabolism leads to an increased first-pass effect and decreased drug bioavailability ($\downarrow F$). Total steady-state drug concentrations will be lower because of decreased drug bioavailability [$\downarrow Css = (\downarrow F[D/\tau])/Cl$]. However, the unbound steady-state drug concentration and pharmacologic effect remain unchanged due to this type of drug interaction because the increase in unbound fraction is offset by the decrease in the total steady-state concentration ($\sim Css_u = \uparrow f_B \downarrow Css$). Route of administration plays an important role in how important plasma protein binding displacement drug interactions are for agents with high hepatic extraction ratios.

Inhibition Drug Interactions

Inhibition of hepatic drug metabolism is probably the most common drug interaction encountered in patients. For drugs with low hepatic extraction ratios, this type of drug interaction produces clinically significant changes in drug pharmacokinetics and effect (Figure 3-6). The addition of a hepatic enzyme inhibitor will decrease intrinsic clearance and total clearance for the drug ($\downarrow Cl = f_B \downarrow Cl'_{int}$). Since volume of distribution remains unaltered, the half-life of the drug will increase ($\uparrow t_{1/2} = [0.693 \cdot V]/\downarrow Cl$). As a result of the total clearance decrease, total steady-state drug concentrations will increase ($\uparrow Css = k_0/\downarrow Cl$). The rise in unbound steady-state drug concentration will mirror that seen with total drug

concentration, and the effect of the drug will increase in proportion to unbound concentration. An example of this drug interaction is the addition of ciprofloxacin to a patient stabilized on theophylline therapy.[48]

For drugs with high hepatic extraction ratios, this category of drug interaction produces variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inhibitor is added, the decrease in intrinsic clearance is usually not substantial enough to cause major pharmacokinetic and pharmacodynamic effects because clearance is a function of liver blood flow (Figure 3-8). However, if the drug is given orally and an enzyme inhibitor is added to therapy, presystemic metabolism of the medication may be greatly depressed, and the first-pass effect can decrease dramatically leading to improved drug bioavailability. This effective increase in administered oral dose will increase the total and unbound steady-state drug concentrations and lead to an increase in the pharmacologic effect of the drug.

Induction Drug Interactions

Drugs with low hepatic extraction ratios exhibit clinically significant drug interactions that alter drug pharmacokinetics and pharmacologic response when hepatic enzyme inducers are coadministered (Figure 3-17). Enzyme inducers increase intrinsic clearance

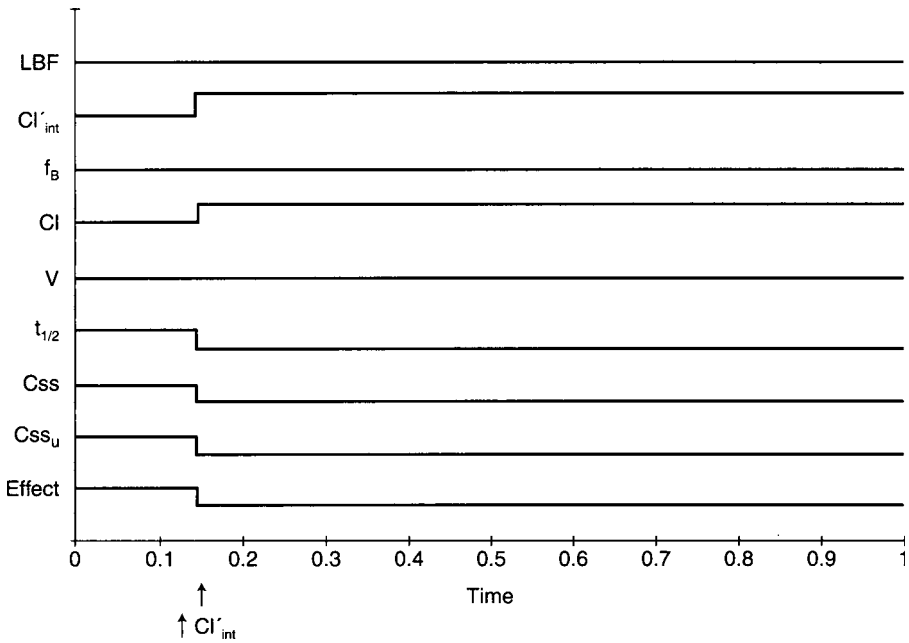

FIGURE 3-17 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

of the drug and thereby increase the total clearance of the medication ($\uparrow Cl = f_B \uparrow Cl'_{int}$). The increase in total clearance will cause a shorter half-life since volume of distribution remains unchanged ($\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$). Increased total clearance will also cause decreased total steady-state concentration ($\downarrow Css = k_0 / \uparrow Cl$), unbound steady-state concentration ($\downarrow Css_u = f_B \downarrow Css$), and pharmacologic effect ($\downarrow effect \propto \downarrow Css_u$). Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of drug interaction with many other medications such as warfarin.[49]

For drugs with high hepatic extraction ratios, this type of drug interaction results in variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inducer is added, the increase in intrinsic clearance is usually not large enough to cause major pharmacokinetic and pharmacologic effect alterations because total clearance is a function of liver blood flow (Figure 3-18). However, if the drug is given orally and an enzyme inducer is added to the treatment regimen, presystemic metabolism of the medication may be increased, and the first-pass effect augmented leading to decreased drug bioavailability. This effective decrease in administered oral dose will decrease the total and unbound steady-state drug concentrations and lead to a decrease in the pharmacologic effect of the agent.

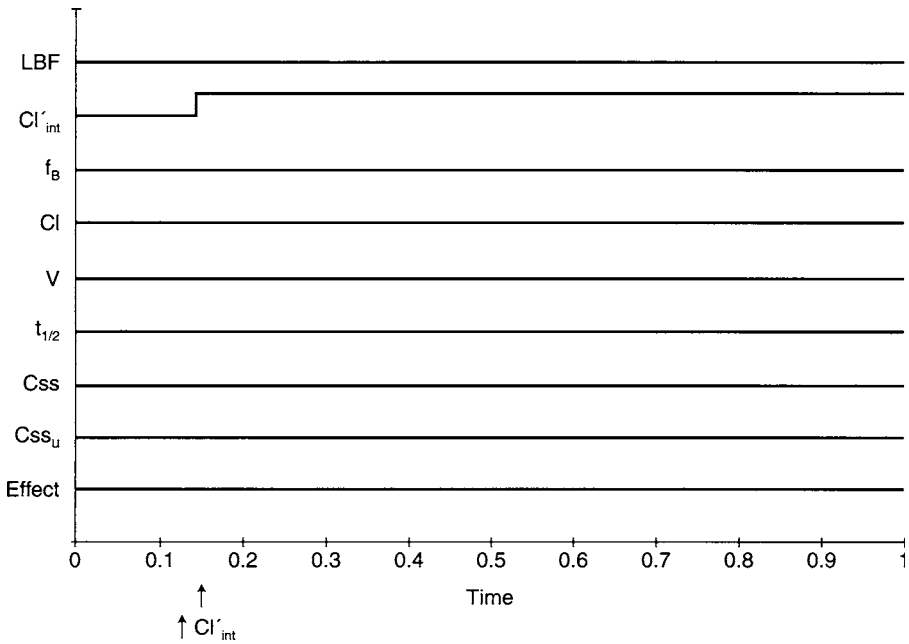

FIGURE 3-18 Changes in physiologic parameters (*LBF* = liver blood flow, Cl'_{int} = intrinsic clearance, f_B = free fraction of drug in the blood), pharmacokinetic parameters (*Cl* = clearance, *V* = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (*Css* = total steady-state concentration; Css_u = unbound steady-state concentration; *effect* = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance increases (indicated by *arrow*). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

Alteration in Organ Blood Flow

By virtue of the pharmacologic effect for a drug, it may be possible for an agent to change liver blood flow. For instance, β-blockers can decrease heart rate and cardiac output which decreases liver blood flow. Since liver blood flow is the predominate factor that determines clearance for high hepatic extraction ratio drugs, this type of interaction is only important for this category of medication. β-blockers decrease lidocaine clearance by decreasing liver blood flow.[50]

If a drug with a high hepatic extraction ratio is administered to a patient, and another agent that decreases liver blood flow is then added to the patient's therapy, total clearance will decrease (Figure 3-10). Since volume of distribution remains unaltered, the half-life of the drug will increase ($\uparrow t_{1/2} = [0.693 \cdot V] / \downarrow Cl$). As a result of the total clearance decrease, total steady-state drug concentrations will increase ($\uparrow Css = k_0 / \downarrow Cl$). The rise in unbound steady-state drug concentration will mirror that seen with total drug concentration, and the effect of the drug will increase in proportion to unbound concentration. If the coadministered drug increases liver blood flow, as can be the case with vasodilators like the calcium channel blockers,[51,52] all of the aforementioned changes will occur in the opposite direction ($\uparrow Cl = \uparrow LBF$; $\downarrow t_{1/2} = [0.693 \cdot V] / \uparrow Cl$; $\downarrow Css = k_0 / \uparrow Cl$; $\downarrow Css_u = f_B \downarrow Css$), and the decline in unbound steady-state concentration will cause a decrease in pharmacologic effect of the drug.

PROBLEMS

1. A creatinine clearance is measured in a 75-year-old Caucasian male patient with multiple myeloma to monitor changes in renal function. The serum creatinine, measured at the midpoint of the 24 hour urine collection, was 2.1 mg/dL. Urine creatinine concentration was 50 mg/dL, and urine volume was 1400 mL. (A). Calculate this patient's creatinine clearance. (B). Estimate the patient's glomerular filtration rate using the modified MDRD equation.

2. A 52-year-old, 65-kg, 5-ft 3-in tall female patient with a methicillin-resistant *Staphylococcus aureus* (MRSA) infection needs to have an initial vancomycin dose computed. In order to do this, an estimated creatinine clearance needs to be calculated. The patient has a serum creatinine value equal to 1.8 mg/dL. Calculate this patient's estimated creatinine clearance and estimated vancomycin clearance [assume vancomycin clearance is Cl (in mL/min/kg) = 0.695 (CrCl in mL/min/kg) + 0.05].

3. A 70-year-old, 80-kg, 5-ft 11-in tall male with a *Pseudomonas aeruginosa* infection needs to have an initial tobramycin dose computed. In order to do this, an estimated creatinine clearance must be calculated. The patient's current serum creatinine equals 2.5 mg/dL and is stable. Compute this patient's estimated creatinine clearance and estimated tobramycin elimination rate constant and half-life [assume tobramycin elimination rate constant is k_e (in h^{-1}) = 0.00293 (CrCl in mL/min) + 0.014].

4. A 51-year-old, 54-kg, 5-ft 4-in female with worsening renal function needs to have her renal function assessed for drug dosage adjustment. Yesterday, at 0800 H, her serum creatinine was 1.3 mg/dL. Today at 0800 H, her serum creatinine was 2.1 mg/dL. Compute her estimated creatinine clearance.

5. A 66-year-old, 120-kg, 5-ft 2-in tall female has a serum creatinine equal to 3.1 mg/dL. Compute an estimated creatinine clearance for this patient.

6. A 59-year-old, 140-kg, 5-ft 8-in tall male with severe heart failure has a serum creatinine equal to 2.4 mg/dL. Compute an estimated creatinine clearance, digoxin clearance, and digoxin volume of distribution for this patient. Assume estimated digoxin clearance in severe heart failure: Cl (in mL/min) = 1.303 (CrCl in mL/min) + 20; estimated digoxin volume of distribution: V (in L) = 226 + [(298 · CrCl)/(29.1 + CrCl)].

7. A 62-year-old, 65-kg male with hepatic cirrhosis (total bilirubin = 2.6 mg/dL, serum albumin = 2.5 mg/dL, prothrombin time prolonged over normal by 8 seconds, slight amount of ascitic fluid, no hepatic encephalopathy) and severe chronic obstructive pulmonary disease needs to have an initial theophylline dose computed. The patient is not a tobacco smoker and does not have heart failure. Compute the patient's Child-Pugh score, estimated theophylline clearance, and theophylline dose to achieve a steady-state concentration equal to 10 mg/L.

8. A 32-year-old, 70-kg, 5-ft 8-in tall, female with chronic renal failure receiving hemodialysis developed atrial fibrillation. She is to receive a new antiarrhythmic, Defibfast, for the treatment of atrial fibrillation. In patients with chronic renal failure, the following average pharmacokinetic parameters were measured in six subjects: V = 0.5 L/kg, $t_{1/2}$ = 36 hours. When these subjects received hemodialysis, the hemodialysis extraction ratio was 33%. The patient just completed a hemodialysis run (Monday, 0800–1200 H). Compute a post-hemodialysis loading dose to achieve a peak concentration of 50 mg/L. The next dialysis period is Wednesday at the same time. Calculate a posthemodialysis dose that will raise the patient's concentration to 50 mg/L.

9. A 47-year-old, 75-kg, 5-ft 9-in tall, male hemodialysis patient with chronic renal failure has a serious gram-negative infection being treated with a new antibiotic, Bactocidal. The following concentrations were obtained: Monday, 1200 H (post-hemodialysis) = 15 mg/L, Monday, 1205 H (post-IV bolus 1000 mg dose) = 65 mg/L, Wednesday, 0800 H (pre-hemodialysis) = 32 mg/L, Wednesday, 1200 H (post-hemodialysis for 4 hours) = 8 mg/L. Compute volume of distribution, elimination rate constant, and half-life for the interdialysis period, and the hemodialysis extraction ratio. What post-hemodialysis dose on Wednesday would achieve a postdose concentration of 100 mg/L? What would be the pre- and posthemodialysis concentrations on Friday (hemodialysis from 0800–1200 H) if that dose was given?

10. A patient receiving hemodialysis has the following concentrations obtained during a hemodialysis run: concentration into artificial kidney = 75 mg/L, concentration leaving artificial kidney = 25 mg/L. Blood flow through the artificial kidney is 400 mL/min. Compute the hemodialysis extraction ratio and clearance.

11. A patient receiving peritoneal dialysis has the following drug concentrations obtained: concentration in the dialysis fluid = 35 mg/L, concentration in serum at midpoint of peritoneal dialysis = 50 mg/L. The volume of dialysis fluid is 2 L, and the dwell time in the peritoneal cavity is 6 hours. Compute peritoneal dialysis for the drug.

12. A patient is receiving phenytoin (a low hepatic extraction ratio drug) for the treatment of tonic-clonic seizures. Because of continued seizure activity, valproic acid is added to the patient's drug regimen. Valproic acid inhibits the clearance of phenytoin and displaces phenytoin from plasma protein binding sites. Assuming that these changes occur instantaneously with the institution of valproic acid therapy, diagram how the following parameters will change for phenytoin: liver blood flow, intrinsic clearance, free fraction of drug in the blood, clearance, volume of distribution, half-life, total steady-state concentration, unbound steady-state concentration, and drug effect.

ANSWERS TO PROBLEMS

1. (A). $CrCl = (U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T) = (50 \text{ mg/dL} \cdot 1400 \text{ mL}) / (2.1 \text{ mg/dL} \cdot 1440 \text{ min}) = 23 \text{ mL/min}$

(B). This patient is a Caucasian male, so none of the modifying factors are needed.

$$GFR = 186 \cdot S_{Cr}^{-1.154} \cdot Age^{-0.203} = 186 \cdot (2.1 \text{ mg/dL})^{-1.154} \cdot (75 \text{ y})^{-0.203} = 33 \text{ mL/min/1.73 m}^2$$

2. Check IBW for patient to see if she is obese:

$IBW = 45 \text{ kg} + (Ht - 60) = 45 \text{ kg} + 2.3(63 - 60) = 52 \text{ kg}$; patient is within 30% of IBW (52 ± 16 kg)

Calculate estimated creatinine clearance:

$$CrCl_{est} = [0.85(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [0.85(140 - 52 \text{ y})65 \text{ kg}] / (72 \cdot 1.8 \text{ mg/dL}) = 37 \text{ mL/min}$$

$$CrCl_{est} = (37 \text{ mL/min}) / 65 \text{ kg} = 0.569 \text{ mL/min/kg}$$

Calculate estimated vancomycin clearance:

$$Cl \text{ (in mL/min/kg)} = 0.695 \text{ (CrCl in mL/min/kg)} + 0.05 = 0.695(0.569 \text{ mL/min/kg}) + 0.05 = 0.446 \text{ mL/min/kg}$$

$$Cl = 0.446 \text{ mL/min/kg}(65 \text{ kg}) = 29 \text{ mL/min}$$

3. Check IBW for patient to see if he is obese:

$IBW = 50 \text{ kg} + (Ht - 60) = 50 \text{ kg} + 2.3(71 - 60) = 75 \text{ kg}$; patient is within 30% of IBW (75 ± 23 kg)

Calculate estimated creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 70 \text{ y})80 \text{ kg}] / (72 \cdot 2.5 \text{ mg/dL}) = 31 \text{ mL/min}$$

Calculate estimated tobramycin elimination rate constant and half-life:

$$k_e(\text{in h}^{-1}) = 0.00293(\text{CrCl in mL/min}) + 0.014 = 0.00293(31 \text{ mL/min}) + 0.014 = 0.105 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.105 \text{ h}^{-1} = 6.6 \text{ h}$$

4. The Jelliffe method is used to estimate creatinine clearance in patients with changing renal function:

Ideal body weight (IBW): IBW = 45 kg + (Ht − 60) = 45 kg + 2.3(64 − 60) = 54 kg

$$\text{Ess}_{\text{female}} = \text{IBW}[25.1 - (0.175 \cdot \text{Age})] = 54\ \text{kg}[25.1 - (0.175 \cdot 51\ \text{y})] = 873.5$$

Average serum creatinine is computed: $\text{Scr}_{\text{ave}} = (1.3\ \text{mg/dL} + 2.1\ \text{mg/dL})/2 = 1.7\ \text{mg/dL}$

$\text{Ess}_{\text{corrected}} = \text{Ess}[1.035 - (0.0337 \cdot \text{Scr}_{\text{ave}})] = 873.5[1.035 - (0.0337 \cdot 1.7\ \text{mg/dL})] = 854.0$

$$\text{E} = \text{Ess}_{\text{corrected}} - \frac{[4\text{IBW}(\text{Scr}_2 - \text{Scr}_1)]}{\Delta t} = 854 - \frac{[4 \cdot 54\ \text{kg}(2.1\ \text{mg/dL} - 1.3\ \text{mg/dL})]}{24\ \text{h} \cdot 60\ \text{min/h}} = 853.9$$

$$\text{CrCl} = \text{E}/(14.4 \cdot \text{Scr}_{\text{ave}}) = 853.9/(14.4 \cdot 1.7\ \text{mg/dL}) = 35\ \text{mL/min}/1.73\ \text{m}^2$$

5. This patient is obese, so the Salazar-Corcoran method is used:

Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in)/(100 cm/m) = 1.57 m

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - \text{age})[(0.287 \cdot \text{Wt}) + (9.74 \cdot \text{Ht}^2)]}{(60 \cdot \text{S}_{\text{Cr}})}$$

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - 66\ \text{y})[(0.287 \cdot 120\ \text{kg}) + (9.74 \cdot \{1.57\ \text{m}\}^2)]}{(60 \cdot 3.1\ \text{mg/dL})} = 25\ \text{mL/min}$$

6. This patient is obese, so the Salazar-Corcoran method is used to estimate creatinine clearance:

Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in)/(100 cm/m) = 1.73 m

$$\text{CrCl}_{\text{est(males)}} = \frac{(137 - \text{age})[(0.285 \cdot \text{Wt}) + (12.1 \cdot \text{Ht}^2)]}{(51 \cdot \text{S}_{\text{Cr}})}$$

$$\text{CrCl}_{\text{est(males)}} = \frac{(137 - 59\ \text{y})[(0.285 \cdot 140\ \text{kg}) + (12.1 \cdot \{1.73\ \text{m}\}^2)]}{(51 \cdot 2.4\ \text{mg/dL})} = 49\ \text{mL/min}$$

Calculate estimated digoxin pharmacokinetic parameters:

Cl (in mL/min) = 1.303(CrCl in mL/min) + 20 = 1.303(49 mL/min) + 20 = 84 mL/min

V (in L) = 226 + [(298 · CrCl)/(29.1 + CrCl)] = 226 + [(298 · 49 mL/min)/(29.1 + 49 mL/min)] = 413 L

7. Child-Pugh score (from Table 3-2): total bilirubin = 2 points, albumin = 3 points, prothrombin time = 3 points, ascites = 2 points, encephalopathy = 1 point. Total = 11 points, severe hepatic dysfunction.

Theophylline clearance (from Table 3-3): Cl = 0.35 mL/min/kg (65 kg) = 22.8 mL/min
Cl = (22.8 mL/min · 60 min/h)/(1000 mL/L) = 1.37 L/h

Theophylline dose: MD = Css · Cl = (10 mg/L)(1.37 L/h) = 14 mg/h of theophylline

8. Calculate pharmacokinetic parameters:

$$V = 0.5 \text{ L/kg } (70 \text{ kg}) = 35 \text{ L}$$

$$k_e = 0.693/t_{1/2} = 0.693/36 \text{ h} = 0.0193 \text{ h}^{-1}$$

Calculate loading dose: $LD = C \cdot V = (50 \text{ mg/L})(35 \text{ L}) = 1750 \text{ mg}$

Calculate predialysis concentration: $C = C_0 e^{-k_e t} = (50 \text{ mg/L}) e^{-(0.0193 \text{h}^{-1})(44 \text{ h})} = 21 \text{ mg/L}$

Calculate posthemodialysis concentration: $C_{postdialysis} = C_{predialysis}(1 - ER_{HD}) = (21 \text{ mg/L}) \cdot (1 - 0.33) = 14 \text{ mg/L}$

Calculate postdialysis dose: $D = V(C_{postdose} - C_{predose}) = (35 \text{ L})(50 \text{ mg/L} - 14 \text{ mg/L}) = 1260 \text{ mg}$

9. Compute pharmacokinetic parameters:

$$V = D/(C_{postdose} - C_{predose}) = 1000 \text{ mg} / (65 \text{ mg/L} - 15 \text{ mg/L}) = 20 \text{ L}$$

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 65 \text{ mg/L} - \ln 32 \text{ mg/L}) / 44 \text{ h} = 0.0161 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.0161 \text{ h}^{-1} = 43 \text{ h}$$

Calculate hemodialysis extraction ratio: $ER_{HD} = (C_{predialysis} - C_{postdialysis}) / C_{predialysis} = (32 \text{ mg/L} - 8 \text{ mg/L}) / 32 \text{ mg/L} = 0.75 \text{ or } 75\%$

Compute postdialysis dose for Wednesday: $D = V (C_{postdose} - C_{predose}) = (20 \text{ L}) \cdot (100 \text{ mg/L} - 8 \text{ mg/L}) = 1840 \text{ mg}$

Calculate predialysis concentration for Friday: $C = C_0 e^{-k_e t} = (100 \text{ mg/L}) e^{-(0.0161 \text{h}^{-1})(44 \text{ h})} = 49 \text{ mg/L}$

Calculate postdialysis concentration for Friday: $C_{postdialysis} = C_{predialysis}(1 - ER_{HD}) = (49 \text{ mg/L})(1 - 0.75) = 12 \text{ mg/L}$

10. $ER_{HD} = (C_{predialysis} - C_{postdialysis}) / C_{predialysis} = (75 \text{ mg/L} - 25 \text{ mg/L}) / 75 \text{ mg/L} = 0.67$ or 67%

$$Cl_{HD} = HDBF \cdot ER_{HD} = (400 \text{ mL/min})(0.67) = 268 \text{ mL/min}$$

11. $Cl_{PD} = (C_{Dialysis} \cdot V_{Dialysis}) / (C_{Serum} \cdot T_{Dialysis}) = (35 \text{ mg/L} \cdot 2000 \text{ mL}) / (50 \text{ mg/L} \cdot 360 \text{ min}) = 3.9 \text{ mL/min}$

12. Please see Figure 3-19 for diagram. Addition of valproic acid will increase the free fraction of phenytoin in the blood and decrease phenytoin intrinsic clearance. Because phenytoin is a low hepatic extraction ratio drug, clearance will not change ($Cl = \uparrow f_B \downarrow Cl'_{int}$). However, phenytoin volume of distribution will increase [$\uparrow V = V_B + (\uparrow f_B / f_T) V_T$] resulting in an increased half-life [$\uparrow t_{1/2} = (0.693 \cdot \uparrow V) / Cl$]. Total phenytoin concentration is unchanged since clearance is stable. But, because of the increase in free fraction, the unbound steady-state concentration rises ($\uparrow Css_u = \uparrow f_B Css$) and drug effect increases.

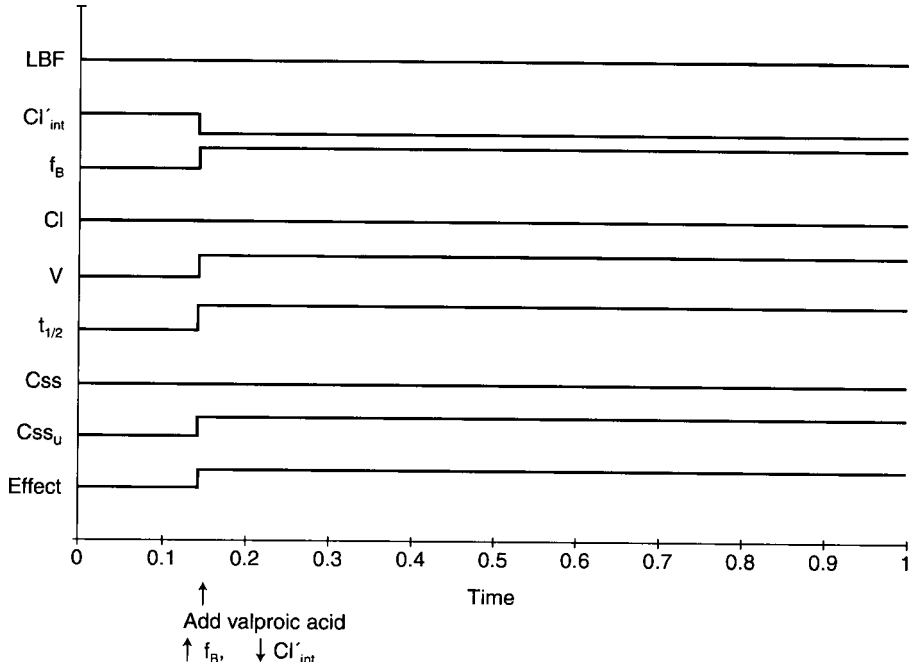

FIGURE 3-19 Solution for problem 12.

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Part II

ANTIBIOTICS

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4

THE AMINOGLYCOSIDE ANTIBIOTICS

INTRODUCTION

The aminoglycoside antibiotics are widely used for the treatment of severe gram-negative infections such as pneumonia or bacteremia, often in combination with a β-lactam antibiotic. Aminoglycosides are also used for gram-positive infections such as infective endocarditis in combination with penicillins when antibiotic synergy is required for optimal killing. Aminoglycoside antibiotics available in the United States that are in common use include gentamicin, tobramycin, netilmicin, and amikacin.

Aminoglycoside antibiotics are bactericidal, and the drugs exhibit concentration-dependent bacterial killing.[1] Antibiotics with concentration-dependent killing characteristically kill bacteria at a faster rate when drug concentrations are higher. Also, aminoglycosides have a concentration-dependent postantibiotic effect. The postantibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC). Because the postantibiotic effect is concentration-dependent for the aminoglycosides, higher drug concentrations lead to a longer postantibiotic effect. The mechanisms of action for aminoglycosides are binding to the 30S ribosomal subunit inhibiting protein synthesis and misreading of mRNA causing dysfunctional protein production.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The MIC for susceptible bacteria is higher for amikacin than it is for the other aminoglycosides. Because the pharmacokinetics is similar for all these drugs, higher doses of amikacin are needed to treat infections. The conventional method of dosing aminoglycoside antibiotics is to administer multiple daily doses (usually every 8 hours).[2] In order to take advantage of concentration-dependent bacterial killing and the postantibiotic effect, extended-interval

(usually the total daily dose given once per day) aminoglycoside administration is also a dosing option.[3] Because of these two different methods of dosage administration, it is important to identify which is being used when discussing serum concentration monitoring.

Conventional Dosing

Aminoglycoside antibiotics are given as short-term ($^1/_2$–1 hour) infusions. If a 1-hour infusion is used, maximum end of infusion "peak" concentrations are measured when the infusion is completed (Figure 4-1). If a $^1/_2$-hour infusion is used, serum concentrations exhibit a distribution phase so that drug in the blood and in the tissues are not yet in equilibrium. Because of this, a $^1/_2$-hour waiting period is allowed for distribution to finish if a $^1/_2$-hour infusion is used before peak concentrations are measured. Therapeutic steady-state peak concentrations for gentamicin, tobramycin, and netilmicin are generally 5–10 μg/mL for gram-negative infections. Infection sites with more susceptible bacteria, such as intra-abdominal infections usually can be treated with steady-state peak concentrations at the lower end of this range (typically 5–7 μg/mL). Infection sites that are difficult to penetrate and with bacteria that have higher MIC values, such as pseudomonal pneumonia usually require steady-state peak concentrations in the higher end of the range (typically 8–10 μg/mL). When gentamicin, tobramycin, or netilmicin are used synergistically with penicillins or other antibiotics for the treatment of gram-positive infections such as infective endocarditis steady-state peak concentrations of 3–5 μg/mL are often times adequate. Therapeutic peak concentrations for amikacin are 15–30 μg/mL.

Exceeding peak steady-state concentrations of 12–14 μg/mL for gentamicin, tobramycin, or netilmicin or 35–40 μg/mL for amikacin when using conventional dosing leads to an increased risk of ototoxicity.[4] The types of ototoxicity that aminoglycosides cause are auditory and vestibular, and the damage is permanent. Aminoglycosides accumulate in the lymph of the inner ear causing ongoing damage to cochlear or vestibular sensory cells.[1] Auditory ototoxicity usually is first noted at high frequencies (>4000 Hz)

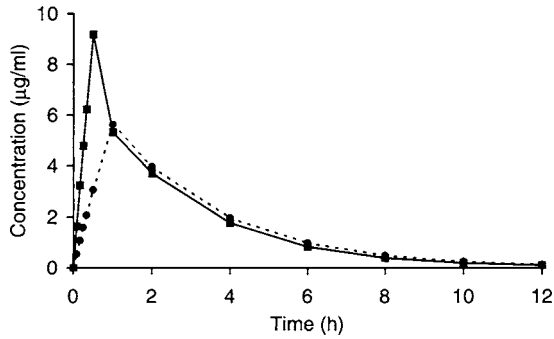


FIGURE 4-1 Concentration/time plot for gentamicin 120 mg given as a $^1/_2$-hour infusion *(squares with solid line)* and as a 1-hour infusion *(circles with dashed line).* When given as a $^1/_2$-hour infusion, end of infusion concentrations are higher because the serum and tissues are not in equilibrium. A $^1/_2$-hour waiting time for aminoglycoside distribution to tissues is allowed before peak concentrations are measured. If aminoglycosides are given as 1-hour infusions, distribution has an opportunity to occur during the infusion time, and peak concentrations can be obtained immediately. In either case, concentrations 1 hour after the infusion was initiated are similar.

and is difficult to detect using clinical means. Audiometry is required to detect high-tone hearing loss and is seldom done in patient care areas. Older patients may have lost the ability to hear in this range for other reasons. If aminoglycoside treatment is not discontinued in individuals with high-frequency auditory ototoxicity, hearing loss will progress to lower frequencies. As a result, aminoglycoside-induced hearing losses are not usually detected until the patient is unable to detect sounds in the conversational frequency zone (<4000 Hz). Often, the first sign of auditory ototoxicity is tinnitus. Vestibular ototoxicity results in the loss of balance. Again, this type of ototoxicity is difficult to detect because many patients treated with aminoglycosides are bed-bound. Besides loss of equilibrium, headache, ataxia, nausea, vomiting, nystagmus, and vertigo can all be signs of vestibular ototoxicity. Although this version of ototoxicity is also permanent, patients can often compensate using visual cues, such as use of the horizon, to maintain balance and avoid ataxia. In some studies, predose ("trough") steady-state concentrations have been found to be related to ototoxicity.[5,6] However, peak steady-state concentrations have also been elevated in these patients which clouds the relationship between serum concentrations and this type of drug-induced adverse effect.

Trough steady-state concentrations (predose or minimum concentrations usually obtained within 30 minutes of the next dose) above 2–3 μg/mL for tobramycin, gentamicin, or netilmicin or 10 μg/mL for amikacin predispose patients to an increased risk of nephrotoxicity.[7,8] Aminoglycoside antibiotics accumulate in the proximal tubular cells of the kidney, decrease the ability of the kidney to concentrate urine, and, ultimately, decrease glomerular filtration.[9–11] Nephrotoxicity due to aminoglycoside therapy is unlikely to occur before 3–5 days of therapy with proper dosing of the antibiotic. Because many patients receiving aminoglycosides are critically ill, other sources of nephrotoxicity, such as hypotension or other nephrotoxic drug therapy, should be ruled out before a diagnosis of aminoglycoside renal damage is made in a patient. Unlike ototoxicity, aminoglycoside-induced nephrotoxicity is usually reversible with little, if any, residual damage if the antibiotic is withdrawn soon after renal function tests change. With proper patient monitoring, mild renal dysfunction resulting in serum creatinine increases of 0.5–2 mg/dL may be the only result of aminoglycoside nephrotoxicity. However, if the patient develops renal failure, the cost of maintaining the patient on dialysis until kidney function returns can exceed $50,000–$100,000 and, if the patient is critically ill, may contribute to his or her death. In some investigations, peak concentrations have been related to nephrotoxicity.[12] However, trough concentrations have also been high in these patients, which obscure the relationship between serum concentrations and nephrotoxicity.

Keeping peak and trough concentrations within the suggested ranges does not completely avoid nephrotoxicity and ototoxicity in patients, but, hopefully, decreases the likelihood that patients will experience these serious adverse effects.[13] Also, even though serum concentrations are controlled within the suggested ranges, duration of therapy exceeding 14 days, large total cumulative doses, and concurrent therapy with other nephrotoxic drugs such as vancomycin can predispose patients to these side effects of the aminoglycoside antibiotics.[14–17]

Extended-Interval Dosing

Because aminoglycoside antibiotics exhibit concentration-dependent bacterial killing and the postantibiotic effect is longer with higher concentrations, investigators began

studying the possibility of giving a higher dose of aminoglycoside once daily.[3,18,19] Generally, these studies have shown comparable microbiologic and clinical cure rates for many infections and about the same rate of nephrotoxicity (~5–10%) as with conventional dosing. Auditory ototoxicity has not been monitored using audiometry in most of these investigations, but loss of hearing in the conversational range as well as signs and symptoms of vestibular toxicity have usually been assessed and found to be similar to aminoglycoside therapy dosed conventionally. Based on this data, clinicians have begun using extended-interval dosing in selected patients. For *Pseudomonas aeruginosa* infections where the organism has an expected MIC ≈ 2 μg/mL, peak concentrations between 20 and 30 μg/mL and trough concentrations <1 μg/mL have been suggested.[3] At the present time, there is not a consensus on how to approach concentration monitoring using this mode of administration.[20–26] Some clinicians measure steady-state peak and trough concentrations while others measure two steady-state postdose concentrations or a single steady-state postdose concentration.[27]

Because of the extremely high peak concentrations obtained during extended-interval dosing of aminoglycosides, it can be difficult to understand why increased toxicity is not seen in patients. The hypothesized reason is that both nephrotoxicity and ototoxicity are due to accumulation of aminoglycoside in the relevant tissue. Because the dosage interval is prolonged in extended-interval administration, aminoglycoside concentrations are low for a long period of time and may allow for diffusion of drug out of tissue and into the blood which avoids drug accumulation in the ear and kidney. Also, some of the uptake mechanisms into the ear and kidney may be saturable, so that high peak serum concentrations of aminoglycosides may not result in high renal or ear tissue concentrations.

Since large doses of aminoglycoside are given as a single dose with this mode of administration, two additional adverse effects become of concern. Because of the manufacturing process used to produce aminoglycoside antibiotics, very low residual amounts of gram-negative endotoxin are sometimes present in the commercial product. Reports of infusion-related hypotension in patients receiving extended-interval aminoglycosides during the late 1990s have been attributed to the amount of toxin administered at one time.[28,29] Acute neuromuscular blockade, usually associated with concurrent administration of anesthetics or neuromuscular blockers, is also a possible adverse effect of aminoglycosides associated with high drug concentrations. Because of the high peak concentrations achieved using extended-interval dosing, surgical and intensive care patients should be monitored for this possible adverse effect.

Differential Toxicity Among Aminoglycosides

Studies are available that attempt to determine nephrotoxicity differences among antibiotics. Gentamicin accumulates to a greater extent in kidney tissue when compared to tobramycin.[11,13,16] Because doses of amikacin are larger than for gentamicin and tobramycin, amikacin in renal accumulation must be adjusted for dosage differences.[9,13] When this is done, amikacin accumulation patterns are similar to gentamicin. Based on these accumulation profiles and associated clinical data and other trials, some clinicians believe that tobramycin is less nephrotoxic than gentamicin or amikacin.[30] There are less conclusive data for netilmicin. Other clinical trials that compare the nephrotoxicity potential of gentamicin and tobramycin indicate that the two drugs are similar in this area.[31,32] Generally, gentamicin is the most widely used aminoglycoside, followed by tobramycin

and netilmicin. This usage pattern is due, in part, to the fact that gentamicin was the first aminoglycoside available generically and was much less expensive than the other drugs for a number of years. Amikacin is usually reserved for use in infections where the organism is resistant to other aminoglycosides.

CLINICAL MONITORING PARAMETERS

Clinicians should always consult the patient's chart to confirm that antibiotic therapy is appropriate for current microbiologic cultures and sensitivities. Also, it should be confirmed that the patient is receiving other appropriate concurrent antibiotic therapy, such as β-lactam or anaerobic agents, when necessary to treat the infection. Patients with severe infections usually have elevated white blood cell counts and body temperatures. Measurement of serial white blood cell counts and body temperatures are useful to determine the efficacy of antibiotic therapy. A white blood cell count with a differential will identify the types of white blood cells that are elevated. A large number of neutrophils and immature neutrophils, clinically known as a "shift to the left," can also be observed in patients with severe bacterial infections. Favorable response to antibiotic treatment is usually indicated by high white blood cell counts decreasing toward the normal range, the trend of body temperatures (plotted as body temperature vs. time, also known as the "fever curve") approaching normal, and any specific infection site tests or procedures resolving. For instance, in pneumonia patients the chest x-ray should be resolving, in patients with an intraabdominal infection abdominal pain and tenderness should be decreasing, or in patients with a wound infection the wound should be less inflamed with less purulent discharge. Clinicians should also be aware that immunocompromised patients with a bacterial infection may not be able to mount a fever or elevated white blood cell count.

Aminoglycoside steady-state peak and trough serum concentrations should be measured in 3–5 estimated half-lives when the drug is given using conventional dosage approaches. Methods to estimate this parameter are given in the initial dose calculation portion of this chapter. Since prolongation of the dosage interval is often used in patients with decreased elimination, a useful clinical rule is to measure serum concentrations after the third dose. If this approach is used, the dosage interval is increased in tandem with the increase in half-life so that 3–5 half-lives have elapsed by the time the third dose is administered. Additionally, the third dose typically occurs 1–3 days after dosing has commenced and this is a good time to assess clinical efficacy of the treatment also. Steady-state serum concentrations, in conjunction with clinical response, are used to adjust the antibiotic dose, if necessary. Methods to adjust aminoglycoside doses using serum concentrations are discussed later in this chapter. If the dosage is adjusted, aminoglycoside elimination changes or laboratory and clinical monitoring indicate that the infection is not resolving or worsening, clinicians should consider rechecking steady-state drug concentrations.

When extended-interval aminoglycoside therapy is used, several different monitoring techniques can be used.[27] Some clinicians measure steady-state peak and trough concentrations while others measure two steady-state postdose concentrations. Other approaches include obtaining only a steady-state trough concentration, or measuring a single aminoglycoside serum concentration 6–14 hours after a dose and using a dosage nomogram to adjust the dosage interval (please see dosing section later in chapter for details).

Serial monitoring of serum creatinine concentrations should be used to detect nephrotoxicity. Ideally, a baseline serum creatinine concentration is obtained before aminoglycoside therapy is initiated and three times weekly during treatment. An increasing serum creatinine test on two or more consecutive measurement occasions indicates that more intensive monitoring of serum creatinine values, such as daily, is needed. If serum creatinine measurements increase more than 0.5 mg/dL over the baseline value (or >25–30% over baseline for serum creatinine values >2 mg/dL) and other causes of declining renal function have been ruled out (other nephrotoxic drugs or agents, hypotension, etc.), alternatives to aminoglycoside therapy or, if that option is not possible, intensive aminoglycoside serum concentration monitoring should be initiated to ensure that excessive amounts of aminoglycoside do not accumulate in the patient. In the clinical setting, audiometry is rarely used to detect ototoxicity because it is difficult to accomplish in severely ill patients. Instead, clinical signs and symptoms of auditory (decreased hearing acuity in the conversational range, feeling of fullness or pressure in the ears, tinnitus) or vestibular (loss of equilibrium, headache, nausea, vomiting, vertigo, nystagmus, ataxia) ototoxicity are monitored at the same time intervals as serum creatinine determination.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

The aminoglycosides are eliminated almost completely (≥90%) unchanged in the urine primarily by glomerular filtration (Table 4-1).[10,13,16] These antibiotics are usually given by short-term ($^1/_2$–1 hour) intermittent intravenous infusions, although they can be given intramuscularly. When aminoglycosides are given intramuscularly they exhibit very good bioavailability of ~100% and are rapidly absorbed with maximal concentrations occurring about 1 hour after injection. Exceptions to this situation are patients who are hypotensive or obese. Hypotensive patients shunt blood flow away from peripheral tissues, such as muscle, to provide maximal blood flow to internal organs. As a result, intramuscularly administered drugs may be malabsorbed in hypotensive patients, such as those with gram-negative sepsis. Care must be taken with obese individuals to use a long enough needle to penetrate subcutaneous fat and enter muscle tissue when administering aminoglycoside antibiotics. Drug injected into poorly perfused fatty tissue will likely be malabsorbed. Oral bioavailability is poor (<10%) so systemic infections cannot be treated by this route of administration. Plasma protein binding is low (<10%).

Manufacture recommended doses for conventional dosing in patients with normal renal function are 3–5 mg/kg/d for gentamicin and tobramycin, 4–6 mg/kg/d for netilmicin, and 15 mg/kg/d for amikacin. These amounts are divided into three equal daily doses for gentamicin, tobramycin, or netilmicin, or two or three equal daily doses for amikacin. Extended-interval doses obtained from the literature for patients with normal renal function are 4–7 mg/kg/d for gentamicin, tobramycin, or netilmicin and 11–20 mg/kg/d for amikacin.[3,19–26,33–38]

EFFECTS OF DISEASE STATES AND CONDITIONS ON AMINOGLYCOSIDE PHARMACOKINETICS AND DOSING

Nonobese adults with normal renal function (creatinine clearance >80 mL/min, Table 4-1) have an average aminoglycoside half-life of 2 hours (range: 1.5–3 hours), and the average aminoglycoside volume of distribution is 0.26 L/kg (range: 0.2–0.3 L/kg) in this population.[39–42]

TABLE 4-1 Disease States and Conditions That Alter Aminoglycoside Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	2 hours (range: 1.5–3 hours)	0.26 L/kg (range: 0.2–0.3 L/kg)	Usual doses 3–5 mg/kg/d for gentamicin, tobramycin, netilmicin, or 15 mg/kg/d for amikacin when using conventional dosing. Usual doses are 5–7 mg/kg/d for gentamicin or tobramycin using extended-interval dosing.
Adult, renal failure	50 hours (range: 36–72 hours)	0.26 L/kg	Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.
Burns	1.5 hours	0.26 L/kg	Burn patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.
Penicillin therapy (patients with creatinine clearance <30 mL/min)	Variable	0.26 L/kg	Some penicillins (penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can bind and inactivate aminoglycosides *in vivo* or *in vitro* (e.g., lab test tubes).
Obesity (>30% over IBW) with normal renal function	2–3 hours	V (in L) = 0.26 [IBW + 0.4 (TBW − IBW)]	Aminoglycosides enter the extracellular fluid contained in adipose tissue requiring a correction factor to estimate volume of distribution.
Cystic fibrosis	1.5 hours	0.35 L/kg	Larger volume of distribution and shorter half-life usually results in larger daily doses.
Acites/overhydration	Variable	V (in L) = (0.26 · DBW) + (TBW − DBW)	Aminoglycosides distribute to excess extracellular fluid; correction equation assumes that weight gain is due to fluid accumulation. Alterations in volume of distribution can cause secondary changes in half-life.

(*Continued*)

TABLE 4-1 Disease States and Conditions That Alter Aminoglycoside Pharmacokinetics (*Continued*)

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Hemodialysis	3–4 hours	0.26 L/kg	While receiving hemodialysis, aminoglycoside half-life will decreases from ~50 hours to ~4 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.
Peritoneal dialysis	36 hours	0.26 L/kg	While receiving peritoneal dialysis, aminoglycoside half-life will decrease from ~50 hours to ~36 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.

Symbol key: IBW is ideal body weight, TBW is total body weight, DBW is dry body weight.

The volume of distribution is similar to extracellular fluid content of the body, and fluid balance will be an important factor when estimating the aminoglycoside volume of distribution for a patient. Patients who have been febrile due to their infections for 24 hours or more may be significantly dehydrated and have lower volumes of distribution until rehydrated.

Because aminoglycosides are eliminated primarily by glomerular filtration, renal dysfunction is the most important disease state that affects aminoglycoside pharmacokinetics.[43,44] The elimination rate constant decreases in proportion to creatinine clearance because of the decline in drug clearance (Figure 4-2).[45,46] This relationship between renal function and aminoglycoside elimination will form the basis for initial dosage computation later in this chapter. Because the kidney is the organ responsible for maintaining fluid and electrolyte balance in the body, patients with renal failure are sometimes overhydrated. Body weight can be an effective way to detect overhydration in a patient. If the usual weight of the patient is 70 kg when they are in normal fluid balance, known as the patient's "dry weight," and the patient is currently 75 kg with signs and symptoms of overhydration (pedal edema, extended neck veins, etc.), the additional 5 kg of weight could be considered extra fluid and added to the estimated volume of distribution for the patient. Since 1 L of water weighs 1 kilogram, the estimated volume of distribution for this patient would be 18.2 L using the patient's dry weight ($V = 0.26\ L/kg \cdot 70\ kg = 18.2\ L$) plus 5 L to account for the additional 5 kg of extra fluid yielding a total volume of distribution equal to 23.2 L ($V = 18.2\ L + 5\ L = 23.2\ L$). Care would be needed to alter the estimated volume of distribution toward normal as the excess fluid was lost and the patient's weight returned to its usual value.

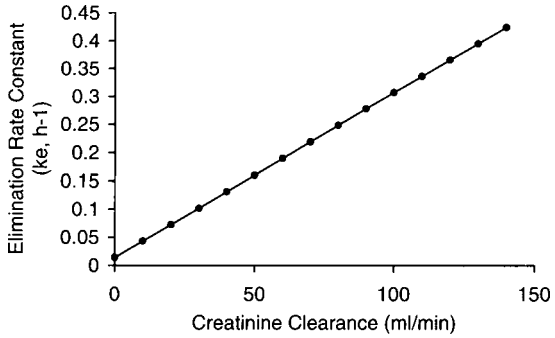


FIGURE 4-2 Relationship between renal and aminoglycoside elimination. The elimination rate constant (k_e) for aminoglycoside antibiotics increases in proportion with creatinine clearance (CrCl). The equation for this relationship is k_e (in h^{-1}) = 0.00293(CrCl in mL/min) + 0.014. This equation is used to estimate the aminoglycoside elimination rate constant in patients for initial dosing purposes.

A major body burn (>40% body surface area) can cause large changes in aminoglycoside pharmacokinetics.[47–49] Forty-eight to seventy-two hours after a major burn, the basal metabolic rate of the patient increases to facilitate tissue repair. Because of the increase in basal metabolic rate, glomerular filtration rate increases which increases aminoglycoside clearance. Because of the increase in drug clearance, the average half-life for aminoglycosides in burn patients is ~1.5 hours. If the patient is in normal fluid balance, the average volume of distribution will be the same as in normal adults (0.26 L/kg). However, since the skin is the organ which prevents fluid evaporation from the body and the integrity of the skin has been violated by thermal injury, these patients can be dehydrated, especially if they have had a fever for more than 24 hours. The result is a lower volume of distribution for aminoglycosides. Alternatively, some burn patients may be overhydrated due to vigorous fluid therapy used to treat hypotension. This will result in a larger than expected aminoglycoside volume of distribution. Unfortunately, there is no precise way to correct for fluid balance in these patients. Frequent use of aminoglycoside serum concentrations are used to guide therapy in this population.

Concurrent therapy with some penicillins can increase aminoglycoside clearance by chemically inactivating both the penicillin and aminoglycoside via formation of a covalent bond between the two antibiotic molecules.[50–54] Penicillin G, ampicillin, nafcillin, carbenicillin, and ticarcillin are the penicillins most likely to cause this interaction. Piperacillin and mezlocillin, as well as cephalosporins, do not inactivate aminoglycosides to an appreciable extent. This *in vivo* interaction is most likely to occur in patients with poor renal function (creatinine clearance <30 mL/min) so that the elimination of both the aminoglycoside and penicillin is slower. Under these conditions, serum concentrations of both antibiotics will be higher for a longer period of time and facilitate the inactivation process. In patients with renal failure receiving an aminoglycoside alone, the addition of one of the interacting penicillins can decrease the aminoglycoside half-life from ~50 hours when given alone to ~12 hours when given in combination and result in a dosage increase for the aminoglycoside. Another place where this interaction is important to note is when patients are receiving concurrent therapy with one of the interacting penicillins and an aminoglycoside antibiotic, and serum concentration monitoring of the aminoglycoside is

planned. When a blood sample is obtained for measurement of the aminoglycoside serum concentration, penicillin contained in the blood collection tube can continue to inactivate aminoglycoside. This will lead to a spuriously low aminoglycoside concentration results which can lead to dosing adjustment errors. For example, a peak gentamicin serum concentration is obtained in a patient receiving concurrent gentamicin and penicillin G therapy. When the blood sample was drawn from the patient, the gentamicin concentration was 8 μg/mL. By the time the sample is processed by the lab, 6 hours expire because of transportation and other factors. Because of this, penicillin G inactivated aminoglycoside molecules, and the concentration of gentamicin decreased to 4 μg/mL. The lab measured this concentration and reported it to the clinicians caring for the patient. Because the desired peak concentration was 8 μg/mL, the dose of gentamicin was doubled so that the reported peak concentration of 4 μg/mL would increase to the target concentration. Of course, since the actual peak concentration was 8 μg/mL in the patient all along, the new peak concentration resulting from the dosage increase would be 16 μg/mL. In order to prevent this *in vitro* inactivation interaction in patients receiving concurrent penicillin and aminoglycoside treatment when the drug assay will not be run for longer than 1–2 hours after specimen collection, blood samples should have the serum separated using centrifugation. The serum is removed and placed in a separate tube, then frozen to prevent the chemical reaction from occurring. Alternatively, a small amount of β-lactamase (<5% of total blood volume to prevent sample dilution) can be added to break the β-lactam bond of the penicillin and avoid inactivation of the aminoglycoside antibiotic.

Aminoglycosides are relatively polar molecules with good water solubility. Because of this, they do not enter adipose cells to any significant extent. However, in patients who weigh more that 30% over their ideal body weight, the volume of distribution for aminoglycosides increases because of the additional extracellular fluid contained in adipose tissue (Figure 4-3).[55–57] The reason that aminoglycoside volume of distribution is affected by this relatively small amount of additional extracellular fluid in adipose tissue is because the baseline volume of distribution for these drugs is relatively small to begin with (0.26 L/kg or ~18 L for a 70-kg person). For other water-soluble drugs with larger volumes of distribution, the additional extracellular fluid contained in adipose tissue may not be a significant factor. Adipose tissue contains ~40% of the extracellular fluid that is present in lean tissue. To compensate for the increased extracellular fluid of adipose tissue and the greater volume of distribution found in obese patients (>30% over ideal body weight), the following formula can be used to estimate aminoglycoside volume of distribution (V in Liter) for initial dosing purposes: $V = 0.26 \cdot [IBW + 0.4(TBW - IBW)]$, where IBW is ideal body weight and TBW is the patient's actual total body weight. In morbidly obese (>90% above ideal body weight) patients with normal serum creatinine concentrations, the clearance of aminoglycoside antibiotics is also increased.[55–57] The reason for the increased drug clearance is larger kidneys which result in larger creatinine clearance rates. Because both volume of distribution and clearance simultaneously change in obese patients to about the same extent, the aminoglycoside half-life value is appropriate for the patient's renal function [$t_{1/2} = (0.693 \cdot V)/Cl$].

Cystic fibrosis is a disease state that affects exocrine glands. In the lung, the result is the production of thick, tenacious sputum that predisposes patients to pulmonary infections. Patients with cystic fibrosis have larger aminoglycoside volumes of distribution (0.35 L/kg) because body composition is altered.[33–36,58–61] Generally cystic fibrosis

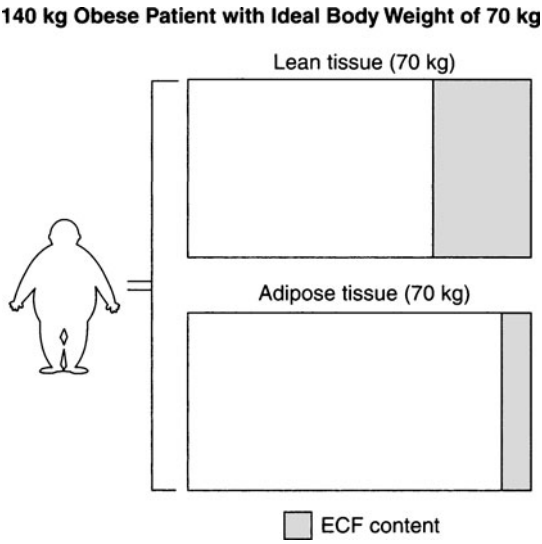


FIGURE 4-3 Schematic of extracellular fluid content of lean and adipose tissue in a morbidly obese patient with an actual body weight of 140 kg and an ideal body weight of 70 kg. Lean tissue contains about 0.26 L/kg extracellular fluid, but adipose tissue has about 40% of the extracellular fluid content that lean tissue does. The equation that estimates volume of distribution for aminoglycosides in obese patients normalizes adipose tissue extracellular content into lean tissue equivalents.

patients have decreased adipose tissue and increased extracellular fluid due to disease-state-induced gastrointestinal malabsorption. These patients also have higher aminoglycoside clearance values due to increased glomerular filtration rates. Because clearance rates tend to increase more than volume of distribution values, the average aminoglycoside half-life is typically shorter in patients with cystic fibrosis ($t_{1/2}$ = 1.5 hours). Extended-interval dosing can be used to treat pulmonary exacerbations in cystic fibrosis patients.[33,35,62,63] Aminoglycosides can also be administered via inhalation at a dose of 300 mg twice daily in a cyclic fashion (4 weeks on, 4 weeks off) for patients with cystic fibrosis.[64]

Liver disease patients with ascites have additional extracellular fluid due to accumulation of ascitic fluid.[65–67] Since aminoglycosides pass into ascitic fluid, the volume of distribution is increased in these patients. The approach to estimating an initial volume of distribution is similar to that used in renal failure patients who are fluid overloaded. The weight of the patient when ascitic fluid is not present is known as the patient's dry weight. If this value is not known and the patient is not obese, ideal body weight can be used as an estimate of the dry weight. A reasonable estimate of the volume of distribution (V in liter) for a patient with ascites, or who is overhydrated for other reasons, can be estimated using the following equation: $V = (0.26 \cdot DBW) + (TBW - DBW)$, where DBW is the patient's dry body weight and TBW is the patient's actual total body weight. Because of the large amount of variation in aminoglycoside volume of distribution for patients with ascites or overhydration, dosing should be guided by aminoglycoside serum concentrations. Also, as excess fluid is lost, clinicians should anticipate a decrease in the volume of distribution for these drugs.

Premature infants (gestational age ≤34 weeks) have a larger amount of body water compared to adults.[37,68–70] Aminoglycoside volume of distribution is larger (0.5–0.6 L/kg) because of this physiologic difference. Additionally, kidneys are not completely developed either so glomerular filtration and aminoglycoside clearance are decreased. A larger volume of distribution and lower clearance rate result in a prolonged average half-life equal to 6–10 hours. Full-term neonates (gestational age ~40 weeks) also have a larger volume of distribution (mean V = 0.4–0.5 L/kg) and lower aminoglycoside clearance resulting in longer half-life values ($t_{1/2}$ = 4–5 hours). By about 6 months, the mean volume of distribution is still large (V = 0.3–0.4 L/kg), but kidney development is complete, aminoglycoside clearance increases, and half-life is shorter ($t_{1/2}$ = 2–3 hours). These values remain relatively constant until about 2 years of age. At that time, aminoglycoside volume of distribution, clearance, and half-life gradually approach adult values at puberty (~12–14 years old). Initial doses for neonates are based on birth weight and age:[71]

		AGE 0–4 WEEK OLD	AGE <1 WEEK OLD		AGE ≥ 1 WEEK OLD	
AMINOGLYCOSIDE	ROUTE	WEIGHT <1200 g	WEIGHT 1200–2000 g	WEIGHT >2000 g	WEIGHT 1200–2000 g	WEIGHT >2000 g
Amikacin	IV, IM	7.5 mg/kg every 18–24 hours	7.5 mg/kg every 12 hours	7.5–10 mg/kg every 12 hours	7.5–10 mg/kg every 8 or 12 hours	10 mg/kg every 8 hours
Gentamicin or Tobramycin	IV, IM	2.5 mg/kg every 18–24 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 8 or 12 hours	2.5 mg/kg every 8 hours

Doses for infants and children are: amikacin 15–22.5 mg/kg/d IV or IM given every 8 hours, gentamicin or tobramycin 7.5 mg/kg/d IV or IM given every 8 hours.[72] Extended-interval aminoglycoside dosing can be conducted in pediatric patients.[73] After initial doses are started, steady-state aminoglycoside serum concentrations are used to individualize doses for either conventional or extended-interval dosing.

Hemodialysis efficiently removes aminoglycoside antibiotics from the body.[74–78] Gentamicin, tobramycin, netilmicin, and amikacin are relatively small molecules that are water soluble and have a small volume of distribution and low plasma protein binding. All of these characteristics lead to very good hemodialysis removal. The average aminoglycoside half-life in a renal failure patient is 50 hours. During hemodialysis with a "low-flux" artificial kidney, half-life decreases to 4 hours and results in about 50% of the drug being removed during a typical dialysis period (3–4 hours). Similarly, hemodialysis performed with a "high-flux" filter decreases aminoglycoside half-life to 2 hours.[79] If the patient is properly hydrated, the volume of distribution for aminoglycosides is 0.26 L/kg.

Hemodialysis procedures, such as ultrafiltration, can be used to assist in the maintenance of proper fluid balance in patients. Because kidneys provide fluid and electrolyte balance, it is not unusual for patients with renal failure receiving hemodialysis to be over- or underhydrated. As previously discussed in the renal failure section in the above paragraphs, body weight is an effective way to assess hydration status and can be used to adjust initial volume of distribution estimates.

Peritoneal dialysis is much less efficient in removing aminoglycosides from the body.[80–82] Peritoneal dialysis will decrease the half-life of aminoglycosides in a renal failure patient from about 50 hours to about 36 hours during the dialysis procedure. If the patient is receiving peritoneal dialysis on a chronic, ongoing basis, such as continuous ambulatory peritoneal dialysis (CAPD), aminoglycoside half-life will be shorter all of the time because of the additional dialysis clearance. Patients receiving continuous ambulatory peritoneal dialysis sometimes develop peritonitis which can be treated by adding aminoglycoside (or other) antibiotics to the peritoneal dialysis fluid. While about one-half of the intraperitoneal aminoglycoside dose is systemically absorbed during a 5–6 hours dwell time, if a patient with peritonitis develops secondary bacteremia, it may be necessary to use parenteral antibiotics to cure the infection.[80–82] Peritonitis causes inflammation of the peritoneal membrane, which facilitates absorption of aminoglycoside administered via dialysis fluid and elimination of aminoglycoside present in the body.

Continuous hemofiltration consists of a family of techniques that provides removal of toxic metabolic substances in patients with acute renal failure.[83] A large amount of variability exists in aminoglycoside removal depending on the type of hemofiltration used in a patient. Average sieving coefficients for the aminoglycoside antibiotics are:[84,85] gentamicin 0.81, tobramycin 0.90, netilmicin 0.93, amikacin 0.95. Because continuous arteriovenous hemofiltration (CAVH) provides an average creatinine clearance of ~30 mL/min, this value is typically used to initiate therapy in patients, then aminoglycoside serum concentration monitoring is used to individualize dosing early in therapy.[86]

DRUG INTERACTIONS

Most important drug interactions are pharmacodynamic, and not pharmacokinetic, in nature. Vancomycin,[14,17,87] amphotericin B,[17] cyclosporin,[88] and furosemide[12,16,17] enhance the nephrotoxicity potential of the aminoglycosides. Each of these agents can cause nephrotoxicity when administered alone. When these drugs are administered concurrently with an aminoglycoside, serum creatinine concentrations should be monitored on a daily basis. Additionally, serum concentrations of vancomycin or cyclosporin, as well as the aminoglycoside, should be measured. Loop diuretics,[89,90] including furosemide, bumetanide, and ethacrynic acid, can cause ototoxicity, and an increased incidence of this adverse effect has been reported when aminoglycosides have been coadministered. If aminoglycoside antibiotics are administered with loop diuretics, clinical signs and symptoms of ototoxicity (auditory: decreased hearing acuity in the conversational range, feeling of fullness or pressure in the ears, tinnitus; vestibular: loss of equilibrium, headache, nausea, vomiting, nystagmus, vertigo, ataxia) should be monitored daily.

Aminoglycosides have intrinsic nondepolarizing neuromuscular blocking activity and may prolong the effects of neuromuscular blocking agents such as succinylcholine.[91]

Surgical and intensive care patients receiving neuromuscular blockers and aminoglycosides should be monitored for this potential adverse effect. As previously discussed, penicillins (primarily penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can inactivate aminoglycosides *in vivo* and in blood specimen tubes intended for the measurement of aminoglycoside serum concentrations.[50–54] These two classes of drugs can also inactive each other in intravenous administration bags and syringes and should not be mixed together.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate aminoglycoside therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows for individualized target serum concentrations to be chosen for a patient, so it can be used for both conventional and extended-interval dosing. Also, each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. However, it is computationally intensive. The *Hull and Sarubbi nomogram* uses the dosing concepts in the pharmacokinetic dosing method. But, in order to simplify calculations, it makes simplifying assumptions: target concentration ranges consistent with conventional dosing only, fixed volume of distribution parameter in the normal range, limited dosage interval selection (no longer than 24 hours). Thus, it should be used only in patients who only have renal dysfunction and/or obesity as complicating factors and only when conventional dosing is to be used. The *Hartford nomogram* has similar strengths and weaknesses when compared to the Hull and Sarubbi nomogram, but is designed for use when extended-interval dosing is desired. This nomogram also incorporates a method to adjust aminoglycoside doses based on serum concentration feedback. *Literature-based recommended dosing* is a commonly used method to prescribe initial doses of aminoglycosides to pediatric patients. Doses are based on those that commonly produce steady-state concentrations within the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of aminoglycosides is to compute the best dose possible for the patient given their set of disease states and conditions that influence aminoglycoside pharmacokinetics and the site and severity of the infection. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

ELIMINATION RATE CONSTANT ESTIMATE

Aminoglycosides are almost totally eliminated unchanged in the urine, and there is a good relationship between creatinine clearance and aminoglycoside elimination rate constant (Figure 4-2). This relationship allows the estimation of the aminoglycoside elimination rate constant for a patient which can be used to compute an initial dose of the antibiotic. Mathematically, the equation for the straight line shown in Figure 4-2 is: $k_e = 0.00293(CrCl) + 0.014$, where k_e is the aminoglycoside elimination rate constant in h^{-1} and CrCl is creatinine clearance in mL/min. A limitation in using elimination rate constant as the elimination parameter in this relationship is that it is a hybrid pharmacokinetic

constant whose value can be influenced by either clearance or volume of distribution (k_e = Cl/V). Because gentamicin, tobramycin, netilmicin, and amikacin have similar pharmacokinetic properties, the same elimination rate constant versus creatinine clearance relationship can be used for all of the antibiotics. For example, the estimated elimination rate constant for an individual with a creatinine clearance of 10 mL/min is 0.043 h^{-1} which yields an estimated half-life of 16 hours [k_e = 0.00293(CrCl) + 0.014 = 0.00293 · (10 mL/min) + 0.014 = 0.043 h^{-1}; $t_{1/2}$ = 0.693/(0.043 h^{-1}) = 16 h]. Taking the patient's renal function into account when deriving initial doses of aminoglycoside antibiotics is the single most important characteristic to assess.

VOLUME OF DISTRIBUTION ESTIMATE

The average volume of distribution for patients without disease states and conditions that change this parameter is 0.26 L/kg. Thus, for a nonobese 70-kg patient, the estimated volume of distribution would be 18.2 L (V = 0.26 L/kg · 70 kg = 18.2 L). If a patient weighs less than their ideal body weight, actual body weight is used to estimate volume of distribution. For patients whose weight is between their ideal body weight and 30% over ideal weight, actual body weight can be used to compute estimated volume of distribution, although some clinicians prefer to use ideal body weight for these individuals. In patients who are more than 30% above their ideal body weight, volume of distribution (V) estimates should include both ideal and actual total body weighs using the following equation: V = 0.26[IBW + 0.4(TBW − IBW)], where V is in L, IBW is ideal body weight in kilograms, and TBW is total body weight in kilograms. For an obese patient whose ideal body weight is 55 kg and total body weight is 95 kg, the estimated volume of distribution would be 18.5 L: V = 0.26[IBW + 0.4(TBW − IBW)] = 0.26[55 kg + 0.4(95 kg − 55 kg)] = 18.5 L. In patients who are overhydrated or have ascites, their dry body weight (weight without the extra fluid) can be used to provide an improved volume of distribution estimate (V in L) using the following formula: V = (0.26 · DBW) + (TBW − DBW), where DBW is the patient's dry body weight and TBW is the patient's actual total body weight. For example, a patient with a significant amount of ascitic fluid currently weighs 80 kg. It is known from previous clinic visits and history that the patient usually weighs 70 kg without the additional fluid. The estimated volume of distribution for this patient would be 28.2 L: V = (0.26 · DBW) + (TBW − DBW) = (0.26 · 70 kg) + (80 kg − 70 kg) = 28.2 L. Other disease states and conditions also influence aminoglycoside volume of distribution, and the values of this parameter given in Table 4-1 will be used when necessary. For instance, the average volume of distribution for cystic fibrosis patients is 0.35 L/kg. Therefore, the estimated volume of distribution for a 55-kg patient with cystic fibrosis is 19.3 L: V = 0.35 L/kg (55 kg) = 19.3 L.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous injection over less than 1 hour, aminoglycosides follow a three-compartment pharmacokinetic model (Figure 4-4). After the end of infusion, serum concentrations drop rapidly because of distribution of drug from blood to tissues (α or distribution phase). If aminoglycosides are infused over 1 hour, the distribution phase is not usually observed. By about 1 hour after the beginning of the antibiotic infusion, drug concentrations decline more slowly, and the elimination rate constant for this segment of the concentration/time curve is the one that varies with renal function (β or elimination phase). Finally, at very low serum concentrations not detected by aminoglycoside concentration assays

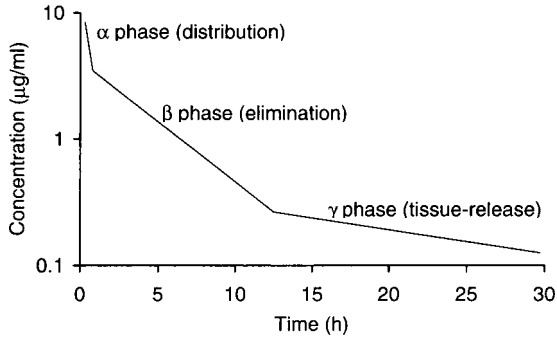


FIGURE 4-4 Multicomparment model characteristics of aminoglycosides. If aminoglycoside antibiotics are given as an intravenous bolus injection, the serum concentration/time curve declines in three distinct phases. The first phase (α or distribution phase) occurs as antibiotic in the blood distributes into tissues, although drug is also cleared from the blood during this time, too. The second phase (β or elimination phase) begins when blood and tissues are in near-equilibrium, and the predominate process is elimination from the body. The half-life for this phase of the curve is dramatically influenced by the patient's renal function ($t_{1/2}$ = 2 hours for normal renal function, $t_{1/2}$ = 50 hours for renal failure). The final phase (γ or tissue-release phase) occurs at very low serum concentrations (<0.5 μg/mL) and represents the release of tissue-bound aminoglycoside into the blood where it will cleared from the body.

in clinical use (≤0.5 μg/mL), drug that was tissue-bound to various organs (especially the kidney) is released from tissue-binding sites and eliminated (γ or tissue-release phase). While this model was instrumental in advancing current ideas regarding aminoglycoside tissue accumulation and nephrotoxicity, it cannot easily be used clinically because of its mathematical complexity.[9–11,13,16] Because of this, the simpler one-compartment model is widely used and allows accurate dosage calculation.[2,3,27,45,46,48,49,92]

Intravenously administered aminoglycosides are given over $^1/_2$–1 hour as intermittent continuous infusions. Since drug is eliminated during the infusion time (and any waiting time that is necessary to allow for distribution to finish), pharmacokinetic equations that take into account this loss are preferred in patients with good renal function. If this is not done, a large amount of drug may be eliminated during infusion and waiting periods, and the peak concentration will be miscalculated. Generally, infusion equations should be used if the patient has a creatinine clearance greater than 30 mL/min. For creatinine clearances of 30 mL/min or less, very little aminoglycoside is eliminated during infusion and waiting period times, and intravenous bolus equations accurately compute peak concentrations.[93] Aminoglycoside steady-state peak (Css_{max}) and trough (Css_{min}) serum concentrations are chosen to treat the patient based on the type, site, and severity of infection as well as the infecting organism. Steady-state versions of one-compartment model intermittent intravenous infusion $\{Css_{max} = [k_0/(k_eV)][(1 - e^{-k_et'}) / (1 - e^{-k_e\tau})]\ Cmin_{ss} = Cmax_{ss}{}^{-[k_e(\tau-t')]}$, where k_0 is the infusion rate, k_e is the elimination rate constant, V is the volume of distribution, t´ is the drug infusion time, and τ is the dosage interval} or intravenous bolus $\{Css_{max} = (D/V)[e^{-k_et} / (1 - e^{-k_e\tau})],\ Css_{max} = Css_{max}\, e^{-k_e\tau}$, where D is the antibiotic dose, V is the volume of distribution, k_e is the elimination rate constant, t is the time Css_{max} was measured, and τ is the dosage interval} equations are chosen based on the patient's renal function to compute the required doses needed to achieve desired

aminoglycoside concentrations. Note that intermittent intravenous infusion equations will work well regardless of the patient's creatinine clearance. However, the intravenous bolus equations are easier to solve, save time, and are less likely to invoke a computational error.

STEADY-STATE CONCENTRATION SELECTION

Aminoglycoside peak steady-state concentrations are selected based on site and severity of infection as well as the infecting organism. Severe infections, such as gram-negative pneumonia or septicemia, or infections with organisms that have a high minimum inhibitory concentration (MIC) such as *Pseudomonas aeruginosa* (typical MIC ≈ 2 μg/mL for gentamicin, tobramycin, or netilmicin) generally require peak steady-state serum concentrations of 8–10 μg/mL for gentamicin, tobramycin, or netilmicin or 25–30 μg/mL for amikacin when using conventional dosing. Moderate infections at sites that are easier to penetrate or with organisms that display lower MIC values, such as intraabdominal infections are usually treated with peak gentamicin, tobramycin, or netilmicin steady-state serum concentrations equal to 5–7 μg/mL or with amikacin peak steady-state serum concentrations equal to 15–25 μg/mL. When treating urinary tract infections due to susceptible organisms or using aminoglycosides for synergy in combination with penicillins or other antibiotics for the treatment of gram-positive infections such as infective endocarditis, steady-state peak concentrations of 3–5 μg/mL are usually adequate for gentamicin, tobramycin, or netilmicin; or 12–15 μg/mL for amikacin. Pyelonephritis is considered a soft-tissue infection, not a urinary tract infection, and requires higher peak steady-state concentrations to achieve a cure. Similar target peak steady-state concentrations for extended-interval aminoglycoside dosing are less established, although concentrations 20–30 μg/mL have been suggested for *Pseudomonas aeruginosa* and other serious infections including pulmonary exacerbations in cystic fibrosis patients. Desirable concentrations for steady-state trough concentrations are chosen based on avoidance of potential toxicity. For conventional dosing, steady-state trough concentrations should be maintained <2 μg/mL for tobramycin, gentamicin, and netilmicin or <5–7 μg/mL for amikacin. Using extended-interval dosing, steady-state trough concentrations should be <1 μg/mL for gentamicin, tobramycin, and netilmicin.

DOSAGE COMPUTATION

The equations given in Table 4-2 are used to compute aminoglycoside doses. One approach is to use different equations depending upon the renal function of the patient (intermittent intravenous infusion for creatinine clearances >30 mL/min, intravenous bolus for creatinine clearances ≤30 mL/min). Alternatively, intermittent intravenous infusion equations can be used for all patients regardless of renal function.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance*.

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

TABLE 4-2A One-Compartment Model Equations Used with Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}[(1 - e^{-nk_e\tau}) / (1 - e^{-k_e\tau})]$	$C = (D/V)[e^{-k_e t} / (1 - e^{-k_e\tau})]$
Intermittent intravenous infusion	$C = [k_0 / (k_eV)](1 - e^{-k_e t'})$	$C = [k_0 / (k_eV)](1 - e^{-k_e t'}) \cdot [(1 - e^{-nk_e\tau}) / (1 - e^{-k_e\tau})]$	$C = [k_0 / (k_eV)][(1 - e^{-k_e t'}) / (1 - e^{-k_e\tau})]$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, t' is the infusion time, k_0 is the infusion rate. Maximum steady-state concentrations are denoted as $Cmax_{ss}$, Css_{max}, or Cmax,ss. Minimum steady-state concentrations are denoted as $Cmin_{ss}$, Css_{min}, or Cmin,ss.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(97\ mL/min) + 0.014 = 0.298\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.298\ h^{-1} = 2.3\ h$$

TABLE 4-2B Pharmacokinetic Constant Computations Utilizing a One-Compartment Model for Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D/C_0$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D / (C_0 - C_{predose})$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D / (C_0 - C_{predose})$ $Cl = k_eV$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, k_0 is the continuous infusion rate, t' is the infusion time, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, $C_{predose}$ is the predose concentration.

TABLE 4-2C Equations Used to Compute Individualized Dosage Regimens for Various Routes of Administration Used with Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e$ $D = Css_{max} V(1 - e^{-k_e\tau})$ $LD = Css_{max} V$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e\tau})$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, k_0 is the continuous infusion rate, t' is the infusion time.

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26 \text{ L/kg } (70 \text{ kg}) = 18.2 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 9 μg/mL and Css_{min} = 1 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 9 \text{ μg/mL} - \ln 1 \text{ μg/mL}) / 0.298 \text{ h}^{-1}] + 1 \text{ h} = 8.4 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 8 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (9 \text{ mg/L} \cdot 0.298 \text{ h}^{-1} \cdot 18.2 \text{ L})\{[1 - e^{-(0.298 \text{ h}^{-1})(8 \text{ h})}] / [1 - e^{-(0.298 \text{ h}^{-1})(1 \text{ h})}]\} = 172 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 170 mg. (Note: μg/mL = mg/L, and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 170 mg every 8 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0/(1 - e^{-k_e\tau}) = 170 \text{ mg} / [1 - e^{-(0.298 \text{ h}^{-1})(8 \text{ h})}] = 187 \text{ mg}$$

As noted, this loading dose is only about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 2.3 hours, the patient should be at steady state after the second dose is given.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 50 \text{ y})70 \text{ kg}] / (72 \cdot 3.5 \text{ mg/dL})$$

$$CrCl_{est} = 25 \text{ mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(25 \text{ mL/min}) + 0.014 = 0.087 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.087 \text{ h}^{-1} = 8 \text{ h}$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26 \text{ L/kg } (70 \text{ kg}) = 18.2 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 9 μg/mL and Css_{min} = 1 μg/mL.

5. *Use intravenous bolus equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] = (\ln 9 \text{ μg/mL} - \ln 1 \text{ μg/mL}) / 0.087 \text{ h}^{-1} = 25 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 24 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose (D) could be administered either way.

$$D = Css_{max}\, V(1 - e^{-k_e\tau})$$

$$D = 9 \text{ mg/L} \cdot 18.2 \text{ L}(1 - e^{-(0.087 \text{ h}^{-1})(24 \text{ h})}) = 143 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 145 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 145 mg every 24 hours.

Note: Although this dose is given once daily, it is not extended-interval dosing because desired serum concentrations are within the conventional range.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\, V = 9 \text{ mg/L} \cdot 18.2 \text{ L} = 164 \text{ mg}$$

Round loading dose to 165 mg. It would be given as the first dose. The next dose would be a maintenance dose given a dosage interval away from the loading dose, in this case 24 hours later.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - \text{age})[(0.287 \cdot \text{Wt}) + (9.74 \cdot \text{Ht}^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35 \text{ y})\{(0.287 \cdot 150 \text{ kg}) + [9.74 \cdot (1.65 \text{ m})^2]\}}{(60 \cdot 1.1 \text{ mg/dL})} = 117 \text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(117\ mL/min) + 0.014 = 0.357\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.357\ h^{-1} = 1.9\ h$$

3. *Estimate volume of distribution (V).*

The patient is obese, so the volume of distribution would be estimated using the following formula:

$$V = 0.26[IBW + 0.4(TBW - IBW)] = 0.26[57\ kg + 0.4(150\ kg - 57\ kg)] = 24.5\ L$$

4. *Choose desired steady-state serum concentrations.*

Intraabdominal infection patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 5–7 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 6 μg/mL and Css_{min} = 0.5 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 6\ \mu g/mL - \ln 0.5\ \mu g/mL) / 0.357\ h^{-1}] + 1\ h = 8\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval is 8 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.357\ h^{-1} \cdot 24.5\ L)\{[1 - e^{-(0.357\ h^{-1})(8\ h)}] / [1 - e^{-(0.357\ h^{-1})(1\ h)}]\} = 165\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose does not need to be rounded. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 165 mg every 8 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 165\ mg / [1 - e^{-(0.357\ h^{-1})(8\ h)}] = 175\ mg$$

As noted, this loading dose is about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 1.9 hours, the patient should be at steady state after the second dose is given.

Example 4 JM is a 20-year-old, 76-kg (height = 5 ft 8 in) male with a gram-negative pneumonia. His current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using extended-interval dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {IBW_{males} = 50 + 2.3(Ht − 60 in) = 50 + 2.3(68 − 60) = 68 kg; % overweight = [100(76 kg − 68 kg)] / 68kg = 12%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 20\ y)76\ kg] / (72 \cdot 1.1\ mg/dL)$$

$$CrCl_{est} = 115\ mL/min.$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(115\ mL/min) + 0.014 = 0.351\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.351\ h^{-1} = 2.0\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26\ L/kg\ (76\ kg) = 19.8\ L$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with extended-interval aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 20–30 μg/mL; steady-state trough (Css_{min}) concentrations should be <1 μg/mL to avoid toxicity. Set Css_{max} = 30 μg/mL and Css_{min} = 0.1 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 30\ \mu g/mL - \ln 0.1\ \mu g/mL) / 0.351\ h^{-1}] + 1\ h = 17.3\ h$$

Dosage intervals for extended-interval dosing should be rounded to clinically acceptable intervals of 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. Some clinicians prefer to avoid the use of extended-interval dosing beyond a dosage interval of 48 hours because serum concentrations can be below the MIC far beyond the time frame afforded by the postantibiotic effect. For these situations, they revert to conventional dosing for the patient. In this case, the patient's dosage interval will be rounded to 24 hours. Because of this, the steady-state trough concentration

would be expected to fall below 0.1 μg/mL. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max}k_eV[(1 - e^{-k_e\tau}) / (1 - e^{-k_et'})]$$

$$k_0 = (30 \text{ mg/L} \cdot 0.351 \text{ h}^{-1} \cdot 19.8 \text{ L})\{[1 - e^{-(0.351 \text{ h}^{-1})(24 \text{ h})}] / [1 - e^{-(0.351 \text{ h}^{-1})(1 \text{ h})}]\} = 704 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 10–50 mg for extended-interval dosing. This dose would be rounded to 700 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 700 mg every 24 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e\tau}) = 700 \text{ mg} / [1 - e^{-(0.351 \text{ h}^{-1})(24 \text{ h})}] = 700 \text{ mg}$$

As noted, this loading dose is about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 2 hours, the patient should be at steady state after the first dose is given.

Example 5 JM is an 80-year-old, 80-kg (5 ft 8 in) male with Streptococcus viridans endocarditis. His current serum creatinine is 1.5 mg/dL, and it has been stable. Ampicillin and gentamicin will be used to treat the infection. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {$IBW_{males} = 50 + 2.3(Ht - 60 \text{ in}) = 50 + 2.3(68 - 60) = 68$ kg; % overweight = [100(80 kg − 68 kg)] / 68 kg = 18%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 80 \text{ y})80 \text{ kg}] / (72 \cdot 1.5 \text{ mg/dL})$$

$$CrCl_{est} = 44 \text{ mL/min.}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(44 \text{ mL/min}) + 0.014 = 0.143 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.143 \text{ h}^{-1} = 4.8 \text{ h}$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26 \text{ L/kg } (80 \text{ kg}) = 20.8 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

S. viridans endocarditis patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 3–5 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 4 μg/mL and Css_{min} = 1 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 4 \text{ μg/mL} - \ln 1 \text{ μg/mL}) / 0.143 \text{ h}^{-1}] + 1 \text{ h} = 11 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (4 \text{ mg/L} \cdot 0.143 \text{ h}^{-1} \cdot 20.8 \text{ L})\{[1 - e^{-(0.143 \text{ h}^{-1})(12 \text{ h})}] / [1 - e^{-(0.143 \text{ h}^{-1})(1 \text{ h})}]\} = 73 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 70 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 70 mg every 12 hours.

Because the patient is receiving concurrent treatment with ampicillin, care would be taken to avoid *in vitro* inactivation in blood sample tubes intended for the determination of aminoglycoside serum concentrations.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 70 \text{ mg} / [1 - e^{-(0.143 \text{ h}^{-1})(12 \text{ h})}] = 85 \text{ mg}$$

The loading dose would be given as the first dose. The next dose would be a maintenance dose given a dosage interval away from the loading dose, in this case 12 hours later.

Example 6 Same patient profile as in example 2, but extended-interval dosing is used.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(25\ mL/min) + 0.014 = 0.087\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.087\ h^{-1} = 8\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26\ L/kg\ (70\ kg) = 18.2\ L$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) >20 μg/mL; steady-state trough (Css_{min}) concentrations should be <1 μg/mL to avoid toxicity. Set Css_{max} = 20 μg/mL and Css_{min} = 0.5 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] = (\ln 20\ \mu g/mL - \ln 0.5\ \mu g/mL) / 0.087\ h^{-1} = 42\ h$$

Dosage intervals for extended-interval dosing should be rounded to clinically acceptable intervals of 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. Some clinicians prefer to avoid the use of extended-interval dosing beyond a dosage interval of 48 hours because serum concentrations can be below the MIC far beyond the time frame afforded by the postantibiotic effect. For these situations, they revert to conventional dosing for the patient. In this case, the dosage interval would be rounded to 48 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose (D) could be administered either way.

$$D = Css_{max}\ V(1 - e^{-k_e\tau})$$

$$D = 20\ mg/L \cdot 18.2\ L[1 - e^{-(0.087\ h^{-1})(48\ h)}] = 358\ mg$$

For extended-interval dosing, aminoglycoside doses should be rounded to the nearest 10–50 mg. This dose would be rounded to 350 mg. (Note: μg/mL = mg/L and this

concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 350 mg every 48 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\, V = 20 \text{ mg/L} \cdot 18.2 \text{ L} = 364 \text{ mg}$$

As noted, this loading dose is about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 8 hours, the patient should be at steady state after the first dose is given.

Example 7 DQ is a 20-year-old, 61-kg (height = 5 ft 8 in) male with a pulmonary exacerbation due to cystic fibrosis. His current serum creatinine is 0.7 mg/dL and is stable. Compute a tobramycin dose for this patient using extended-interval dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 20 \text{ y})61 \text{ kg}] / (72 \cdot 0.7 \text{ mg/dL})$$

$$CrCl_{est} = 145 \text{ mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(145 \text{ mL/min}) + 0.014 = 0.439 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.439 \text{ h}^{-1} = 1.6 \text{ h}$$

4. *Estimate volume of distribution (V).*

The patient has cystic fibrosis, so the volume of distribution equals 0.35 L/kg:

$$V = 0.35 \text{ L/kg } (61 \text{ kg}) = 21.4 \text{ L}$$

5. *Choose desired steady-state serum concentrations.*

Cystic fibrosis patients treated with extended-interval aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 20–30 μg/mL; steady-state trough (Css_{min}) concentrations should be <1 μg/mL to avoid toxicity. Set Css_{max} = 30 μg/mL and Css_{min} = 0.01 μg/mL.

6. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 30\ \mu g/mL - \ln 0.01\ \mu g/mL) / 0.439\ h^{-1}] + 1\ h = 19.2\ h$$

Dosage intervals for extended-interval dosing should be rounded to clinically acceptable intervals of 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. Some clinicians prefer to avoid the use of extended-interval dosing beyond a dosage interval of 48 hours because serum concentrations can be below the MIC far beyond the time frame afforded by the postantibiotic effect. For these situations, they revert to conventional dosing for the patient. In this case, the patient's dosage interval will be rounded to 24 hours. Because of this, the steady-state trough concentration would be expected to fall below 0.01 µg/mL. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (30\ mg/L \cdot 0.439\ h^{-1} \cdot 21.4\ L)\{[1 - e^{-(0.439\ h^{-1})(24\ h)}] / [1 - e^{-(0.439\ h^{-1})(1\ h)}]\} = 793\ mg$$

Aminoglycoside doses should be rounded to the nearest 10–50 mg for extended-interval dosing. This dose would be rounded to 800 mg. (Note: µg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 800 mg every 24 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 800\ mg / (1 - e^{-(0.439\ h^{-1})(24\ h)}) = 800\ mg$$

As noted, this loading dose is about 10% greater than the maintenance dose and wouldn't be given to the patient. Since the expected half-life is 1.6 hours, the patient should be at steady state after the first dose is given.

Hull and Sarubbi Nomogram Method

For patients who do not have disease states or conditions that alter volume of distribution, the only two patient-specific factors that change when using the pharmacokinetic dosing method is patient weight and creatinine clearance. Because of this, it is possible to make a simple nomogram to handle uncomplicated patients with a standard volume of distribution (Table 4-3). The Hull and Sarubbi aminoglycoside dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations.[45,46] With a simple modification, it can also be used for obese

TABLE 4-3 Aminoglycoside Dosage Chart (Adapted from Sarubbi and Hull[45])

1. Compute patient's creatinine clearance (CrCl) using Cockcroft-Gault method: CrCl = [(140 − age)BW] / ($S_{Cr} \times 72$). Multiply by 0.85 for females. Use Salazar-Cocoran method if weight >30% above IBW.
2. Use patient's weight if within 30% of IBW, otherwise use adjusted dosing weight = IBW + [0.40(TBW − IBW)]
3. Select loading dose in mg/kg to provide peak serum concentrations in range listed below for the desired aminoglycoside antibiotic:

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM CONCENTRATIONS
Tobramycin Gentamicin Netilmicin	1.5–2.0 mg/kg	4–10 µg/mL
Amikacin Kanamycin	5.0–7.5 mg/kg	15–30 µg/mL

4. Select maintenance dose (as percentage of loading dose) to continue peak serum concentrations indicated above according to desired dosage interval and the patient's creatinine clearance. To maintain usual peak/trough ratio, use dosage intervals in clear areas.

Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (mL/min)	EST. HALF-LIFE (HOURS)	8 HOURS (%)	12 HOURS (%)	24 HOURS (%)
>90	2–3	90	–	–
90	3.1	84	–	–
80	3.4	80	91	–
70	3.9	76	88	–
60	4.5	71	84	–
50	5.3	65	79	–
40	6.5	57	72	92
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7*	25.9	19	28	47
5*	31.5	16	23	41
2*	46.8	11	16	30
0*	69.3	8	11	21

*Dosing for patients with CrCl ≤10 mL/min should be assisted by measuring serum concentrations.

patients. If the patient is ≥30% above ideal body weight, an adjusted body weight (ABW) can be calculated and used as the weight factor [ABW (in kg) = IBW + 0.4(TBW − IBW), where IBW is ideal body weight in kilograms and TBW is actual total body weight in kilograms].[55–57] As can be seen, this equation is derived from the computation for volume of distribution in obese patients. Also, the Salazar and Corcoran method of estimating creatinine clearance in obese patients should be used to compute renal function in these individuals.[94–97]

Steady-state peak concentrations are selected as discussed in the pharmacokinetic dosing method section and used to determine a loading dose from the nomogram (Table 4-3). Logically, lower loading doses produce lower expected peak concentrations, and higher loading doses result in higher expected peak concentrations. Once the loading dose is found the patient's creatinine clearance is used to estimate the half-life, dosage interval, and maintenance dose (as a percent of the administered loading dose). The maintenance dose supplied by the nomogram is the percent of the loading dose that was eliminated during the different dosage interval time frames, and will, therefore, provide the same estimated peak concentration at steady state as that supplied by the loading dose. To illustrate how the nomogram is used, the same conventional-dosing patient examples utilized in the previous section will be repeated for this dosage approach using the same example number. Since the nomogram uses slightly different estimates for volume of distribution and elimination rate constant, some minor differences in suggested doses are expected. Because the cystic fibrosis example requires a different volume of distribution (0.35 L/kg), the Hull and Sarubbi nomogram cannot be used.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 µg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

$$LD = 2\ mg/kg(70\ kg) = 140\ mg$$

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 2–3 hours, the maintenance dose (MD) is 90% of the loading dose [MD = 0.90(140 mg) = 126 mg], and the dosage interval is 8 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 125 mg every 8 hours.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 µg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

$$LD = 2\ mg/kg(70\ kg) = 140\ mg$$

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 9.9 hours, the maintenance dose (MD) is 81% of the loading dose [MD = 0.81(140 mg) = 113 mg], and the dosage interval is 24 hours. Note: Because of the $Cmax_{ss}$ and $Cmin_{ss}$ chosen for this patient, the 24-hour dosage interval was used.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 115 mg every 24 hours.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$\mathrm{CrCl_{est(females)}} = \frac{(146 - 35\ \mathrm{y})\{(0.287 \cdot 150\ \mathrm{kg}) + [9.74 \cdot (1.65\ \mathrm{m})^2]\}}{(60 \cdot 1.1\ \mathrm{mg/dL})} = 117\ \mathrm{mL/min}$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Choose desired steady-state serum concentrations.*

Intraabdominal infection patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 5–7 μg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 1.7 mg/kg will provide a peak concentration of 5–7 μg/mL.

Because the patient is obese, adjusted body weight (ABW) will be used to compute the dose:

$$\mathrm{ABW} = \mathrm{IBW} + 0.4(\mathrm{TBW} - \mathrm{IBW}) = 57\ \mathrm{kg} + 0.4(150\ \mathrm{kg} - 57\ \mathrm{kg}) = 94\ \mathrm{kg}$$

$$\mathrm{LD} = 1.7\ \mathrm{mg/kg}(94\ \mathrm{kg}) = 160\ \mathrm{mg}$$

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 2–3 hours, the maintenance dose (MD) is 90% of the loading dose [MD = 0.90(160 mg) = 144 mg], and the dosage interval is 8 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 145 mg every 8 hours.

Example 5 JM is an 80-year-old, 80-kg (5 ft 8 in) male with S. viridans endocarditis. His current serum creatinine is 1.5 mg/dL, and it has been stable. Ampicillin and gentamicin will be used to treat the infection. Compute a gentamicin dose for this patient using conventional dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {$\mathrm{IBW_{males}} = 50 + 2.3(\mathrm{Ht} - 60\ \mathrm{in}) = 50 + 2.3(68 - 60) = 68$ kg; % overweight = [100(80 kg − 68 kg)] / 68 kg = 18%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\mathrm{CrCl_{est}} = [(140 - \mathrm{age})\mathrm{BW}] / (72 \cdot \mathrm{S_{Cr}}) = [(140 - 80\ \mathrm{y})80\ \mathrm{kg}] / (72 \cdot 1.5\ \mathrm{mg/dL})$$

$$\mathrm{CrCl_{est}} = 44\ \mathrm{mL/min}$$

2. *Choose desired steady-state serum concentrations.*

S. viridans endocarditis patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 3–5 μg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 1.5 mg/kg will provide a peak concentration of 5–7 μg/mL. This is the lowest dose suggested by the nomogram and will be used in this example. However, some clinicians may substitute a loading dose of 1–1.2 mg/kg designed to produce a steady-state peak concentration equal to 3–4 μg/mL.

LD = 1.5 mg/kg(80 kg) = 120 mg or LD =1.2 mg/kg (80 kg) = 96 mg, rounded to 95 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 6.5 hours, suggesting that a 12-dosage interval is appropriate. The maintenance dose (MD) is 72% of the loading dose [MD = 0.72(120 mg) = 86 mg or MD = 0.72(95 mg) = 68 mg], and the dosage interval is 12 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 85 mg every 12 hours or 70 mg every 12 hours, depending on the loading dose chosen.

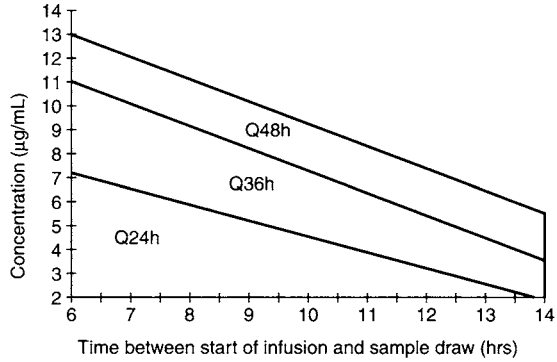
Because the patient is receiving concurrent treatment with ampicillin, care would be taken to avoid *in vitro* inactivation in blood sample tubes intended for the determination of aminoglycoside serum concentrations.

Hartford Nomogram Method for Extended-Interval Dosing

Extended-interval dosing is now a mainstream method used to administer aminoglycoside antibiotics. Conventional dosing is still preferred for endocarditis patients because the aminoglycoside is usually used for antibiotic synergy. Extended-interval doses obtained from the literature for patients with normal renal function are 4–7 mg/kg/d for gentamicin, tobramycin, or netilmicin and 11–20 mg/kg/d for amikacin.[3,19–26,33–38] The most widely used extended-interval aminoglycoside dosage nomogram for patients with renal dysfunction is the Hartford nomogram which uses a 7-mg/kg dose (Table 4-4).[3] Because the nomogram is essentially the concentration-time graph for gentamicin after a single dose of 7 mg/kg, it cannot be used for other dosage rates. The initial dose is 7 mg/kg of gentamicin (although it has not been tested with netilmicin, because of the pharmacokinetic similarity among the antibiotics it should be possible to use this aminoglycoside as well). The dosage interval is set according to the patient's creatinine clearance (Table 4-4).

The Hartford nomogram includes a method to adjust doses based on gentamicin serum concentrations. This portion of the nomogram contains average serum concentration/time lines for gentamicin in patients with creatinine clearances of 60 mL/min, 40 mL/min, and 20 mL/min. A gentamicin serum concentration is measured 6–14 hours after the first dose is given, and this concentration/time point is plotted on the graph (Table 4-4). The suggested dosage interval is indicated by which zone the serum concentration/time point falls in. To illustrate how the nomogram is used, the same patient examples utilized in the pharmacokinetic dosing section will be repeated for this dosage approach using the same example number. Because the cystic fibrosis example requires a different volume of

TABLE 4-4 Hartford Nomogram for Extended-Interval Aminoglycosides (Adapted from Nicolau, et al[3])



ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

1. Administer 7-mg/kg gentamicin with initial dosage interval:

ESTIMATED CrCl	INITIAL DOSAGE INTERVAL
≥60 mL/min	q24 h
40–59 mL/min	q36 h
20–39 mL/min	q48 h
<20 mL/min	monitor serial concentrations and administer next dose when <1 µg/mL

2. Obtain timed serum concentration, 6–14 hours after dose (ideally first dose).
3. Alter dosage interval to that indicated by the nomogram zone (above q48 h zone, monitor serial concentrations, and administer next dose when <1 µg/mL).

distribution (0.35 L/kg) and extended-interval dosing has not been adequately tested in patients with endocarditis, the Hartford nomogram should not be used in these situations.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using extended-interval dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Compute initial dose and dosage interval (Table 4-4).*

A dose (D) of 7 mg/kg will provide a peak concentration >20 µg/mL.

$$D = 7\ mg/kg(70\ kg) = 490\ mg$$

Dosage interval would be 24 hours using the nomogram. Extended-interval aminoglycoside doses should be rounded to the nearest 10–50 mg.

The prescribed maintenance dose would be 500 mg every 24 hours.

3. *Determine dosage interval using serum concentration monitoring.*

A gentamicin serum concentration measured 10 hours after the dose equals 3 μg/mL. Based on the nomogram, a dosage interval of 24 hours is the correct value and does not need to be altered.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Compute initial dose and dosage interval (Table 4-4).*

A dose (D) of 7 mg/kg will provide a peak concentration >20 μg/mL.

$$D = 7\ mg/kg(70\ kg) = 490\ mg$$

Dosage interval would be 48 hours using the nomogram. Extended-interval aminoglycoside doses should be rounded to the nearest 10–50 mg.

The prescribed maintenance dose would be 500 mg every 48 hours.

3. *Determine dosage interval using serum concentration monitoring.*

A gentamicin serum concentration measured 13 hours after the dose equals 9 μg/mL. Based on the nomogram, a dosage interval of 48 hours is too short and serial concentrations should be monitored. When the gentamicin serum concentration is <1 μg/mL, the next dose can be given. Based on the patient's estimated elimination rate constant [$k_e = 0.00293(CrCl) + 0.014 = 0.00293(25\ mL/min) + 0.014 = 0.087\ h^{-1}$; $t_{1/2} = 0.693/k_e = 0.693 / 0.087\ h^{-1} = 8\ h$], it will take approximately 3–4 half-lives or about an additional 24–32 hours after the gentamicin serum concentration for the value to drop below 1 μg/mL.

Some clinicians prefer to avoid the use of extended-interval dosing beyond a dosage interval of 48 hours because serum aminoglycoside concentrations can be below the MIC far beyond the time frame afforded by the postantibiotic effect. For these situations, they revert to conventional dosing for the patient.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using extended-interval dosing.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Compute initial dose and dosage interval (Table 4-4).*

A dose (D) of 7 mg/kg will provide a peak concentration >20 μg/mL. Because the patient is obese, adjusted body weight (ABW) will be used to compute the dose: ABW = IBW + 0.4(TBW − IBW) = 57 kg + 0.4(150 kg − 57 kg) = 94 kg.

$$D = 7\ mg/kg(94\ kg) = 658\ mg$$

Dosage interval would be 24 hours using the nomogram. Extended-interval aminoglycoside doses should be rounded to the nearest 10–50 mg.

The prescribed maintenance dose would be 650 mg every 24 hours.

3. *Determine dosage interval using serum concentration monitoring.*

A gentamicin serum concentration measured 8 hours after the dose equals 4 μg/mL. Based on the nomogram, a dosage interval of 24 hours is the correct value and does not need to be altered.

Assuming linear pharmacokinetics, clinicians have begun to use the Hartford nomogram for doses other than 7 mg/kg. Because this approach has not been formally evaluated, extreme care should be exercised when using this approach. For example, if the clinical situation warrants it, a dose of 5 mg/kg could be administered to a patient, the initial dosage intervals suggested in the Hartford nomogram used, and a serum concentration measured to confirm the dosage interval. Assuming linear pharmacokinetics, the critical concentrations for changing dosage intervals on the Hartford nomogram graph would be decreased to $^5/_7$ (the ratio of the 5 mg/kg dose administered to the 7 mg/kg dose suggested by the nomogram). Additionally, a similar nomogram for gentamicin or tobramycin doses of 5 mg/kg is also available.[98,99]

Literature-Based Recommended Dosing

Because of the large amount of variability in aminoglycoside pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard aminoglycoside doses for pediatric patients is warranted. The original computation of these doses was based on the pharmacokinetic dosing methods described

in the previous section, and subsequently modified based on clinical experience. In general, the expected aminoglycoside steady-state serum concentrations used to compute these doses were similar to those for adults given conventional dosing. Suggested initial aminoglycoside doses for various pediatric patients are listed in the *Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing* section. Doses for neonates that are below 10 mg are usually rounded to the nearest tenth of a milligram. If serum creatinine values are available, estimated creatinine clearance can be computed using equations that are specific for pediatric patients [age 0–1 year, $CrCl_{est}$ (in mL/min/1.73 m^2) = (0.45 · Ht) / S_{Cr}; age 1–20 years, $CrCl_{est}$ (in mL/min/1.73 m^2) = (0.55 · Ht) / S_{Cr}, where Ht is in cm and S_{Cr} is in mg/dL].[100]

Example 1 MM is a 3-day-old, 1015-g male with suspected neonatal sepsis. His serum creatinine has not been measured, but it is assumed that it is typical for his age and weight. Compute an initial gentamicin dose for this patient.

1. *Compute initial dose and dosage interval.*

Often, serum creatinine measurements are not available for initial dosage computation in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatrics dosage recommendations given in earlier in the chapter, a patient in this age and weight category should receive gentamicin 2.5 mg/kg every 18–24 hours. Because the patient is in the lower end of the age range, it is likely he has lower renal function due to poor organ maturation. Based on this information, the longer dosage interval will be chosen. (Note: Grams will be converted to kilograms before the computation is made.)

$$\text{Dose} = 2.5 \text{ mg/kg}(1.015 \text{ kg}) = 2.5 \text{ mg}$$

The prescribed dose would be 2.5 mg every 24 hours.

USE OF AMINOGLYCOSIDE SERUM CONCENTRATIONS TO ALTER DOSAGES

Because of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce aminoglycoside serum concentrations that are expected. Because of this, aminoglycoside serum concentrations are measured in many patients to ensure that therapeutic, nontoxic levels are present. However, not all patients may require serum concentration monitoring. For example, if it is expected that only a limited number of doses will be administered as is the case for surgical prophylaxis or an appropriate dose for the renal function and concurrent disease states of the patient is prescribed (e.g., 1 mg/kg every 8 hours for 3–5 days in a patient with a creatinine clearance of 80–120 mL/min for antibiotic synergy in the treatment of methicillin-sensitive *Staphylococcus aureus* aortic or mitral valve endocarditis), aminoglycoside serum concentration monitoring may not be necessary. Whether or not aminoglycoside concentrations are measured, important patient parameters (fever curves, white blood cell counts, serum creatinine concentrations, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When aminoglycoside serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change aminoglycoside doses since these antibiotics follow *linear pharmacokinetics*. Sometimes, it is not possible to simply change the dose, and the dosage interval must also be changed to achieve desired serum concentrations. In this case, it may be possible to use *pharmacokinetic concepts* to alter the aminoglycoside dose that the patient needs. In some situations, it may be necessary to compute the aminoglycoside pharmacokinetic parameters for the patient using the *Sawchuk-Zaske method* and utilize these to calculate the best drug dose. Some clinicians advocate using individualized *area under the concentration-time curve* determinations to individualize aminoglycoside doses. Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured.

Linear Pharmacokinetics Method

Because aminoglycoside antibiotics follow linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or $D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state peak or trough concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and it may not be possible to attain desired serum concentrations by only changing the dose.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 170 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 9 μg/mL and 1 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 1.4 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(97\ mL/min) + 0.014 = 0.298\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.298\ h^{-1} = 2.3\ h$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (9\ \mu g/mL / 12\ \mu g/mL)\ 170\ mg = 128\ mg, \text{ round to } 130\ mg$$

The new suggested dose would be 130 mg every 8 hours to be started at next scheduled dosing time.

4. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (130\ mg / 170\ mg)\ 1.4\ \mu g/mL = 1.1\ \mu g/mL$$

This steady-state trough concentration should be safe and effective for the infection that is being treated.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. A tobramycin dose of 165 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 6 μg/mL and 0.5 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 4 μg/mL and <0.5 μg/mL (e.g., below assay limits), respectively. Calculate a new tobramycin dose that would provide a steady-state peak of 6 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(\text{CrCl}) + 0.014 = 0.00293(117 \text{ mL/min}) + 0.014 = 0.357 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.357 \text{ h}^{-1} = 1.9 \text{ h}$$

Because the patient has been receiving tobramycin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (6 \text{ μg/mL} / 4 \text{ μg/mL}) 165 \text{ mg} = 247 \text{ mg, round to 250 mg}$$

The new suggested dose would be 250 mg every 8 hours to be started at next scheduled dosing time.

4. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration. However, in this situation the trough concentration is below assay limits and was reported as <0.5 μg/mL. Because of this, the maximum value that the steady-state trough could possibly be is 0.5 μg/mL, and this value can be used to compute a rough approximation of the expected concentration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (250 \text{ mg} / 165 \text{ mg}) 0.5 \text{ μg/mL} = 0.8 \text{ μg/mL}$$

Thus, the steady-state trough concentration should be no greater than 0.8 μg/mL. This steady-state trough concentration should be safe and effective for the infection that is being treated.

Example 3 QZ is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 3 days since admission. A gentamicin dose of 550 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and <1 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 37 μg/mL and 1 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 30 μg/mL and a steady-state trough <1μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{est} = [(140 - \text{age})\text{BW}] / (72 \cdot S_{Cr}) = [(140 - 50 \text{ y})70 \text{ kg}] / (72 \cdot 0.9 \text{ mg/dL})$$

$$\text{CrCl}_{est} = 97 \text{ mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(97\ mL/min) + 0.014 = 0.298\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.298\ h^{-1} = 2.3\ h$$

Because the patient has been receiving gentamicin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (30\ \mu g/mL / 37\ \mu g/mL)\ 550\ mg = 446\ mg, \text{ round to } 450\ mg$$

The new suggested dose would be 450 mg every 24 hours to be started at next scheduled dosing time.

4. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (450\ mg / 550\ mg)\ 1\ \mu g/mL = 0.8\ \mu g/mL$$

This steady-state trough concentration should be safe and effective for the infection that is being treated.

Pharmacokinetic Concepts Method

As implied by the name, this technique derives alternate doses by estimating actual pharmacokinetic parameters or surrogates for pharmacokinetic parameters.[101] It is a very useful way to calculate drug doses when the linear pharmacokinetic method is not sufficient because a dosage change that will produce a proportional change in steady-state peak and trough concentrations is not appropriate. The only requirement is a steady-state peak and trough aminoglycoside serum concentration pair obtained before and after a dose (Figure 4-5). The following steps are used to compute new aminoglycoside doses:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-5).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-5).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life*. For example, a patient receives a gentamicin dose of 80 mg given every 8 hours that produces a steady-state peak equal to 7 μg/mL and a steady-state trough equal to 3.2 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-5). The time between the measured steady-state peak and the extrapolated trough concentration is

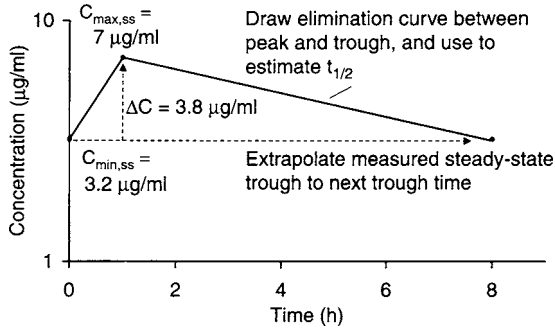


FIGURE 4-5 Graphical representation of the Pharmacokinetic Concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize aminoglycoside therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

7 hours (the 8-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. Because the serum concentration declined by approximately half from the peak concentration to the trough concentration, the aminoglycoside half-life for this patient is approximately 7 hours. This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example, the patient is receiving a gentamicin dose equal to 80 mg every 8 hours which produced steady-state peak and trough concentrations of 7 μg/mL and 3.2 μg/mL, respectively. The difference between the peak and trough values is 3.8 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 7 μg/mL and 1 μg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* In this example, the patient currently has the desired peak concentration of 7 μg/mL. In 1 half-life, the serum concentration will decline to 3.5 μg/mL, in an additional half-life the gentamicin concentration will decrease to 1.8 μg/mL, and in 1 more half-life the concentration will decline to 0.9 μg/mL (Figure 4-6). Since the approximate half-life is 7 hours and 3 half-lives are required for serum concentrations to decrease from the desired peak concentration to the desired trough concentration, the dosage interval should be 21 hours (7 hours × 3 half-lives). This value would be rounded off to the clinically acceptable value of 24 hours, and the actual trough concentration would be expected to be slightly lower than 0.9 μg/mL.

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 7 μg/mL, and the expected trough concentration is 0.9 μg/mL. The change in

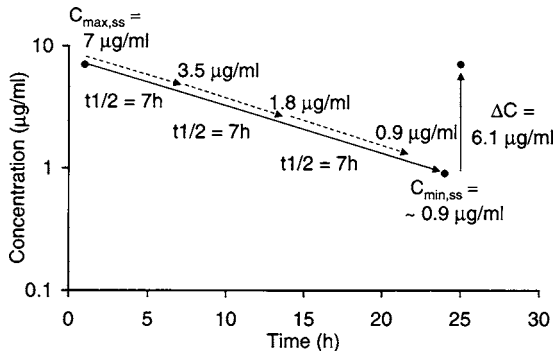


FIGURE 4-6 The Pharmacokinetic Concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

concentration between these values is 6.1 µg/mL. It is known from measured serum concentrations that administration of 80 mg changes serum concentrations by 3.8 µg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. Therefore, a simple ratio will be used to compute the required dose: $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old}$, where D_{new} and D_{old} are the new and old doses, respectively; ΔC_{new} is the change in concentration between the peak and trough for the new dose; and ΔC_{old} is the change in concentration between the peak and trough for the old dose. (Note: This relationship is appropriate because doses are given into a fixed, constant volume of distribution; it is not because the drug follows linear pharmacokinetics so this method will work whether the agent follows nonlinear or linear pharmacokinetics.) For this example: D_{new} = (6.1 µg/mL / 3.8 µg/mL) 80 mg = 128 mg, which would be rounded to 130 mg. Gentamicin 130 mg every 24 hours would be started 24 hours after the last dose of the previous dosage regimen.

Once this method is mastered, it can be used without the need for a calculator. The following are examples that use the Pharmacokinetic Concepts method to change aminoglycoside doses.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 115 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 µg/mL and <2 µg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 µg/mL and 3.5 µg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 µg/mL and a trough of <2 µg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(25\ mL/min) + 0.014 = 0.087\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.087\ h^{-1} = 8\ h$$

Because the patient has been receiving gentamicin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Pharmacokinetic Concepts method to compute a new dose.*

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-7).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-7).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving a gentamicin dose of 115 mg given every 24 hours that produces a steady-state peak equal to 12 μg/mL and a steady-state trough equal to 3.5 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-7). The time between the measured steady-state peak and the extrapolated trough concentration is 23 hours (the 24-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 12 μg/mL to 6 μg/mL, and an additional half-life for the serum concentration to decrease from 6 μg/mL to 3 μg/mL. The concentration of 3 μg/mL is very close to the extrapolated

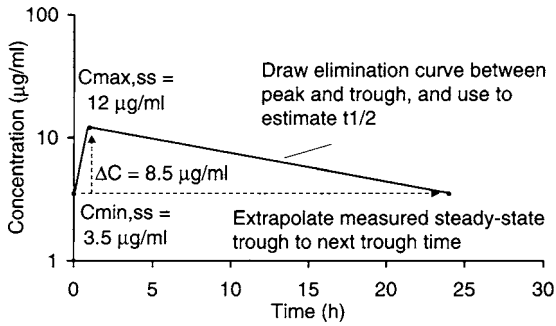


FIGURE 4-7 Graphical representation of the Pharmacokinetic Concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize aminoglycoside therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

trough value of 3.5 µg/mL. Therefore, 2 half-lives expired during the 23-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 12 hours (23 hours / 2 half-lives = ~12 hours). This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example, the patient is receiving a gentamicin dose equal to 115 mg every 24 hours which produced steady-state peak and trough concentrations of 12 µg/mL and 3.5 µg/mL, respectively. The difference between the peak and trough values is 8.5 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 9 µg/mL and <2 µg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations (Figure 4-8).* Using the desired concentrations, it will take 1 half-life for the peak concentration of 9 µg/mL to decrease to 4.5 µg/mL, 1 more half-life for the serum concentration to decrease to 2.3 µg/mL, and an additional half-life for serum concentrations to decline to 1.2 µg/mL. Therefore, the dosage interval will need to be approximately 3 half-lives or 36 hours (12 hours × 3 half-lives = 36 hours). When a dosage interval such as 36 hours is used, care must be taken that the scheduled doses are actually administered as the drug will only be given every other day and sometimes this type of administration schedule is overlooked and doses are missed.

7. *Determine the new dose for the desired concentrations (Figure 4-8).* The desired peak concentration is 9 µg/mL, and the expected trough concentration is 1.2 µg/mL. The change in concentration between these values is 7.8 µg/mL. It is known from measured serum concentrations that administration of 115 mg changes serum concentrations by 8.5 µg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old} =$

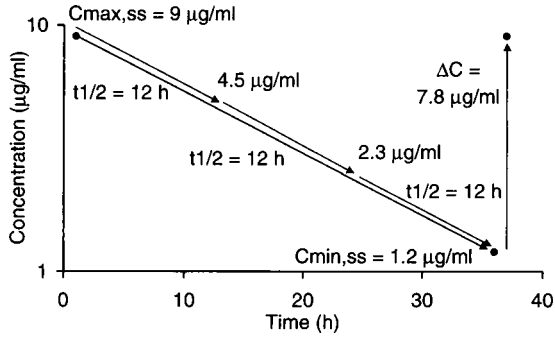


FIGURE 4-8 The Pharmacokinetic Concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

(7.8 μg/mL / 8.5 μg/mL) 115 mg = 105 mg. Gentamicin 105 mg every 36 hours would be started 36 hours after the last dose of the previous dosage regimen.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. A tobramycin dose of 165 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 6 μg/mL and 0.5 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 5 μg/mL and 2.6 μg/mL, respectively. Calculate a new tobramycin dose that would provide a steady-state peak of 6 μg/mL and a steady-state trough ≤1 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the tobramycin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(117\ mL/min) + 0.014 = 0.357\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.357\ h^{-1} = 1.9\ h$$

Because the patient has been receiving tobramycin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Pharmacokinetic Concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-9).

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-9).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving a tobramycin dose of 165 mg given every 8 hours that produces a steady state peak equal to 5 μg/mL and a steady-state trough equal to 2.6 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-9). The time between the measured steady-state peak and the extrapolated trough concentration is 7 hours

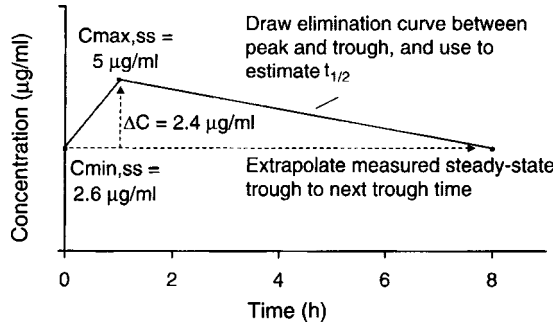


FIGURE 4-9 Graphical representation of the Pharmacokinetic Concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize aminoglycoside therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

(the 8-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 5 µg/mL to 2.5 µg/mL. The concentration of 2.6 µg/mL is very close to the extrapolated trough value of 2.5 µg/mL. Therefore, 1 half-life expired during the 7-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 7 hours. This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example the patient is receiving a tobramycin dose equal to 165 mg every 8 hours which produced steady-state peak and trough concentrations of 5 µg/mL and 2.6 µg/mL, respectively. The difference between the peak and trough values is 2.4 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 6 µg/mL and ≤1 µg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations. Using the desired concentrations, it will take 1 half-life for the peak concentration of 6 µg/mL to decrease to 3 µg/mL, 1 more half-life for the serum concentration to decrease to 1.5 µg/mL, and an additional half-life for serum concentrations to decline to 0.8 µg/mL. Therefore, the dosage interval will need to be approximately 3 half-lives or 21 hours (7 hours × 3 half-lives = 21 hours) which would be rounded to 24 hours.

G. Determine the new dose for the desired concentrations. The desired peak concentration is 6 µg/mL, and the expected trough concentration is 0.8 µg/mL. The change in concentration between these values is 5.2 µg/mL. It is known from measured serum concentrations that administration of 165 mg changes serum concentrations by 2.4 µg/mL

and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old} = (5.2\ \mu g/mL / 2.4\ \mu g/mL)\ 165\ mg = 358\ mg$, rounded to 360 mg. Tobramycin 360 mg every 24 hours would be started 24 hours after the last dose of the previous dosage regimen.

Sawchuk-Zaske Method

The Sawchuk-Zaske method of adjusting aminoglycoside doses was among the first techniques available to change doses using serum concentrations.[2,47–49,92] It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose to achieve desired aminoglycoside concentrations. The standard Sawchuk-Zaske method conducts a small pharmacokinetic experiment using 3–4 aminoglycoside serum concentrations obtained during a dosage interval and does not require steady-state conditions. The modified Sawchuk-Zaske methods assume that steady state has been achieved and require only a pair of steady-state concentrations obtained during a dosage interval. The Sawchuk-Zaske method has also been successfully used to dose vancomycin and theophylline.

STANDARD SAWCHUK-ZASKE METHOD

The standard version of the Sawchuk-Zaske method does not require steady-state concentrations. A trough aminoglycoside concentration is obtained before a dose, a peak aminoglycoside concentration is obtained after the dose is infused (immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion), and 1–2 additional postdose serum aminoglycoside concentrations are obtained (Figure 4-10). Ideally, the 1–2 postdose concentrations should be obtained at least 1 estimated half-life from each other to minimize the influence of assay error. The postdose serum concentrations are used to calculate the aminoglycoside elimination rate constant and half-life (Figure 4-10). The half-life can be computed by graphing the postdose concentrations on semilogarithmic paper, drawing the best straight line through the data points, and determining the time needed for serum concentrations to decline by one-half. Once the half-life is known, the elimination rate constant (k_e) can be computed: $k_e = 0.693/t_{1/2}$. Alternatively, the elimination rate constant can be

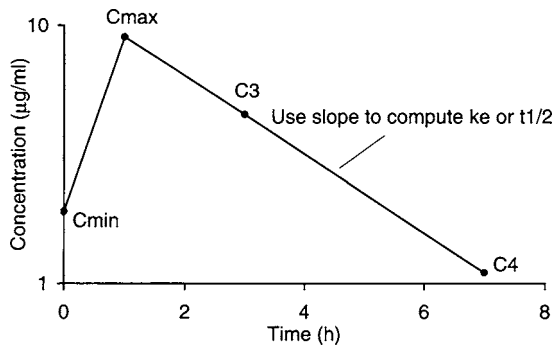


FIGURE 4-10 The Sawchuk-Zaske method for individualization of aminoglycoside doses uses a trough (C_{min}), peak (C_{max}), and 1–2 additional postdose concentrations (C_3, C_4) to compute a patient's own, unique pharmacokinetic parameters. This version of the Sawchuk-Zaske method does not require steady-state conditions. The peak and trough concentrations are used to calculate the volume of distribution, and the postdose concentrations (C_{max}, C_3, C_4) are used to compute half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired aminoglycoside concentrations.

directly calculated using the postdose serum concentrations [$k_e = (\ln C_1 - \ln C_2) / \Delta t$, where C_1 and C_2 are postdose serum concentrations and Δt is the time that expired between the times that C_1 and C_2 were obtained), and the half-life can be computed using the elimination rate constant ($t_{1/2} = 0.693 / k_e$). The volume of distribution (V) is calculated using the following equation

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{min} e^{-k_e t'})]}$$

where D is the aminoglycoside dose, t' is the infusion time, k_e is the elimination rate constant, C_{max} is the peak concentration and C_{min} is the trough concentration. The elimination rate constant and volume of distribution measured in this fashion are the patient's own, unique aminoglycoside pharmacokinetic constants and can be used in one-compartment model intravenous infusion equations to compute the required dose to achieve any desired serum concentration.

STEADY-STATE SAWCHUK-ZASKE METHOD: PEAK/TROUGH VERSION

If a steady-state peak and trough aminoglycoside concentration pair is available for a patient, the Sawchuk-Zaske method can be used to compute patient pharmacokinetic parameters and aminoglycoside doses (Figure 4-11). Since the patient is at steady state, the measured trough concentration obtained before the dose was given can be extrapolated to the next dosage time and used to compute the aminoglycoside elimination rate constant [$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t'$, where Css_{max} and Css_{min} are the steady-state peak and trough serum concentrations and t' and τ are the infusion time and dosage interval], and the half-life can be computed using the elimination rate constant ($t_{1/2} = 0.693 / k_e$). The volume of distribution (V) is calculated using the following equation:

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]}$$

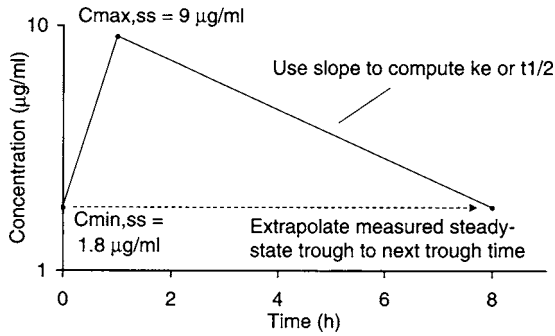


FIGURE 4-11 The steady-state peak/trough version of the Sawchuk-Zaske method uses a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair to individualize aminoglycoside therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The steady-state peak and trough concentrations are used to calculate the volume of distribution and half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired aminoglycoside concentrations.

where D is the aminoglycoside dose, t′ is the infusion time, k_e is the elimination rate constant, Css_{max} is the steady-state peak concentration, and Css_{min} is the steady-state trough concentration. The elimination rate constant and volume of distribution measured in this way are the patient's own, unique aminoglycoside pharmacokinetic constants and can be used in one-compartment model intravenous infusion equations to compute the required dose to achieve any desired serum concentration. The dosage calculations are similar to those done in the initial dosage section of this chapter, except that the patient's real pharmacokinetic parameters are used in the equations instead of population pharmacokinetic estimates.

STEADY-STATE SAWCHUK-ZASKE METHOD: TWO POSTDOSE CONCENTRATIONS VERSION

Sometimes, steady-state trough concentrations will be below the assay limit or it is not possible to measure a predose concentration. Trough concentrations that are too low to accurately measure occur commonly during therapy with extended-interval aminoglycoside dosing. In these cases, it may be preferable to measure two postdose steady-state concentrations and use these to compute values that can be used in the Sawchuk-Zaske method (Figure 4-12).

The two postdose steady-state concentrations should be drawn at least one estimated half-life apart in order to minimize the effect of assay error on the calculations. While one of the two steady-state concentrations can be a peak concentration, it is not a requirement. During extended-interval dosing, some patients may have longer distribution phases so many clinicians suggest that the first postdose be obtained several hours after the completion of the infusion for this method of administration. The second postdose concentration

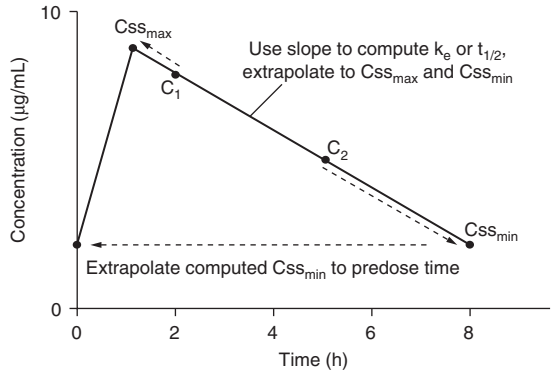


FIGURE 4-12 The steady-state two postdose concentration version of the Sawchuk-Zaske method uses two postdose concentrations (C_1 and C_2) to individualize aminoglycoside therapy. Once the concentrations are obtained, they are extrapolated either mathematically or graphically to determine steady-state peak (Css_{max}) and trough (Css_{min}) values. The elimination rate constant is calculated using the measured concentrations: $k_e = (\ln C_1 - \ln C_2) / \Delta t$, where C_1 and C_2 are the first and second steady-state postdose concentrations and Δt is the time that expired between the two concentrations. Steady-state peak and trough concentrations are calculated using the following equations: $Css_{max} = C_1 / (e^{-k_e t})$, where C_1 is the first measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_1 and Css_{max}; $Css_{min} = C_2 e^{-k_e t}$, where C_2 is the second measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_2 and Css_{min}.

should be drawn early enough in the dosage interval so that it is not below assay limits (typically no later than 14–16 hours postdose during extended-interval or 4–6-hours postdose during conventional dosing for patients with CrCl > 60 mL/min).

Once the concentrations are obtained, they are extrapolated either mathematically or graphically (Figure 4-12) to determine peak and trough values. The elimination rate constant is calculated using the measured concentrations: $k_e = (\ln C_1 - \ln C_2)/\Delta t$, where C_1 and C_2 are the first and second steady-state postdose concentrations and Δt is the time that expired between the two concentrations. If one of the concentrations is a peak concentration, it is unnecessary to extrapolate it, and only the trough concentration needs to be computed. However, if neither concentration is a peak, both steady-state peak and trough concentrations need to be calculated: $Css_{max} = C_1 / (e^{-k_e t})$, where C_1 is the first measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_1 and Css_{max}; $Css_{min} = C_2 e^{-k_e t}$, where C_2 is the second measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_2 and Css_{min}.

The volume of distribution (V) is calculated using the following equation:

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]}$$

where D is the aminoglycoside dose, t' is the infusion time, k_e is the elimination rate constant, Css_{max} is the steady-state peak concentration, and Css_{min} is the steady-state trough concentration. The elimination rate constant and volume of distribution measured in this fashion are the patient's own, unique aminoglycoside pharmacokinetic constants and can be used in one-compartment model intravenous infusion equations to compute the required dose to achieve any desired serum concentration. The dosage calculations are similar to those done in the initial dosage section of this chapter, except that the patient's real pharmacokinetic parameters are used in the equations instead of population pharmacokinetic estimates.

To illustrate the similarities and differences between the Pharmacokinetic Concepts and the Sawchuk-Zaske methods, some of the same cases used in the previous section will be used as examples here.

Example 1 JH is a 24-year-old, 70-kg (6 ft 0 in) male with gram-negative pneumonia. His current serum creatinine is 1.0 mg/dL, and it has been stable over the last 7 days since admission. An amikacin dose of 400 mg every 8 hours was prescribed. After the third dose, the following amikacin serum concentrations were obtained:

TIME	AMIKACIN CONCENTRATION (μg/mL)
0800 H	2.0
0800–0900 H	Amikacin 400 mg
0900 H	22.1
1100 H	11.9
1600 H	2.5

Medication administration sheets were checked, and the previous dose was given 2 hours early (2200 H the previous day). Because of this, it is known that the patient is not at steady state. Calculate a new amikacin dose that would provide a steady-state peak of 28 μg/mL and a trough between 3 μg/mL.

Use Sawchuk-Zaske method to compute a new dose.

1. *Plot serum concentration/time data (Figure 4-13). Because serum concentrations decrease in a straight line, use any two postdose concentrations to compute the patient's elimination rate constant and half-life.*

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 22.1\ \mu g/mL - \ln 2.5\ \mu g/mL) / (16\ H - 09\ H)$$
$$= 0.311\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.311\ h^{-1} = 2.2\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(400\ mg/1h)[1 - e^{-(0.311\ h^{-1})(1\ h)}]}{0.311\ h^{-1}\{22.1\ mg/L - [2.0\ mg/L\ e^{-(0.311\ h^{-1})(1\ h)}]\}}$$

$$V = 16.7\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 28 μg/mL and 3 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 28\ \mu g/mL - \ln 3\ \mu g/mL) / 0.311\ h^{-1}] + 1\ h = 8\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

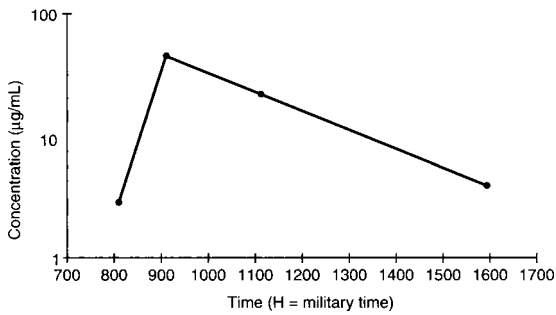


FIGURE 4-13 Graph of amikacin serum concentrations used in Sawchuk-Zaske method example.

$$k_0 = (28 \text{ mg/L} \cdot 0.311 \text{ h}^{-1} \cdot 16.7 \text{ L})\{[1 - e^{-(0.311 \text{ h}^{-1})(8 \text{ h})}] / [1 - e^{-(0.311 \text{ h}^{-1})(1 \text{ h})}]\}$$
$$= 499 \text{ mg, rounded to } 500 \text{ mg}$$

A dose of amikacin 500 mg every 8 hours would be prescribed to begin 8 hours after the last dose of the previous regimen.

Example 2 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 115 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 μg/mL and <2 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 3.5 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL and a trough <2 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est}} = [(140 - \text{age})\text{BW}] / (72 \cdot S_{\text{Cr}}) = [(140 - 50 \text{ y})70 \text{ kg}] / (72 \cdot 3.5 \text{ mg/dL})$$

$$\text{CrCl}_{\text{est}} = 25 \text{ mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(\text{CrCl}) + 0.014 = 0.00293(25 \text{ mL/min}) + 0.014 = 0.087 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.087 \text{ h}^{-1} = 8 \text{ h}$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln \text{Css}_{\text{max}} - \ln \text{Css}_{\text{min}}) / \tau - t' = (\ln 12 \text{ μg/mL} - \ln 3.5 \text{ μg/mL}) / (24 \text{ h} - 1 \text{ h}) = 0.054 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.054 \text{ h}^{-1} = 12.8 \text{ h}$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[\text{Css}_{\text{max}} - (\text{Css}_{\text{min}} e^{-k_e t'})]} = \frac{(115 \text{ mg/1h})[1 - e^{-(0.054 \text{ h}^{-1})(1 \text{ h})}]}{0.054 \text{ h}^{-1}\{12 \text{ mg/L} - [3.5 \text{ mg/L } e^{-(0.054 \text{h}^{-1})(1 \text{ h})}]\}}$$

$$V = 12.9 \text{ L}$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 9 μg/mL and 1.5 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t'):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 9\ \mu g/mL - \ln 1.5\ \mu g/mL) / 0.054\ h^{-1}] + 1\ h$$

$$= 34\ h, \text{ rounded to } 36\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (9\ mg/L \cdot 0.054\ h^{-1} \cdot 12.9\ L)\{[1 - e^{-(0.054\ h^{-1})(36\ h)}] / [1 - e^{-(0.054\ h^{-1})(1\ h)}]\}$$
$$= 102\ mg, \text{ rounded to } 100\ mg$$

A dose of gentamicin 100 mg every 36 hours would be prescribed to begin 36 hours after the last dose of the previous regimen. This dose is very similar to that derived for the patient using the Pharmacokinetic Concepts method (105 mg every 36 hours).

Example 3 ZW is a 35–year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. A tobramycin dose of 165 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 6 µg/mL and 0.5 µg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 5 µg/mL and 2.6 µg/mL, respectively. Calculate a new tobramycin dose that would provide a steady-state peak of 6 µg/mL and a steady-state trough ≤1µg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese ($IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg). The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the tobramycin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(117\ mL/min) + 0.014 = 0.357\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.357\ h^{-1} = 1.9\ h$$

Because the patient has been receiving tobramycin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t' = (\ln 5\ \mu g/mL - \ln 2.6\ \mu g/mL) / (8\ h - 1\ h) = 0.093\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.093\ h^{-1} = 7.5\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(165\ mg/1\ h)[1 - e^{-(0.093\ h^{-1})(1\ h)}]}{0.093\ h^{-1}\{5\ mg/L - [2.6\ mg/L\ e^{-(0.093\ h^{-1})(1\ h)}]\}}$$

$$V = 59.9\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 6 μg/mL and 0.8 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 6\ \mu g/mL - \ln 0.8\ \mu g/mL) / 0.093\ h^{-1}] + 1\ h$$
$$= 23\ h, \text{ rounded to } 24\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.093\ h^{-1} \cdot 59.9\ L)\{[1 - e^{-(0.093\ h^{-1})(24\ h)}] / [1 - e^{-(0.093\ h^{-1})(1\ h)}]\}$$
$$= 336\ mg, \text{ rounded to } 335\ mg$$

A dose of gentamicin 335 mg every 24 hours would be prescribed to begin 24 hours after the last dose of the previous regimen. This dose is very similar to that derived for the patient using the Pharmacokinetic Concepts method (360 mg every 24 hours).

Example 4 PL is a 52-year-old, 67-kg (5 ft 6 in) female with neutropenia and gram-negative sepsis. Her current serum creatinine is 1.5 mg/dL, and it has been stable over the last 5 days. A gentamicin dose of 110 mg every 12 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 μg/mL and <2 μg/mL, respectively. After the third dose, steady-state concentrations were measured and were 3.8 μg/mL 1 hour after the end of a 1-hour infusion and 1.6 μg/mL 4 hours after the first concentration. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL and a trough <2 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]0.85\} / (72 \cdot S_{Cr}) = \{[(140 - 52\ y)67\ kg]0.85\} / (72 \cdot 1.5\ mg/dL)$$

$$CrCl_{est} = 46\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(46\ mL/min) + 0.014 = 0.149\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.149\ h^{-1} = 4.7\ h$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

1. *Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 3.8\ \mu g/mL - \ln 1.6\ \mu g/mL) / (4\ h) = 0.216\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.216\ h^{-1} = 3.2\ h$$

2. *Extrapolate measured concentrations to steady-state peak and trough values.*

$$Css_{max} = C_1 / (e^{-k_e t}) = (3.8\ \mu g/mL) / [e^{-(0.216\ h^{-1})(1\ h)}] = 4.7\ \mu g/mL$$

$$Css_{min} = C_2 e^{-k_e t} = (1.6\ \mu g/mL)[e^{-(0.216\ h^{-1})(6\ h)}] = 0.4\ \mu g/mL$$

3. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(110\ mg/1\ h)[1 - e^{-(0.216\ h^{-1})(1\ h)}]}{0.216\ h^{-1}\{4.7\ mg/L - [0.4\ mg/L\ e^{-(0.216\ h^{-1})(1\ h)}]\}}$$

$$V = 22.6\ L$$

4. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 9 μg/mL and 1.5 μg/mL, respectively.

5. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 9\ \mu g/mL - \ln 1.5\ \mu g/mL) / 0.216\ h^{-1}] + 1\ h$$
$$= 9.3\ h, \text{ rounded to } 8\ h$$

6. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (9 \text{ mg/L} \cdot 0.216 \text{ h}^{-1} \cdot 22.6 \text{ L})\{[1 - e^{-(0.216 \text{ h}^{-1})(8 \text{ h})}] / [1 - e^{-(0.216 \text{ h}^{-1})(1 \text{ h})}]\}$$
$$= 186 \text{ mg, rounded to } 185 \text{ mg}$$

A dose of gentamicin 185 mg every 8 hours would be prescribed to begin approximately 8 hours after the last dose of the current regimen.

Example 5 KE is a 67-year-old, 81-kg (5 ft 11 in) male with a hepatic abcess. His current serum creatinine is 1.9 mg/dL, and it has been stable over the last 5 days. A gentamicin dose of 400 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 20 μg/mL and <1 μg/mL, respectively. After the third dose, steady-state concentrations were measured and were 17.5 μg/mL 2 hours after the end of a 1-hour infusion and 4.8 μg/mL 16 hours after the end of infusion. Calculate a new gentamicin dose that would provide a steady-state peak of 20 μg/mL and a trough <1 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 67 \text{ y}) 81 \text{ kg}] / (72 \cdot 1.9 \text{ mg/dL})$$

$$CrCl_{est} = 43 \text{ mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(43 \text{ mL/min}) + 0.014 = 0.140 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.140 \text{ h}^{-1} = 5.0 \text{ h}$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

1. *Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 17.5 \text{ μg/mL} - \ln 4.8 \text{ μg/mL}) / (14 \text{ h}) = 0.092 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.092 \text{ h}^{-1} = 7.5 \text{ h}$$

2. *Extrapolate measured concentrations to steady-state peak and trough values.*

$$Css_{max} = C_1 / (e^{-k_e t}) = (17.5 \text{ μg/mL}) / [e^{-(0.092 \text{ h}^{-1})(2 \text{ h})}] = 21.0 \text{ μg/mL}$$

$$Css_{min} = C_2 e^{-k_e t} = (4.8 \text{ μg/mL})[e^{-(0.092 \text{ h}^{-1})(7 \text{ h})}] = 2.5 \text{ μg/mL}$$

3. *Compute the patient's volume of distribution*

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(400 \text{ mg}/1 \text{ h})[1 - e^{-(0.092 \text{ h}^{-1})(1 \text{ h})}]}{0.092 \text{ h}^{-1}\{21 \text{ mg/L} - [2.5 \text{ mg/L } e^{-(0.092 \text{ h}^{-1})(1 \text{ h})}]\}}$$

$V = 20.4$ L

4. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 20 μg/mL and 0.5 μg/mL, respectively.

5. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 20 \text{ μg/mL} - \ln 0.5 \text{ μg/mL}) / 0.092 \text{ h}^{-1}] + 1 \text{ h}$
$= 41$ h, rounded to 36 h

6. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$k_0 = (20 \text{ mg/L} \cdot 0.092 \text{ h}^{-1} \cdot 20.4 \text{ L})\{[1 - e^{-(0.092 \text{ h}^{-1})(36 \text{ h})}] / [1 - e^{-(0.092 \text{ h}^{-1})(1 \text{ h})}]\}$
$= 411$ mg, rounded to 400 mg

A dose of gentamicin 400 mg every 36 hours would be prescribed to begin approximately 12 hours after the last dose of the current regimen.

Area Under the Curve Method

Area under the concentration-time curve (AUC) is the best measurement of total exposure to a drug, and some clinicians recommend adjustment of aminoglycoside doses so that target steady-state AUC values are achieved instead of altering doses to attain target steady state peak and trough concentrations. Most often, the AUC method is used with extended-interval aminoglycoside dosing. Different therapeutic AUC values have been suggested by various investigations studying this dosing method. A target AUC equal to 70–120 (mg · h)/L for gentamicin or tobramycin will be used in examples and problems for this section (approximately: 5 mg/kg ≈ 72 (mg · h)/L, 6 mg/kg ≈ 86 (mg · h)/L, and 7 mg/kg ≈ 101 (mg · h)/L for patients with normal renal function).[21,23,102–104] Steady-state peak and trough concentrations should also be evaluated when a dosage change is made to assure they are in the appropriate range.

To make use of this approach, the patient is started on an appropriate dose of extended-interval gentamicin or tobramycin. Typical doses of 5–7 mg/kg/d are used as an initial dose, with the dosage interval determined by renal function.[3,99] After steady state has been achieved, two postdose serum concentrations are drawn. The two concentrations should be drawn at least one estimated half-life apart in order to minimize the effect of assay error on the calculations. While one of the two steady-state concentrations can be a peak concentration, it is not a requirement. During extended-interval dosing, some patients may have longer distribution phases so many clinicians suggest that the

first postdose concentration be obtained several hours after the completion of the infusion. The second postdose concentration should be drawn early enough in the dosage interval so that it is not below assay limits (typically no later than 14–16 hours post dose for patients with CrCl > 60 mL/min).

Once the concentrations are obtained, they are extrapolated either mathematically or graphically (Figure 4-14) to determine steady-state peak and trough values. The elimination rate constant is calculated using the measured concentrations: $k_e = (\ln C_1 - \ln C_2) / \Delta t$, where C_1 and C_2 are the first and second steady-state postdose concentrations and Δt is the time that expired between the two concentrations. If one of the concentrations is a peak concentration, it is unnecessary to extrapolate it, and only the trough concentration needs to be computed. However, if neither concentration is a peak, both steady-state peak and trough concentrations need to be calculated: $Css_{max} = C_1 / (e^{-k_e t})$, where C_1 is the first measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_1 and Css_{max}; $Css_{min} = C_2 e^{-k_e t}$, where C_2 is the second measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_2 and Css_{min}.

The steady-state area under the concentration-time curve during the dosage interval (AUC_{ss}) is computed using the following equation:[21,23,102–104]

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{C_{max,ss} - C_{min,ss}}{k_e} \right)$$

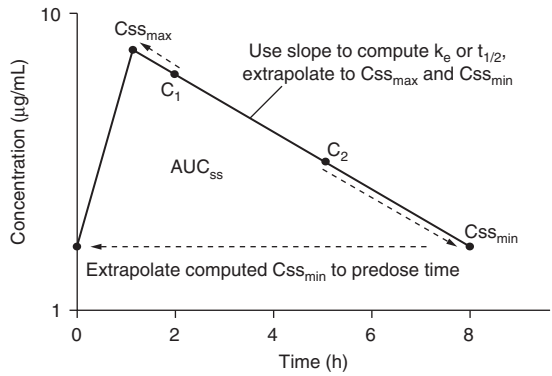


FIGURE 4-14 The Area Under the Curve (AUC) method uses two postdose concentrations (C_1 and C_2) to individualize aminoglycoside therapy. Once the concentrations are obtained, they are extrapolated either mathematically or graphically to determine steady-state peak and trough values. The elimination rate constant is calculated using the measured concentrations: $k_e = (\ln C_1 - \ln C_2) / \Delta t$, where C_1 and C_2 are the first and second steady-state postdose concentrations and Δt is the time that expired between the two concentrations. Steady-state peak and trough concentrations are calculated using the following equations: $Css_{max} = C_1 / (e^{-k_e t})$, where C_1 is the first measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_1 and Css_{max}; $Css_{min} = C_2 e^{-k_e t}$, where C_2 is the second measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_2 and Css_{min}. The steady-state area under the concentration-time curve during the dosage interval (AUC_{ss}) is computed using the following equation:

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{Css_{max} - Css_{min}}{k_e} \right)$$

The dose is adjusted to attain the target AUC_{ss} using linear pharmacokinetics: $D_{new} = (AUC_{ss,new} / AUC_{ss,old})D_{old}$, where D_{new} denotes the new computed dose and D_{old} the original dose, and $AUC_{ss,new}$ and $AUC_{ss,old}$ are the new target AUC_{ss} and the old original AUC_{ss}, respectively. Once the new dose has been determined, Css_{max} and Css_{min} should be calculated to ensure their values are also appropriate for the infection that is being treated: $C_{ss,new} = (D_{new} / D_{old})C_{ss,old}$, where D_{new} denotes the new computed dose and D_{old} the original dose, and $C_{ss,new}$ and $C_{ss,old}$ are the new target C_{ss} and the old original C_{ss}, respectively. This calculation is repeated separately for both Css_{max} and Css_{min}.

Example 1 KE is a 23-year-old, 59-kg (5 ft 4 in) female with salpingitis. Her current serum creatinine is 0.6 mg/dL, and it has been stable over the last 3 days. A gentamicin dose of 250 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 25 μg/mL and <1 μg/mL, respectively. After the third dose, steady-state concentrations were measured and equaled 9.6 μg/mL 2 hours after the end of a 1-hour infusion and 2.6 μg/mL 6 hours after the end of infusion. Calculate a new gentamicin dose that would provide a steady-state AUC of 81 (mg · h)/L.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]0.85\} / (72 \cdot S_{Cr}) = \{[(140 - 23\ y)59\ kg]0.85\} / (72 \cdot 0.6\ mg/dL)$$

$$CrCl_{est} = 136\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(136\ mL/min) + 0.014 = 0.413\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.413\ h^{-1} = 1.7\ h$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state AUC method to compute a new dose.*

1. *Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t' is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 9.6\ \mu g/mL - \ln 2.6\ \mu g/mL) / (4\ h) = 0.327\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.327\ h^{-1} = 2.1\ h$$

2. *Extrapolate measured concentrations to steady-state peak and trough values.*

$$Css_{max} = C_1 / (e^{-k_e t}) = (9.6\ \mu g/mL) / [e^{-(0.327\ h^{-1})(2\ h)}] = 18.5\ \mu g/mL$$

$$Css_{min} = C_2 e^{-k_e t} = (2.6\ \mu g/mL)[e^{-(0.327\ h^{-1})(17\ h)}] = 0.01\ \mu g/mL$$

3. *Compute the patient's AUC_{ss} (Note: mg/L = μg/mL and this substitution was made to aid the calculation).*

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{Css_{max} - Css_{min}}{k_e} \right)$$

$$AUC_{ss} = \frac{18.5 \text{ mg/L} - 0.01 \text{ mg/L}}{0.327 \text{ h}^{-1}} + \left(0.065 \cdot \frac{18.5 \text{ mg/L} - 0.01 \text{ mg/L}}{0.327 \text{ h}^{-1}} \right)$$

$$AUC_{ss} = 60.2 \text{ (mg} \cdot \text{h)/L}$$

4. *Choose new target AUC_{ss}.* For the purposes of this example, a desired steady state of AUC of 81 (mg · h)/L was chosen.

5. *Determine the new dose for the desired AUC_{ss}.*

$D_{new} = (AUC_{ss,new}/AUC_{ss,old})D_{old} = \{[81 \text{ (mg} \cdot \text{h)/L}] / [60.2 \text{ (mg} \cdot \text{h)/L}]\}250 \text{ mg}$
$= 336$ mg, rounded to 350 mg

6. *Determine the new steady-state peak and trough concentrations.*

$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (350 \text{ mg} / 250 \text{ mg})\ 18.5 \text{ μg/mL} = 25.9 \text{ μg/mL}$ for the peak

$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (350 \text{ mg} / 250 \text{ mg})\ 0.01 \text{ μg/mL} = 0.01 \text{ μg/mL}$ for the trough

These steady-state peak and trough concentrations are acceptable for the infection being treated and the new prescribed dose would be 350 mg every 24 hours.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[105–109] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, renal function, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be

used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. When only a limited number of aminoglycoside concentrations are available, Bayesian pharmacokinetic computer programs can be used to compute a complete patient pharmacokinetic profile that includes clearance, volume of distribution, and half-life. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[110]

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 170 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 9 μg/mL and 1 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 1.4 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL and steady-state trough of 1 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 13.5 L, a half-life equal to 2.1 h, and an elimination rate constant of 0.326 h^{-1}.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 135 mg every 8 hours will produce a steady-state peak concentration of 9.2 μg/mL and a steady-state trough concentration of 0.9 μg/mL. Using the simpler linear pharmacokinetics method previously described in the chapter, a similar dose of 140 mg every 8 hours was computed.

Example 2 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 115 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 μg/mL and <2 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 3.5 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL and a steady-state trough equal to 1.5 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 14.6 L, a half-life equal to 14.7 h, and an elimination rate constant of 0.047 h^{-1}. These values are slightly different than those computed using the Steady-state Sawchuk-Zaske method (V = 12.9 L, $t_{1/2}$ = 12.8 h, k_e = 0.054 h^{-1}) because the patient probably was not at steady state when the serum concentrations were drawn.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 110 mg every 36 hours will produce a steady-state peak concentration of 9 μg/mL and a steady-state trough concentration of 1.7 μg/mL. Using the Steady-state Sawchuk-Zaske and Pharmacokinetic Concepts methods previously described in the chapter, similar doses of 100 mg every 36 hours and 105 mg every 36 hours, respectively, were computed.

Example 3 JH is a 24-year-old, 70-kg (6 ft 0 in) male with gram-negative pneumonia. His current serum creatinine is 1.0 mg/dL, and it has been stable over the last 7 days since admission. An amikacin dose of 400 mg every 8 hours was prescribed. After the third dose, the following amikacin serum concentrations were obtained:

TIME	AMIKACIN CONCENTRATION (μg/mL)
0800 H	2.0
0800–0900 H	Amikacin 400 mg
0900 H	22.1
1100 H	11.9
1600 H	2.5

Medication administration sheets were checked, and the previous dose was given 2 hours early (2200 H the previous day). Because of this, it is known that the patient is not at steady state. Calculate a new amikacin dose that would provide a steady-state peak of 28 μg/mL and a trough between 3–5 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 17.1 L, a half-life equal to 2.4 h, and an elimination rate constant of 0.292 h^{-1}. These values are similar to those computed using the Sawchuk-Zaske method (V = 17.0 L, $t_{1/2}$ = 2.2 h, k_e = 0.311 h^{-1}).

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 500 mg every 8 hours will produce a steady-state peak concentration of 28 μg/mL and a steady-state trough concentration of 3.6 μg/mL. Using the Sawchuk-Zaske method previously described in this chapter, the identical dose of 500 mg every 8 hours was computed.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing approaches link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Tables 4-5A and 4-5B.

TABLE 4-5A Conventional Dosing Schemes

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Sawchuk-Zaske method
Nomogram/Pharmacokinetic Concepts	Hull and Sarubbi nomogram (adults) or literature-based recommended dosing (pediatrics)	Pharmacokinetic Concepts method
Computerized	Bayesian computer program	Bayesian computer program

TABLE 4-5B Extended-Interval Dosing Schemes

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Sawchuk-Zaske method or Area Under the Curve method
Nomogram/Concepts	Hartford nomogram	Hartford nomogram (1 concentration) or Pharmacokinetic Concepts method (≥2 concentations)
Computerized	Bayesian computer program	Bayesian computer program

SPECIAL DOSING CONSIDERATIONS

Hemodialysis Dosing

Aminoglycoside antibiotics are eliminated by dialysis, so renal failure patients receiving hemodialysis must have aminoglycoside dosage regimens that take dialysis clearance into account. Hemodialysis and other extracorporeal methods of drug removal are completely discussed in Chapter 3 (Computation of Initial Doses and Modification of Doses Using Drug Serum Concentrations section).

Example 1 A 62-year-old, 65-kg (5 ft 8 in) male who has chronic renal failure, and receives hemodialysis three times weekly with a low-flux dialysis filter. An initial dosage regimen for tobramycin needs to be computed for a patient to achieve peak concentrations of 6–7 mg/L and postdialysis concentrations 1–2 mg/L.

Initial Dosage Determination

1. Patients with renal failure are prone to having poor fluid balance because their kidneys are not able to provide this important function. Because of this, the patient should be assessed for overhydration (due to renal failure) or underhydration (due to renal failure and increased loss due to fever).

> Weight is a good indication of fluid status, and this patient's weight is less than his ideal weight [IBW_{male} = 50 kg + 2.3(Ht − 60 in) = 50 kg + 2.3(68 − 60) = 68 kg]. Other indications of state of hydration (skin turgor, etc.) indicate that the patient has normal fluid balance at this time. Because of this, the average volume of distribution for aminoglycoside antibiotics equal to 0.26 L/kg can be used.

2. A loading dose of tobramycin would be appropriate for this patient because the expected half-life is long (~50 h); administration of maintenance doses only might not result in therapeutic maximum concentrations for a considerable time period while drug accumulation is occurring. The loading dose is to be given after hemodialysis ends at 1300 H on Monday (hemodialysis conducted on Monday, Wednesday, and Friday from 0900 – 1300 H).

> Because the patient is expected to have a long half-life compared to the infusion time of the drug ($^1/_2$ − 1 h), little drug will be eliminated during the infusion period, and IV bolus one-compartment model equations can be used. The loading dose for

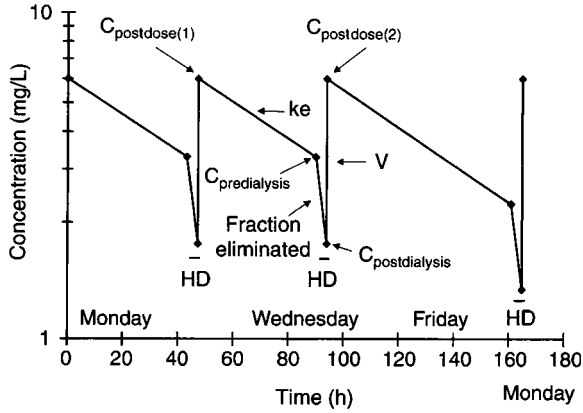


FIGURE 4-15 Concentration/time graph for tobramycin in a hemodialysis patient using estimated, population pharmacokinetic parameters. The initial dose was given postdialysis at 1400H on Monday (time = 0 h). Hemodialysis periods are shown by small horizontal bars labeled with HD, and days are indicated on the time line. In order to compute patient-specific pharmacokinetic parameters, four serum concentrations are measured. The elimination rate constant (k_e) is computed using two concentrations after dosage administration ($C_{postdose(1)}$ and $C_{predialysis}$), the fraction eliminated by dialysis by two concentrations ($C_{predialysis}$ and $C_{postdialysis}$) before and after dialysis, and the volume of distribution using two concentrations ($C_{postdialysis}$ and $C_{postdose(2)}$) after another dosage administration.

this patient would be based on the expected volume of distribution: V = 0.26 L/kg · 65 kg = 16.9 L; LD = C_{max} · V = 6 mg/L · 16.9 L = 101 mg, rounded to 100 mg (LD is loading dose, C_{max} is the maximum concentration after drug administration). This loading dose was given at 1400 H (Figure 4-15).

Until the next dialysis period at 0900 H on Wednesday, tobramycin is cleared only by the patient's own body mechanisms. The expected elimination rate constant (k_e) for a patient with a creatinine clearance of approximately zero is: k_e (in h^{-1}) = 0.00293 · CrCl + 0.014 = 0.00293 (0 mL/min) + 0.014 = 0.014 h^{-1}. The expected concentration at 0900 H on Wednesday is: $C = C_0e^{-k_et}$, where C is the concentration at t hours after the initial concentration of C_0; $C = (6\ mg/L)e^{-(0.014\ h^{-1})(43\ h)}$ = 3.3 mg/L.

3. While the patient is receiving hemodialysis, tobramycin is eliminated by the patient's own mechanisms plus dialysis clearance. During hemodialysis with a low-flux filter, the average half-life for aminoglycosides is 4 hours. Because the patient is dialyzed for 4 hours, the tobramycin serum concentration should decrease by $^1/_2$–1.7 mg/L, or using formal computations: $k_e = 0.693/(t_{1/2}) = 0.693/4\ h = 0.173\ h^{-1}$; $C = C_0e^{-k_et} = (3.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.7\ mg/L$.

At this time, a postdialysis replacement dose could be given to increase the maximum concentration to its original value of 6 mg/L: Replacement dose = (C_{max} – $C_{baseline}$)V = (6 mg/L – 1.7 mg/L)16.9 L = 73 mg, round to 75 mg (where C_{max} is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The

postdialysis replacement dose of 75 mg was administered at 1400 H on Wednesday. Because all time frames and pharmacokinetic parameters are the same for Monday to Wednesday and Wednesday to Friday, the postdialysis replacement dose on Friday at 1400 H would also be 75 mg.

However, more time elapses from Friday after drug administration to Monday before dialysis (67 hours), the next day for hemodialysis to be conducted in the patient and this needs to be accounted for: $C = C_0e^{-k_et} = (6\ mg/L)e^{-(0.014\ h^{-1})(67\ h)} = 2.3\ mg/L$. Again, a 4-hour hemodialysis period would decrease serum concentrations by $^1/_2$ to 1.2 mg/L: $C = C_0e^{-k_et} = (2.3\ mg/L)e^{-(0.173\ h^{-1})(4\ h)} = 1.2\ mg/L$. At this time, a postdialysis replacement dose could be given to increase the maximum concentration to the original value of 6 mg/L: Replacement dose = $(C_{max} - C_{baseline})V = (6\ mg/L - 1.2\ mg/L)16.9\ L = 81\ mg$, round to 80 mg (where C_{max} is the maximum postdose concentration and $C_{baseline}$ is the predose concentration). The postdialysis replacement dose of 80 mg was administered at 1400 H on Monday.

Because all time frames and pharmacokinetic parameters will be the same in subsequent weeks, the following postdialysis replacement doses would be prescribed postdialysis at 1400: Wednesday and Friday 75 mg, Monday 80 mg. In this particular example, recommended daily doses are within 5 mg of each other, and if the clinician wished, the same postdialysis dose could be given on each day. However, this will not be true in every case.

Use of Aminoglycoside Serum Concentrations to Alter Dosages

1. Since the initial dosage scheme outlined for this patient used average, estimated pharmacokinetic parameters, it is likely that the patient has different pharmacokinetic characteristics. It is possible to measure the patient's own unique pharmacokinetic parameters using four serum concentrations (Figure 4-15).

The intradialysis elimination rate constant can be determined by obtaining postdose ($C_{postdose(1)}$) and predialysis ($C_{predialysis}$) concentrations [$k_e = (C_{postdose(1)} - C_{predialysis}) / \Delta t$, where Δt is the time between the two concentrations], the fraction of drug eliminated by dialysis can be computed using predialysis and postdialysis ($C_{postdialysis}$) concentrations (fraction eliminated = $[(C_{predialysis} - C_{postdialysis}) / C_{predialysis}]$, and the volume of distribution can be calculated using postdialysis and postdose concentrations $[V = D / (C_{postdose(2)} - C_{predialysis})]$.

Note that if the drug has a postdialysis "rebound" in drug concentrations, postdialysis serum samples should be obtained after blood and tissue have had the opportunity to reequilibrate. In the case of aminoglycosides, postdialysis samples should be collected no sooner than 3–4 hours after the end of dialysis.

2. Once individualized pharmacokinetic parameters have been measured, they can be used in the same equations used to compute initial doses in the previous section in place of average, population pharmacokinetic parameters and used to calculate individualized doses for dialysis patients. It is also possible to use a mixture of measured and population-estimated pharmacokinetic parameters. For instance, a clinician may wish to measure the elimination rate constant or volume of distribution for a patient, but elect to use an average population estimate for fraction of drug removed by the artificial kidney.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that antibiotic therapy is appropriate for current microbiologic cultures and sensitivities. Also, it should be confirmed that the patient is receiving other appropriate concurrent antibiotic therapy, such as β-lactam or anaerobic agents, when necessary to treat the infection.

1. PQ is a 75-year-old, 62-kg (5 ft 9 in) male with gram-negative sepsis. His current serum creatinine is 1.3 mg/dL, and it has been stable since admission. Compute a gentamicin dose for this patient to provide a steady-state peak concentration of 8 μg/mL and a steady-state trough concentration of 1.5 μg/mL using conventional dosing.
2. Patient PQ (please see problem 1) was prescribed gentamicin 110 mg every 12 hours. Steady-state gentamicin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of gentamicin) was 9.5 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 3.0 μg/mL. Compute a revised gentamicin dose for this patient to provide a steady-state peak concentration of 8 μg/mL and a steady-state trough concentration of 1 μg/mL using conventional dosing.
3. ZW is a 35-year-old, 75-kg (5 ft 7 in) female with gram-negative pneumonia and chronic renal failure. Her current serum creatinine is 3.7 mg/dL, and it has been stable since admission. Compute a gentamicin dose for this patient to provide a steady-state peak concentration of 10 μg/mL and a steady-state trough concentration of 1.0 μg/mL using conventional dosing.
4. Patient ZW (please see problem 3) was prescribed gentamicin 120 mg every 24 hours. Steady-state gentamicin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of gentamicin) was 7 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was <0.5 μg/mL. Compute a revised gentamicin dose for this patient to provide a steady-state peak concentration of 10 μg/mL and a steady-state trough concentration of <2 μg/mL using conventional dosing.
5. JK is a 55-year-old, 140-kg (5 ft 8 in) male with an intraabdominal infection secondary to a knife wound. His current serum creatinine is 0.9 mg/dL, and it has been stable since admission. Compute a gentamicin dose for this patient to provide a steady-state peak concentration of 6 μg/mL and a steady-state trough concentration of 0.5 μg/mL using conventional dosing.
6. Patient JK (please see problem 5) was prescribed gentamicin 120 mg every 8 hours. Steady-state gentamicin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$ hour infusion of gentamicin) was 5.9 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 2.5 μg/mL. Compute a revised gentamicin dose for this patient to provide a steady-state peak concentration of 6 μg/mL and a steady-state trough concentration of <1 μg/mL using conventional dosing.
7. AF is a 45-year-old, 140-kg (5 ft 2 in) female with an S. viridans endocarditits. Her current serum creatinine is 2.4 mg/dL and is stable. Compute a tobramycin dose for

this patient to provide a steady-state peak concentration of 4 μg/mL, and a steady-state trough concentration of 0.5 μg/mL using conventional dosing.

8. Patient AF (please see problem 7) was prescribed tobramycin 100 mg every 12 hours. Steady-state tobramycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of tobramycin) was 6.2 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 1.5 μg/mL. Compute a revised tobramycin dose for this patient to provide a steady-state peak concentration of 4 μg/mL and a steady-state trough concentration of ≤1 μg/mL using conventional dosing.

9. FH is a 24-year-old, 60-kg (5 ft 7 in) male with cystic fibrosis and *Pseudomonas aeruginosa* cultured from a sputum culture. He was hospitalized due to worsening pulmonary function tests. His current serum creatinine is 0.7 mg/dL. Compute a tobramycin dose for this patient to provide a steady-state peak concentration of 10 μg/mL, and a steady-state trough concentration of <2 μg/mL using conventional dosing.

10. Patient FH (please see problem 9) was prescribed tobramycin 250 mg every 8 hours. Steady- state tobramycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of tobramycin) was 7.9 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 1 μg/mL. Compute a revised tobramycin dose for this patient to provide a steady-state peak concentration of 10 μg/mL and a steady-state trough concentration of 1–2 μg/mL using conventional dosing.

11. TY is a 66-year-old, 65-kg (5 ft 5 in) female with a suspected tubo-ovarian abscess secondary to hysterectomy surgery. While in the hospital, she developed ascites due to preexisting liver cirrhosis and her current weight is 72 kg. Her current serum creatinine is 1.4 mg/dL. Compute a gentamicin dose for this patient to provide a steady-state peak concentration of 6 μg/mL, and a steady-state trough concentration of <2 μg/mL using conventional dosing.

12. Patient TY (please see problem 11) was prescribed gentamicin 120 mg every 12 hours. Steady-state gentamicin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of gentamicin) was 4 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 0.8 μg/mL. Compute a revised gentamicin dose for this patient to provide a steady-state peak concentration of 6 μg/mL and a steady-state trough concentration of 1 μg/mL using conventional dosing.

13. UQ is a 27-year-old, 85-kg (6 ft 2 in) male trauma patient with a gram-negative pneumonia and is currently on a respirator. He sustained multiple injuries secondary to a motor vehicle accident 2 weeks ago and lost a large amount of blood at the accident site. He developed acute renal failure due to prolonged hypotension and poor perfusion of his kidneys (current postdialysis serum creatinine is 5.3 mg/dL). He is currently receiving hemodialysis on Mondays, Wednesdays, and Fridays from 0800–1200 H using a low-flux dialysis filter. Recommend a gentamicin dosage regimen that will achieve peak concentrations of 8 μg/mL and postdialysis concentrations of ~2 μg/mL. The first dose of the regimen will be given immediately after hemodialysis is finished on Wednesday at 1200 H.

14. Patient UQ (please see problem 13) was prescribed gentamicin 180 mg loading dose and 130 mg after each dialysis. The following serum concentrations were obtained:

DATE/TIME	DESCRIPTION	CONCENTRATION
Friday at 1200 H	Postdose (130 mg)	6.4 μg/mL
Monday at 0800 H	Predialysis	2.2 μg/mL
Monday at 1300 H	Postdialysis (1 hour after end of dialysis to allow for rebound in serum concentrations)	0.7 μg/mL
Monday at 1400 H	Postdose (130 mg)	6.9 μg/mL

Use these serum concentrations to compute the patient's own pharmacokinetic parameters for gentamicin and a new dosage schedule that will achieve peak concentrations of 8 μg/mL and postdialysis concentrations of <2 μg/mL.

15. LS is a 67-year-old, 60-kg (5 ft 2 in) female with a serum creatinine equal to 1.8 mg/dL placed on tobramycin for a hospital acquired gram-negative pneumonia. The prescribed dose was tobramycin 80 mg every 8 hours (infused over 1 hour) and 2 doses have been given at 0800 and 1600 H. A trough concentration of 2.9 μg/mL was obtained at 1530 H ($^1/_2$ hour before the second dose) and a peak concentration of 5.2 μg/mL was obtained at 1705 H (5 minutes after infusion of the second dose). Compute the dose to give Css_{max} = 8 μg/mL and Css_{min} = 1.5 μg/mL.

16. KK is a 52-year-old, 87-kg (6 ft 2 in) male status post appendectomy who developed a fever, elevated white blood cell count, and abdominal pain 24 hours after surgery. His current serum creatinine is 1.4 mg/dL and stable. (A) Compute an initial extended-interval gentamicin dose for this patient. (B) Nine hours after the second dose of gentamicin 610 mg every 24 hours, a gentamicin serum concentration equal to 8.2 μg/mL is measured. Compute a revised gentamicin dose for this patient to provide steady-state peak concentrations above 20 μg/mL and steady-state trough concentrations below 1 μg/mL.

17. XS is a 45-year-old, 65-kg (5 ft 4 in) female bone marrow transplant recipient who develops a neutropenic fever. Her current serum creatinine is 1.1 mg/dL. She is administered tobramycin 5 mg/kg daily (325 mg) as part of her antibiotic therapy. A tobramycin serum concentration was obtained 5 hours after the first dose and equaled 19 μg/mL. Compute a revised tobramycin dose for this patient to provide steady-state peak concentrations above 25 μg/mL and steady-state trough concentrations below 1 μg/mL.

18. DT is a 3-day-old, 2050-g female with suspected neonatal sepsis. Her serum creatinine has not been measured, but it is assumed that it is typical for her age and weight. Compute an initial tobramycin dose for this patient.

19. Patient DT (please see preceding problem) was prescribed tobramycin 5 mg every 12 hours. Steady-state tobramycin concentrations were obtained, and the peak concentration (obtained $^1/_2$ hour after a $^1/_2$-hour infusion of tobramycin) was 4.5 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 0.9 μg/mL. Compute a revised tobramycin dose for this patient to provide a

steady-state peak concentration of 6 μg/mL and a steady-state trough concentration of 1.5 μg/mL using conventional dosing.

20. UL is a 7-year-old, 24-kg (3 ft 11 in) male with gram-negative sepsis. His serum creatinine is 0.5 mg/dL, and it has been stable for the last 2 days. Compute an initial gentamicin dose for this patient.

21. Patient UL (please see preceding problem) was prescribed gentamicin 60 mg every 8 hours and was expected to achieve steady-state peak and trough concentrations equal to 8 μg/mL and <2 μg/mL, respectively. Steady-state concentrations were measured and were 4.5 μg/mL 1 hour after the end of a 1-hour infusion and 1.5 μg/mL 4 hours after the end of infusion. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL and a trough of 1 μg/mL.

22. RD is a 59-year-old, 79-kg (5 ft 11 in) male with a gram-negative pneumonia. His current serum creatinine is 1.5 mg/dL, and it has been stable over the last 3 days. A gentamicin dose of 450 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and <1 μg/mL, respectively. After the second dose, steady-state concentrations were measured and were 16.1 μg/mL 2 hours after the end of a 1-hour infusion and 2.5 μg/mL 16 hours after the end of infusion. Calculate a new gentamicin dose that would provide a steady-state peak of 30 μg/mL and a trough of <1 μg/mL.

23. KE is a 23-year-old, 67-kg (5 ft 8 in) male with peritonitis. His current serum creatinine is 0.8 mg/dL, and it has been stable over the last 3 days. A tobramycin dose of 350 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 25 μg/mL and <1 μg/mL, respectively. After the second dose, steady-state concentrations were measured and equaled 9.6 μg/mL 2 hours after the end of a 1-hour infusion and 2.6 μg/mL 6 hours after the end of infusion. Calculate a new tobramycin dose that would provide a steady-state AUC of 81 (mg · h)/L.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.* The initial gentamicin dose for patient PQ would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(43\ mL/min) + 0.014 = 0.140\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.140\ h^{-1} = 4.9\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26 \text{ L/kg } (62 \text{ kg}) = 16.1 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative sepsis patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 8 μg/mL and Css_{min} = 1.5 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose.*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 8 \text{ μg/mL} - \ln 1.5 \text{ μg/mL}) / 0.140 \text{ h}^{-1}] + 1 \text{ h}$$
$$= 12.9 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (8 \text{ mg/L} \cdot 0.140 \text{ h}^{-1} \cdot 16.1 \text{ L})\{[1 - e^{-(0.140 \text{ h}^{-1})(12 \text{ h})}] / [1 - e^{-(0.140 \text{ h}^{-1})(1 \text{ h})}]\}$$
$$= 112 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 110 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 110 mg every 12 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 110 \text{ mg} / [1 - e^{-(0.140 \text{ h}^{-1})(12 \text{ h})}] = 135 \text{ mg}$$

The gentamicin dose computed using the Hull and Sarubbi nomogram would be:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Choose desired steady-state serum concentrations.*

Gram-negative sepsis patients treated with gentamicin require steady-state peak concentrations (Css_{max}) equal to 8–10 µg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

$$LD = 2\ mg/kg(62\ kg) = 124\ mg, \text{ rounded to } 125\ mg$$

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 6.5 hours (suggesting that a 12-hour dosage interval is appropriate), the maintenance dose (MD) is 72% of the loading dose [MD = 0.72(125 mg) = 90 mg], and the dosage interval is 12 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 90 mg every 12 hours.

2. *Solution to problem 2.* The revised gentamicin dose for patient PQ using the Pharmacokinetic Concepts method would be calculated as follows:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-16).*

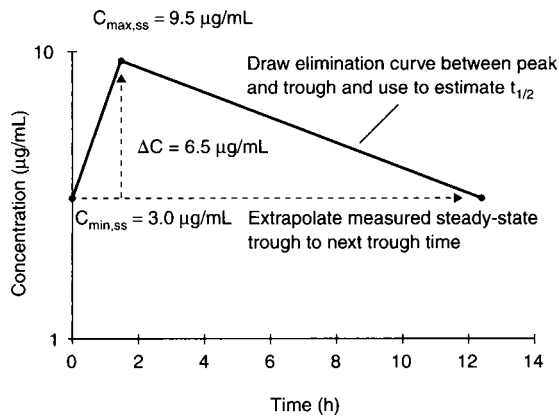


FIGURE 4-16 Solution to problem 2 using Pharmacokinetic Concepts method.

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-16).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving a gentamicin dose of 110 mg given every 12 hours that produces a steady-state peak equal to 9.5 μg/mL and a steady-state trough equal to 3.0 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-16). The time between the measured steady-state peak and the extrapolated trough concentration is 11 hours (the 12-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 9.5 μg/mL to 4.8 μg/mL, and an additional half-life for the serum concentration to decrease from 4.8 μg/mL to 2.4 μg/mL. The concentration of 3.0 μg/mL is close to, but slightly above, the extrapolated trough value of 2.4 μg/mL. Therefore, 1.75 half-lives expired during the 12-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 7 hours (11 hours / 1.75 half-lives = ~7 hours). This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionately with the dose size.* In the current example, the patient is receiving a gentamicin dose equal to 110 mg every 12 hours which produced steady-state peak and trough concentrations of 9.5 μg/mL and 3 μg/mL, respectively. The difference between the peak and trough values is 6.5 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 8 μg/mL and 1 μg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* Using the desired concentrations, it will take 1 half-life for the peak concentration of 8 μg/mL to decrease to 4 μg/mL, 1 more half-life for the serum concentration to decrease to 2 μg/mL, and an additional half-life for serum concentrations to decline to 1 μg/mL. Therefore, the dosage interval will need to be approximately 3 half-lives or 21 hours (7 hours × 3 half-lives = 21 hours). The dosage interval would be rounded to the clinically acceptable value of 24 hours.

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 8 μg/mL, and the expected trough concentration is 1 μg/mL. The change in concentration between these values is 7 μg/mL. It is known from measured serum concentrations that administration of 110 mg changes serum concentrations by 6.5 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} /$

$\Delta C_{old})D_{old}$ = (7 μg/mL / 6.5 μg/mL) 110 mg = 118 mg, rounded to 120 mg. Gentamicin 120 mg every 24 hours would be started 24 hours after the last dose of the previous dosage regimen.

The revised gentamicin dose for patient PQ using the Steady-state Sawchuk-Zaske method would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t' = (\ln 9.5\ \mu g/mL - \ln 3\ \mu g/mL) / (12\ h - 1\ h)$$
$$= 0.105\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.105\ h^{-1} = 6.6\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(110\ mg/1\ h)[1 - e^{-(0.105\ h^{-1})(1\ h)}]}{0.105\ h^{-1}\{9.5\ mg/L - [3\ mg/L\ e^{-(0.105\ h^{-1})(1\ h)}]\}}$$

$$V = 15.4\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 8 μg/mL and 1 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 8\ \mu g/mL - \ln 1\ \mu g/mL) / 0.105\ h^{-1}] + 1\ h$$
$$= 21\ h, \text{ round to } 24\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (8\ mg/L \cdot 0.105\ h^{-1} \cdot 15.4\ L)\{[1 - e^{-(0.105\ h^{-1})(24\ h)}] / [1 - e^{-(0.105\ h^{-1})(1\ h)}]\}$$
$$= 119\ mg, \text{ rounded to } 120\ mg$$

A dose of gentamicin 120 mg every 24 hours would be prescribed to begin 24 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the Pharmacokinetic Concepts method (120 mg every 24 hours).

3. *Solution to problem 3.* The initial gentamicin dose for patient ZW would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85 \\ CrCl_{est} &= 25\ mL/min \end{aligned}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(25\ mL/min) + 0.014 = 0.088\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.088\ h^{-1} = 7.9\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

$$V = 0.26\ L/kg\ (75\ kg) = 19.5\ L$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 10 μg/mL and Css_{min} = 1 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose.*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 10\ \mu g/mL - \ln 1\ \mu g/mL) / 0.088\ h^{-1}] + 1\ h = 27\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 24 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (10\ mg/L \cdot 0.088\ h^{-1} \cdot 19.5\ L)\{[1 - e^{-(0.088\ h^{-1})(24\ h)}] / [1 - e^{-(0.088\ h^{-1})(1\ h)}]\} = 179\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 180 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 180 mg every 24 hours.

6. Compute loading dose (LD), if needed.

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 180 \text{ mg} / [1 - e^{-(0.088 \text{ h}^{-1})(24 \text{ h})}] = 205 \text{ mg}$$

The gentamicin dose computed using the Hull and Sarubbi nomogram would be:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - \text{age})BW] / (72 \cdot S_{Cr})\}0.85$$
$$= \{[(140 - 35 \text{ y})75 \text{ kg}] / (72 \cdot 3.7 \text{ mg/dL})\}0.85$$
$$CrCl_{est} = 25 \text{ mL/min}$$

2. *Choose desired steady-state serum concentrations.*

Gram-negative sepsis patients treated with gentamicin require steady-state peak concentrations (Css_{max}) equal to 8–10 µg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

$$LD = 2 \text{ mg/kg}(75 \text{ kg}) = 150 \text{ mg}$$

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 9.9 hours (suggesting that a 24-hour dosage interval is appropriate), the maintenance dose (MD) is 81% of the loading dose [MD = 0.81(150 mg) = 122 mg], and the dosage interval is 24 hours. Note: 24-hour dosage interval chosen because longer time period is needed for concentration to drop from 10 µg/mL to 1 µg/mL.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 120 mg every 24 hours. Note: 24-hour dosage interval chosen because longer time period needed for concentration to decline from 10 µg/mL to 1µg/mL.

4. *Solution to problem 4.* Compute modified dose for ZW using linear pharmacokinetics:

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (10 \text{ µg/mL} / 7 \text{ µg/mL})\ 120 \text{ mg} = 171 \text{ mg}$, round to 170 mg

The new suggested dose would be 170 mg every 24 hours to be started at next scheduled dosing time.

2. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration. The measured trough concentration was below assay limits (<0.5 μg/mL), so the maximum value it could be is 0.5 μg/mL:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (170 \text{ mg} / 120 \text{ mg})\ 0.5 \text{ μg/mL} = 0.7 \text{ μg/mL}$$

The steady-state trough concentration would be expected to be no greater than 0.7 μg/mL, and should be safe and effective for the infection that is being treated.

5. *Solution to problem 5.* The initial gentamicin dose for patient JK would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3(Ht − 60) = 50 + 2.3(68 in − 60) = 68.4 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - \text{age})[(0.285 \cdot \text{Wt}) + (12.1 \cdot \text{Ht}^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55 \text{ y})\{(0.285 \cdot 140 \text{ kg}) + [12.1 \cdot (1.73 \text{ m})^2]\}}{(51 \cdot 0.9 \text{ mg/dL})} = 136 \text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(\text{CrCl}) + 0.014 = 0.00293(136 \text{ mL/min}) + 0.014 = 0.412 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.412 \text{ h}^{-1} = 1.7 \text{ h}$$

3. *Estimate volume of distribution (V).*

The patient is overweight so the volume of distribution is estimated using the equation that corrects for obesity:

$$V = 0.26 \text{ L/kg [IBW} + 0.4(\text{TBW} - \text{IBW})]$$
$$= 0.26 \text{ L/kg}[68.4 \text{ kg} + 0.4(140 \text{ kg} - 68.4 \text{ kg})] = 25.2 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

Intraabdominal sepsis patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 5–6 μg/mL; steady-state trough

(Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 6 μg/mL and Css_{min} = 0.5 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose.*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$
$$= [(\ln 6\ \mu g/mL - \ln 0.5\ \mu g/mL) / 0.412\ h^{-1}] + 1\ h = 7\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 8 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.412\ h^{-1} \cdot 25.2\ L)\{[1 - e^{-(0.412\ h^{-1})(8\ h)}] / [1 - e^{-(0.412\ h^{-1})(1\ h)}]\} = 178\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 180 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 180 mg every 8 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 180\ mg / [1 - e^{-(0.412\ h^{-1})(8\ h)}] = 187\ mg$$

Because the patient has a short aminoglycoside half-life, the loading dose is similar to the maintenance dose, and the loading dose would be omitted.

The gentamicin dose computed using the Hull and Sarubbi nomogram would be:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese (IBW_{males} (in kg) = 50 + 2.3(Ht − 60) = 50 + 2.3(68 in − 60) = 68.4 kg). The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{(51 \cdot 0.9\ mg/dL)} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Choose desired steady-state serum concentrations.*

Gram-negative sepsis patients treated with gentamicin require steady-state peak concentrations (Css_{max}) equal to 5–6 μg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 1.5 mg/kg will provide a peak concentration of 5–6 μg/mL. The patient is obese, so the patient's adjusted body weight (ABW) will be used as the weight factor in the nomogram.

ABW (in kg) = IBW + 0.4(TBW − IBW) = 68.4 kg + 0.4(140 kg − 68.4 kg) = 97 kg

LD = 1.5 mg/kg (97 kg) = 146 mg, rounded to 145 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is 2–3 hours (suggesting that an 8-hour dosage interval is appropriate), the maintenance dose (MD) is 90% of the loading dose [MD = 0.90(145 mg) = 131 mg], and the dosage interval is 8 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 130 mg every 8 hours.

6. *Solution to problem 6.* The revised gentamicin dose for patient JK using the Pharmacokinetic Concepts method would be calculated as follows:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-17).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-17).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving an gentamicin dose of 120 mg given every 8 hours that produces a steady-state peak equal to 5.9 μg/mL and a steady-state trough equal to 2.5 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-17). The time between the measured steady-state peak and the extrapolated trough concentration is 7 hours (the 8-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 5.9 μg/mL to 3.0 μg/mL, and about

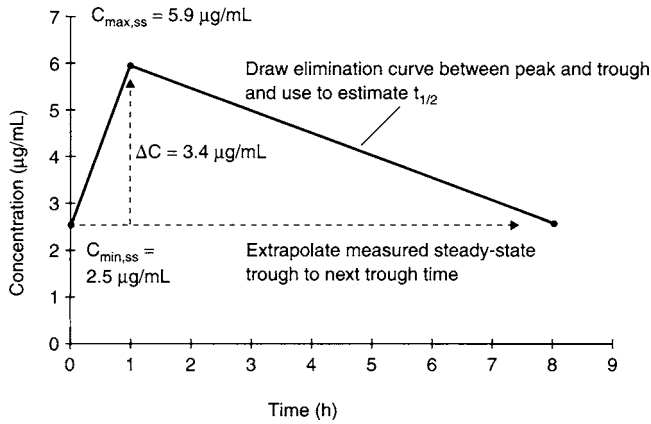


FIGURE 4-17 Solution to Problem 6 using Pharmacokinetic Concepts method.

1/4 of an additional half-life for the serum concentration to decrease from 3.0 µg/mL to 2.5 µg/mL. Therefore, 1.25 half-lives expired during the 7-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 6 hours (7 hours / 1.25 half-lives = ~6 hours). This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionately with the dose size.* In the current example, the patient is receiving a gentamicin dose equal to 120 mg every 8 hours which produced steady-state peak and trough concentrations of 5.9 µg/mL and 2.5 µg/mL, respectively. The difference between the peak and trough values is 3.4 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 6 µg/mL and <1 µg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* Using the desired concentrations, it will take 1 half-life for the peak concentration of 6 µg/mL to decrease to 3 µg/mL, 1 more half-life for the serum concentration to decrease to 1.5 µg/mL, and an additional half-life for serum concentrations to decline to 0.8 µg/mL. Therefore, the dosage interval will need to be approximately 3 half-lives or 18 hours (6 hours × 3 half-lives = 18 hours).

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 6 µg/mL, and the expected trough concentration is 0.8 µg/mL. The change in concentration between these values is 5.2 µg/mL. It is known from measured serum concentrations that administration of 120 mg changes serum concentrations by 3.4 µg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: D_{new} =

$(\Delta C_{new} / \Delta C_{old})D_{old} = (5.2\ \mu g/mL / 3.4\ \mu g/mL)\ 120\ mg = 184\ mg$. Gentamicin 185 mg every 18 hours would be started 18 hours after the last dose of the previous dosage regimen.

The revised gentamicin dose for patient JK using the Steady-state Sawchuk-Zaske method would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t' = (\ln 5.9\ \mu g/mL - \ln 2.5\ \mu g/mL) / (8\ h - 1\ h) = 0.123\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.123\ h^{-1} = 5.6\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(120\ mg/1h)\,[1 - e^{-(0.123\ h^{-1})(1\ h)}]}{0.123\ h^{-1}\{5.9\ mg/L - [2.5\ mg/L\ e^{-(0.123\ h^{-1})(1\ h)}]\}}$$

$$V = 30.6\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 6 μg/mL and 0.8 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$

$$= [(\ln 6\ \mu g/mL - \ln 0.8\ \mu g/mL) / 0.123\ h^{-1}] + 1\ h = 17\ h, \text{ round to } 18\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.123\ h^{-1} \cdot 30.6\ L)\{[1 - e^{-(0.123\ h^{-1})(18\ h)}) / (1 - e^{-(0.123\ h^{-1})(1\ h)}]\}$$

$$= 174\ mg, \text{ rounded to } 175\ mg$$

A dose of gentamicin 175 mg every 18 hours would be prescribed to begin 18 hours after the last dose of the previous regimen. This dose is very similar to that derived for the patient using the Pharmacokinetic Concepts method (185 mg every 18 hours).

7. *Solution to problem 7.* The initial tobramycin dose for patient AF would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(62 − 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 45\ y)\{(0.287 \cdot 140\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 2.4\ mg/dL)} = 45\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the tobramycin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(45\ mL/min) + 0.014 = 0.146\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.146\ h^{-1} = 4.7\ h$$

3. *Estimate volume of distribution (V).*

The patient is obese, so the volume of distribution would be estimated using the following formula:

$$V = 0.26[IBW + 0.4(TBW - IBW)] = 0.26[50\ kg + 0.4(140\ kg - 50\ kg)] = 22.3\ L$$

4. *Choose desired steady-state serum concentrations.*

Endocarditis patients treated with aminoglycoside antibiotics for gram-positive synergy require steady-state peak concentrations (Css_{max}) equal to 3–4 μg/mL; steady-state trough (Css_{min}) concentrations should be <1 μg/mL to avoid toxicity. Set Css_{max} = 4 μg/mL and Css_{min} = 0.5 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose (Table 4-2).*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$
$$= [(\ln 4\ \mu g/mL - \ln 0.5\ \mu g/mL) / 0.146\ h^{-1}] + 1\ h = 15\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval is rounded to 12 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (4\ mg/L \cdot 0.146\ h^{-1} \cdot 22.3\ L)\{[1 - e^{-(0.146\ h^{-1})(12\ h)}] / [1 - e^{-(0.146\ h^{-1})(1\ h)}]\} = 79\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would to be rounded to 80 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 80 mg every 12 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = k_0 / (1 - e^{-k_e \tau}) = 80 \text{ mg} / [1 - e^{-(0.146 \text{ h}^{-1})(12 \text{ h})}] = 97 \text{ mg}$$

This loading dose would be rounded to 100 mg and would be given as the first dose. The first maintenance dose would be given 12 hours later.

The tobramycin dose computed using the Hull and Sarubbi nomogram would be:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60 in) = 45 + 2.3(62 − 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 45 \text{ y})\{(0.287 \cdot 140 \text{ kg}) + [9.74 \cdot (1.57 \text{ m})^2]\}}{(60 \cdot 2.4 \text{ mg/dL})} = 45 \text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m

2. *Choose desired steady-state serum concentrations.*

Gram-positive endocarditis patients treated with aminoglycoside antibiotics for synergy require steady-state peak concentrations (Css_{max}) equal to 3–4 μg/mL.

3. *Select loading dose (Table 4-3).*

A loading dose (LD) of 1.5 mg/kg will provide a peak concentration of 5–7 μg/mL. This is the lowest dose suggested by the nomogram and will be used in this example. However, some clinicians may substitute a loading dose of 1–1.2 mg/kg designed to produce a steady-state peak concentration equal to 3–4 μg/mL.

Because the patient is obese, adjusted body weight (ABW) will be used to compute the dose:

$$ABW = IBW + 0.4(TBW - IBW) = 50 \text{ kg} + 0.4(140 \text{ kg} - 50 \text{ kg}) = 86 \text{ kg}$$

LD = 1.5 mg/kg(86 kg) = 129 mg, rounded to 130 mg or
LD = 1.2 mg/kg (86 kg) = 103 mg, rounded to 100 mg

4. *Determine estimated half-life, maintenance dose, and dosage interval.*

From the nomogram the estimated half-life is ~6 hours, suggesting that a 12 hour dosage interval is appropriate. The maintenance dose (MD) is 72% of the loading dose [MD = 0.72(130 mg) = 94 mg or MD = 0.72(100 mg) = 72 mg], and the dosage interval is 12 hours.

Aminoglycoside doses should be rounded to the nearest 5–10 mg. Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

The prescribed maintenance dose would be 95 mg every 12 hours or 70 mg every 12 hours, depending on the loading dose chosen.

8. *Solution to problem 8.* Compute modified dose for AF using linear pharmacokinetics:

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 6.2\ \mu g/mL)\ 100\ mg = 65\ mg$$

The new suggested dose would be 65 mg every 12 hours to be started at next scheduled dosing time.

2. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (65\ mg / 100\ mg)\ 1.5\ \mu g/mL = 1\ \mu g/mL$$

This steady-state trough concentration should be safe and effective for the infection that is being treated.

The revised tobramycin dose for patient AF using the Pharmacokinetic Concepts method would be calculated as follows:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-18).*

2. *Since the patient is at steady-state, the trough concentration can be extrapolated to the next trough value time (Figure 4-18).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving a tobramycin dose of 100 mg given every 12 hours that produces a steady-state peak equal to 6.2 µg/mL and a steady-state trough equal to 1.5 µg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-18). The time between the measured steady-state peak and the extrapolated trough concentration is 11 hours (the 12-hour dosage interval minus

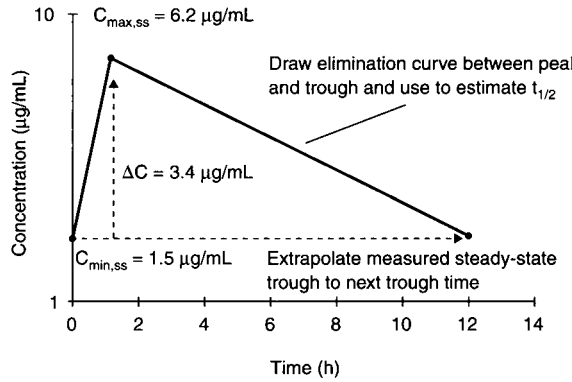


FIGURE 4-18 Solution to problem 8 using Pharmacokinetic Concepts method.

the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 6.2 μg/mL to 3.1 μg/mL, and an additional half-life for the concentration to decrease from 3.1 μg/mL to 1.6 μg/mL. The concentration of 1.5 μg/mL is very close to the extrapolated trough value of 1.6 μg/mL. Therefore, 2 half-lives expired during the 11-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is ~6 hours. This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example, the patient is receiving a tobramycin dose equal to 100 mg every 12 hours which produced steady-state peak and trough concentrations of 6.2 μg/mL and 1.5 μg/mL, respectively. The difference between the peak and trough values is 4.7 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 4 μg/mL and ≤1 μg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* Using the desired concentrations, it will take 1 half-life for the peak concentration of 4 μg/mL to decrease to 2 μg/mL, and 1 more half-life for the serum concentration to decrease to 1 μg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 12 hours (6 hours × 2 half-lives = 12 hours).

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 4 μg/mL, and the expected trough concentration is 1 μg/mL. The change in concentration between these values is 3.0 μg/mL. It is known from measured

serum concentrations that administration of 100 mg changes serum concentrations by 4.7 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old}$ = (3.0 μg/mL / 4.7 μg/mL)100 mg = 64 mg, rounded to 65 mg. Tobramycin 65 mg every 12 hours would be started 12 hours after the last dose of the previous dosage regimen.

The revised tobramycin dose for patient AF using the Steady-state Sawchuk-Zaske method would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t' = (\ln 6.2\ \mu g/mL - \ln 1.5\ \mu g/mL) / (12\ h - 1\ h)$$
$$= 0.129\ h^{-1}$$
$$t_{1/2} = 0.693 / k_e = 0.693 / 0.129\ h^{-1} = 5.4\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(100\ mg/1\ h)\,[1 - e^{-(0.129\ h^{-1})(1\ h)}]}{0.129\ h^{-1}\{6.2\ mg/L - [1.5\ mg/L\ e^{-(0.129\ h^{-1})(1\ h)}]\}}$$

$$V = 19.2\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 4 μg/mL and ≤1 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$
$$= [(\ln 4\ \mu g/mL - \ln 1\ \mu g/mL)\ /\ 0.129\ h^{-1}] + 1\ h = 12\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (4\ mg/L \cdot 0.129\ h^{-1} \cdot 19.2\ L)\{[1 - e^{-(0.129\ h^{-1})(12\ h)}]\ /\ [1 - e^{-(0.129\ h^{-1})(1\ h)}]\} = 65\ mg$$

A dose of tobramycin 65 mg every 12 hours would be prescribed to begin 12 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the linear pharmacokinetics method and the Pharmacokinetic Concepts method (65 mg every 12 hours).

9. *Solution to problem 9.* The initial tobramycin dose for patient FH would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 24\ y)60\ kg] / (72 \cdot 0.7\ mg/dL)$$

$$CrCl_{est} = 138\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the tobramycin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(138\ mL/min) + 0.014 = 0.419\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.419\ h^{-1} = 1.7\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.35 L/kg for cystic fibrosis patients:

$$V = 0.35\ L/kg\ (60\ kg) = 21\ L$$

4. *Choose desired steady-state serum concentrations.*

Cystic fibrosis patients with a sputum culture positive for *Pseudomonas aeruginosa* and a pulmonary exacerbation treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 10 μg/mL and Css_{min} = 1 μg/mL.

5. *Use intermittent intravenous infusion equations to compute dose.*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$
$$= [(\ln 10\ \mu g/mL - \ln 1\ \mu g/mL) / 0.419\ h^{-1}] + 1\ h = 6.5\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 8 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (10\ mg/L \cdot 0.419\ h^{-1} \cdot 21\ L)\{[1 - e^{-(0.419\ h^{-1})(8\ h)}] / [1 - e^{-(0.419\ h^{-1})(1\ h)}]\} = 248\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 250 mg every 8 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses for patients with creatinine clearance values above 60 mL/min are usually close to maintenance doses so are often not given to this patient population.

$LD = k_0 / (1 - e^{-k_e \tau}) = 250 \text{ mg} / [1 - e^{-(0.419 \text{ h}^{-1})(8 \text{ h})}] = 259 \text{ mg}$, rounded to 260 mg

10. *Solution to problem 10.* Compute modified dose for FH using linear pharmacokinetics:

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old} = (10 \text{ μg/mL} / 7.9 \text{ μg/mL}) \, 250 \text{ mg} = 316 \text{ mg}$$

The new suggested dose would be 315 mg every 8 hours to be started at next scheduled dosing time.

2. Check steady-state trough concentration for new dosage regimen.

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new} / D_{old}) C_{ss,old} = (315 \text{ mg} / 250 \text{ mg}) \, 1 \text{ μg/mL} = 1.3 \text{ μg/mL}$$

This steady-state trough concentration should be safe and effective for the infection that is being treated.

The revised tobramycin dose for patient FH using the Pharmacokinetic Concepts method would be calculated as follows:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-19).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-19).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving a tobramycin dose of 250 mg given every 8 hours that produces a steady-state peak equal to 7.9 μg/mL and a steady-state trough equal to 1 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-19). The time between the measured steady-state peak and the extrapolated trough concentration is 7 hours (the 8-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 7.9 μg/mL to 4 μg/mL, an additional

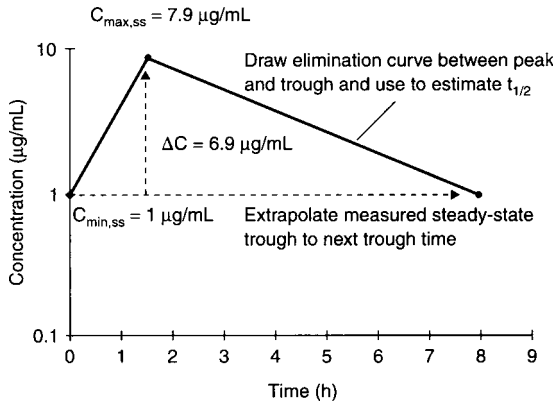


FIGURE 4-19 Solution to problem 10 using Pharmacokinetic Concepts method.

half-life for the serum concentration to decrease from 4 µg/mL to 2 µg/mL, and another half-life for the concentration to decline from 2 µg/mL to 1 µg/mL. Therefore, 3 half-lives expired during the 7 hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 2 hours (7 hours / 3 half-lives = ~2 hours). This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example the patient is receiving a tobramycin dose equal to 250 mg every 8 hours which produced steady-state peak and trough concentrations of 7.9 µg/mL and 1 µg/mL, respectively. The difference between the peak and trough values is 6.9 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 10 µg/mL and 1 µg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* Using the desired concentrations, it will take 1 half-life for the peak concentration of 10 µg/mL to decrease to 5 µg/mL, 1 more half-life for the serum concentration to decrease to 2.5 µg/mL, an additional half-life for serum concentrations to decline from 2.5 µg/mL to 1.3 µg/mL, and a final half-life for serum concentrations to reach 0.7 µg/mL. Therefore, the dosage interval will need to be approximately 4 half-lives or 8 hours (2 hours × 4 half-lives = 8 hours).

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 10 µg/mL, and the expected trough concentration is 0.7 µg/mL. The change in concentration between these values is 9.3 µg/mL. It is known from measured serum concentrations that administration of 250 mg changes serum

concentrations by 6.9 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old} = (9.3\ \mu g/mL / 6.9\ \mu g/mL)\ 250\ mg = 336\ mg$, rounded to 335 mg. Tobramycin 335 mg every 8 hours would be started 8 hours after the last dose of the previous dosage regimen.

The revised tobramycin dose for patient FH using the Steady-state Sawchuk-Zaske method would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t'$$
$$= (\ln 7.9\ \mu g/mL - \ln 1\ \mu g/mL) / (8\ h - 1\ h) = 0.295\ h^{-1}$$
$$t_{1/2} = 0.693 / k_e = 0.693 / 0.295\ h^{-1} = 2.3\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\ (1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(250\ mg/1\ h)\ [1 - e^{-(0.295\ h^{-1})(1\ h)}]}{0.295\ h^{-1}\{7.9\ mg/L - [1\ mg/L\ e^{-(0.295\ h^{-1})(1\ h)}]\}}$$

$V = 30.3\ L$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 10 μg/mL and 1 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 10\ \mu g/mL - \ln 1\ \mu g/mL) / 0.295\ h^{-1}] + 1\ h$$
$$= 8.8\ h, \text{ round to } 8\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$
$$k_0 = (10\ mg/L \cdot 0.295\ h^{-1} \cdot 30.3\ L)\{[1 - e^{-(0.295\ h^{-1})(8\ h)}] / [1 - e^{-(0.295\ h^{-1})(1\ h)}]\}$$
$$= 316\ mg, \text{ rounded to } 315\ mg$$

A dose of tobramycin 315 mg every 8 hours would be prescribed to begin 8 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the linear pharmacokinetics (315 mg every 8 hours) and is very similar to that calculated by the Pharmacokinetic Concepts methods (335 mg every 8 hours).

11. *Solution to problem 11.* The initial gentamicin dose for patient TY would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW] \cdot 0.85\} / (72 \cdot S_{Cr})$$
$$= \{[(140 - 66\ y)65\ kg] \cdot 0.85\} / (72 \cdot 1.4\ mg/dL)$$
$$CrCl_{est} = 41\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(41\ mL/min) + 0.014 = 0.133\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.133\ h^{-1} = 5.2\ h$$

3. *Estimate volume of distribution (V).*

The patient has excess extracellular fluid due to ascites, and the formula used to take this into account will be used. The patient's dry weight (DBW) before ascitic fluid accumulated was 65 kg, and her current weight (TBW) has increased to 72 kg:

$$V = (0.26 \cdot DBW) + (TBW - DBW) = V = (0.26 \cdot 65\ kg) + (72\ kg - 65\ kg) = 23.9\ L$$

4. *Choose desired steady-state serum concentrations.*

For the purposes of this example, a steady-state peak concentration (Css_{max}) equal to 6 μg/mL and steady-state trough (Css_{min}) concentration equal to 1 μg/mL will be used to design the dosage regimen.

5. *Use intermittent intravenous infusion equations to compute dose.*

Calculate required dosage interval (τ) using a 1-hour infusion:

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 6\ \mu g/mL - \ln 1\ \mu g/mL) / 0.133\ h^{-1}] + 1\ h$$
$$= 14.5\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $^1/_2$ hour after a $^1/_2$-hour infusion, so the dose could be administered either way.

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.133\ h^{-1} \cdot 23.9\ L)\{[1 - e^{-(0.133\ h^{-1})(12\ h)}] / [1 - e^{-(0.133\ h^{-1})(1\ h)}]\} = 122\ mg$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 120 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 120 mg every 12 hours.

6. *Compute loading dose (LD), if needed.*

Loading doses for patients with creatinine clearance values below 60 mL/min can be given:

$$LD = k_0 / (1 - e^{-k_e \tau}) = 120 \text{ mg} / [1 - e^{-(0.133 \text{ h}^{-1})(12 \text{ h})}] = 151 \text{ mg, rounded to } 150 \text{ mg}$$

The loading dose would be given as the first dose and subsequent doses would be maintenance doses.

12. *Solution to problem 12.* Compute modified dose for TY using linear pharmacokinetics:

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old} = (6 \text{ μg/mL} / 4 \text{ μg/mL}) \ 120 \text{ mg} = 180 \text{ mg}$$

The new suggested dose would be 180 mg every 12 hours to be started at next scheduled dosing time

2. *Check steady-state trough concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new} / D_{old}) C_{ss,old} = (180 \text{ mg} / 120 \text{ mg}) \ 0.8 \text{ μg/mL} = 1.2 \text{ μg/mL}$$

This steady-state trough concentration should be safe and effective for the infection that is being treated.

The revised gentamicin dose for patient TY using the Pharmacokinetic Concepts method would be calculated as follows:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 4-20).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 4-20).*

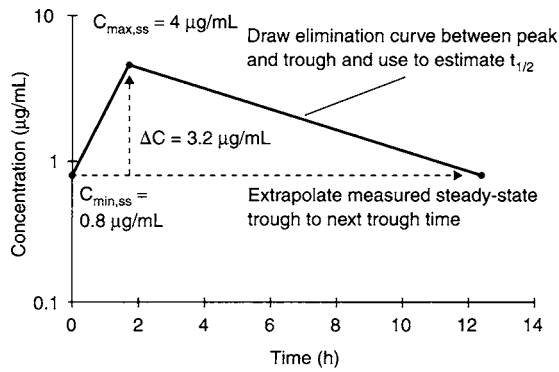


FIGURE 4-20 Solution to problem 12 using Pharmacokinetic Concepts method.

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* The patient is receiving an gentamicin dose of 120 mg given every 12 hours that produces a steady-state peak equal to 4 μg/mL and a steady-state trough equal to 0.8 μg/mL, and the dose is infused over $^1/_2$ hour and the peak concentration is drawn $^1/_2$ hour later (Figure 4-20). The time between the measured steady-state peak and the extrapolated trough concentration is 11 hours (the 12-hour dosage interval minus the 1-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 4 μg/mL to 2 μg/mL, and an additional half-life for the serum concentration to decrease from 2 μg/mL to 1 μg/mL. The concentration of 1 μg/mL is close to the observed value of 0.8 μg/mL. Therefore, 2 half-lives expired during the 11-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 6 hours (11 hours / 2 half-lives = ~6 hours). This information will be used to set the new dosage interval for the patient.

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example, the patient is receiving a gentamicin dose equal to 120 mg every 12 hours which produced steady-state peak and trough concentrations of 4 μg/mL and 0.8 μg/mL, respectively. The difference between the peak and trough values is 3.2 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 6 μg/mL and 1 μg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* Using the desired concentrations, it will take 1 half-life for the peak concentration of 6 μg/mL to decrease to 3 μg/mL, and an additional half-life for serum concentrations to decline from 3 μg/mL to 1.5 μg/mL. This concentration is close to the desired trough concentration of 1 μg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 12 hours (6 hours × 2 half-lives = 12 hours).

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 6 μg/mL, and the expected trough concentration is 1.5 μg/mL. The change in concentration between these values is 4.5 μg/mL. It is known from measured serum concentrations that administration of 120 mg changes serum concentrations by 3.2 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new} / \Delta C_{old}) D_{old}$ = (4.5 μg/mL / 3.2 μg/mL) 120 mg = 168 mg, rounded to 170 mg. Gentamicin 170 mg every 12 hours would be started 12 hours after the last dose of the previous dosage regimen.

The revised gentamicin dose for patient TY using the Steady-state Sawchuk-Zaske method would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)*

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t' = (\ln 4\ \mu g/mL - \ln 0.8\ \mu g/mL) / (12\ h - 1\ h) = 0.146\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.146\ h^{-1} = 4.7\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(120\ mg/1\ h)\,[1 - e^{-(0.146\ h^{-1})(1\ h)}]}{0.146\ h^{-1}\{4\ mg/L - [0.8\ mg/L\ e^{-(0.146\ h^{-1})(1\ h)}]\}}$$

$$V = 33.7\ L$$

3. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 6 μg/mL and 1 μg/mL, respectively.

4. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a 1-hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t' = [(\ln 6\ \mu g/mL - \ln 1.0\ \mu g/mL) / 0.146\ h^{-1}] + 1\ h$$

$$= 13.3\ h, \text{ round to } 12\ h$$

5. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6\ mg/L \cdot 0.146\ h^{-1} \cdot 33.7\ L)\{[1 - e^{-(0.146\ h^{-1})(12\ h)}] / [1 - e^{-(0.146\ h^{-1})(1\ h)}]\} = 180\ mg$$

A dose of gentamicin 180 mg every 12 hours would be prescribed to begin 12 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the linear pharmacokinetics (180 mg every 12 hours) and is very similar to that derived by the Pharmacokinetic Concepts methods (170 mg every 12 hours).

13. *Solution to problem 13.* The initial gentamicin dose for patient UQ would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient is not obese. The patient is in acute renal failure and receiving hemodialysis. Because dialysis removes creatinine, the serum creatinine cannot be used to estimate creatinine clearance for the patient. Since the patient's renal function is poor enough to require dialysis, the creatinine clearance will be assumed to equal zero.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(0 \text{ mL/min}) + 0.014 = 0.\ 014 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.014 \text{ h}^{-1} = 50 \text{ h}$$

3. *Estimate volume of distribution (V).*

The patient has renal failure and would need to be assessed for volume status to rule out over- and underhydration. In this case, the patient is in good fluid balance, and the volume of distribution from the normal value of 0.26 L/kg would be used:

$$V = 0.26 \text{ L/kg } (85 \text{ kg}) = 22.1 \text{ L}$$

4. *Choose desired steady-state serum concentrations.*

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 μg/mL; steady-state trough (Css_{min}) concentrations should be <2 μg/mL to avoid toxicity. Set Css_{max} = 8 μg/mL and Css_{min} ~2 μg/mL.

5. *Compute first dose.*

Because the patient has renal failure with a gentamicin half-life ~50 hours, very little antibiotic is eliminated during the $^1/_2$–1-hour infusion time. Simple intravenous bolus equations can be used to compute doses in this case.

$$LD = C_{max}V = 8 \text{ mg/L} \cdot 22.1 \text{ L} = 177 \text{ mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 180 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for C_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 180 mg postdialysis at 1200 H on Wednesday.

6. *Estimate predialysis and postdialysis aminoglycoside concentration.*

The next dialysis session will occur on Friday at 0800 H. The time expired between the dose given on Wednesday at 1200 H and this hemodialysis period is 44 hours (Figure 4-21). During the interdialysis time period only the patient's own, endogenous clearance will eliminate gentamicin. The predialysis serum concentration will be:

$$C = C_0e^{-k_et} = (8 \text{ μg/mL})e^{-(0.014 \text{ h}^{-1})(44 \text{ h})} = 4.3 \text{ μg/mL}$$

The average half-life of aminoglycosides during hemodialysis with a low-flux membrane is 4 hours. Since the usual dialysis time is 3–4 hours with a low-flux filter, intradialysis elimination can be computed:

$$k_e = 0.693/t_{1/2} = 0.693 / 4 \text{ h} = 0.173 \text{ h}^{-1}$$

$$C = C_0e^{-k_et} = (4.3 \text{ μg/mL})e^{-(0.173 \text{ h}^{-1})(4 \text{ h})} = 2.2 \text{ μg/mL}$$

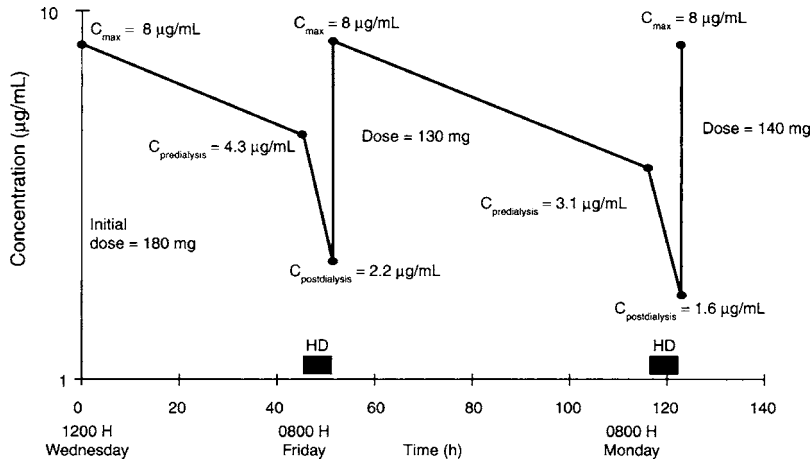


FIGURE 4-21 Solution to problem 13.

Alternatively, because aminoglycoside half-life on dialysis is 4 hours, and the dialysis period is 4 hours, one can deduce that the postdialysis serum concentration will be $^1/_2$ the predialysis value.

7. *Calculate postdialysis replacement dose.*

The postdialysis serum concentration of 2.2 μg/mL is an estimate of the actual serum concentration and is close enough to the target concentration that a postdialysis dose will be administered immediately at the end of the procedure.

$$\text{Replacement dose} = (C_{max} - C_{baseline})V = (8 \text{ mg/L} - 2.2 \text{ mg/L})\ 22.1 \text{ L}$$
$$= 128 \text{ mg, rounded to } 130 \text{ mg}$$

8. *Compute predialysis and postdialysis concentrations plus postdialysis dose for next dialysis cycle.*

The Friday-to-Monday dialysis cycle includes an extra day, so the concentration profile for that time period will be estimated (Figure 4-21). The time between the gentamicin dose given at 1200 H on Friday and the next dialysis period at 0800 H on Monday is 68 hours.

$$C = C_0e^{-k_et} = (8 \text{ μg/mL})e^{-(0.014 \text{ h}^{-1})(68 \text{ h})} = 3.1 \text{ μg/mL predialysis on Monday}$$

$$C = C_0e^{-k_et} = (3.1 \text{ μg/mL})e^{-(0.173 \text{ h}^{-1})(4 \text{ h})} = 1.6 \text{ μg/mL postdialysis on Monday}$$

Replacement dose = $(C_{max} - C_{baseline})V$ = (8 mg/L − 1.6 mg/L) 22.1 L = 141 mg, rounded to 140 mg. The dialysis periods for this patient are scheduled, and since the dosage recommendation is based on estimated pharmacokinetic parameters, a postdialysis dose of 130 mg could be suggested so that all doses were uniform.

14. *Solution to problem 14.* The revised gentamicin dose for patient UQ using intravenous bolus equations would be calculated as follows:

1. *Compute the patient's elimination rate constant and half-life.*

$$k_e = (\ln C_{postdose(1)} - \ln C_{predialysis}) / \Delta t = (\ln 6.4\ \mu g/mL - \ln 2.2\ \mu g/mL) / (68\ h) = 0.0157\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.0157\ h^{-1} = 44\ h$$

2. *Compute the patient's volume of distribution.*

$$V = \frac{D}{C_{postdose(2)} - C_{postdialysis}} = \frac{130\ mg}{6.9\ mg/L - 0.7\ mg/L}$$

$$V = 21\ L$$

3. *Compute the fraction of drug eliminated by the dialysis procedure.*

$$\text{Fraction eliminated} = (C_{predialysis} - C_{postdialysis}) / C_{predialysis}$$
$$= (2.2\ \mu g/mL - 0.7\ \mu g/mL) / 2.2\ \mu g/mL = 0.68 \text{ or } 68\%$$

The fraction remaining after hemodialysis is 1 − fraction eliminated = 1 − 0.68 = 0.32 or 32%.

4. *Compute predialysis and postdialysis concentrations plus postdialysis dose for next dialysis cycle using patient's own pharmacokinetic parameters.*

The time between the gentamicin concentration obtained at 1400 H on Monday and the next dialysis period at 0800 H on Wednesday is 42 hours.

$$C = C_0 e^{-k_e t} = (6.9\ \mu g/mL) e^{-(0.0157\ h^{-1})(42\ h)} = 3.6\ \mu g/mL \text{ predialysis on Wednesday}$$

The fraction remaining after hemodialysis is 0.32 or 32%

$$\text{Fraction remaining} = 0.32 \cdot 3.6\ \mu g/mL = 1.2\ \mu g/mL$$

$$\text{Replacement dose} = (C_{max} - C_{baseline})V = (8\ mg/L - 1.2\ mg/L)\ 21\ L$$
$$= 143\ mg, \text{ rounded to } 145\ mg$$

15. *Solution to problem 15.* This patient is an older individual with poor renal function ($CrCl_{est}$ = {[(140 − age)BW] · 0.85} / (72 · S_{Cr}) = {[(140 − 67 y)60 kg] · 0.85} / (72 · 1.8 mg/dL) = 29 mL/min) and is not at steady state when the serum concentrations were obtained. Because of this, a Bayesian pharmacokinetic computer program is the best method to compute revised doses for this individual.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 21.4 L, a half-life equal to 13.5 hours, and an elimination rate constant of 0.051 h^{-1}.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 150 mg every 36 hours will produce a steady-state peak concentration of 8.1 μg/mL and a steady-state trough concentration of 1.3 μg/mL.

16. *Solution to problem 16.* This patient could receive an extended-interval gentamicin dose between 5 mg/kg and 7 mg/kg.

(A) Using the Hartford nomogram initial dosing guidelines:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 52\ y)87\ kg] / (72 \cdot 1.4\ mg/dL)$$

$$CrCl_{est} = 76\ mL/min$$

2. *Compute initial dose and dosage interval (Table 4-4).*

A dose (D) of 7 mg/kg will provide a peak concentration > 20 μg/mL.

$$D = 7\ mg/kg(87\ kg) = 609\ mg, \text{ round to } 600\ mg$$

Since the patient's estimated creatinine clearance is >60 mL/min, a dosage interval of 24 hours is chosen.

The prescribed maintenance dose would be 600 mg every 24 hours.

(B) Using the Hartford nomogram to individualize dosage interval:

3. *Determine dosage interval using serum concentration monitoring (Table 4-4).*

A gentamicin serum concentration measured 9 hours after the dose equals 8.2 μg/mL. Based on the nomogram, a dosage interval of 36 hours is the correct value and would be instituted with the next dose: 600 mg every 36 hours.

(C) Using a Bayesian pharmacokinetic computer dosing program to individualize dose and dosage interval:

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 21.5 L, a half-life equal to 4.7 hours, and an elimination rate constant of 0.149 h^{-1}.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 550 mg every 24 hours will produce a

steady-state peak concentration of 24.4 μg/mL and a steady-state trough concentration of 0.8 μg/mL.

17. *Solution to problem 17.* This patient had extended-interval tobramycin therapy instituted by other clinicians at a rate of 5 mg/kg/d. The tobramycin dose is less than 7 mg/kg, and the serum concentration was not obtained 6–14 hours after the dose. Because of these reasons, the Hartford nomogram cannot be used, and a Bayesian pharmacokinetic computer program is the best method to compute revised doses for this individual.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 11.6 L, a half-life equal to 6.6 hours, and an elimination rate constant of 0.105 h^{-1}.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

If the patient continued to receive the prescribed dose, the estimated steady-state peak and trough concentrations are 28.9 μg/mL and 2.6 μg/mL. The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 300 mg every 36 hours will produce a steady-state peak concentration of 25.1 μg/mL and a steady-state trough concentration of 0.6 μg/mL.

18. *Solution for problem 18.*

The initial tobramycin dose for patient DT would be calculated as follows:

1. *Compute initial dose and dosage interval.*

Often, serum creatinine measurements are not available for initial dosage computation in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatric dosage recommendations given earlier in this chapter, a patient in this age and weight category should receive tobramycin 2.5 mg/kg every 12 hours. (*Note: Grams will be converted to kilograms before the computation is made*).

$$\text{Dose} = 2.5 \text{ mg/kg}(2.050 \text{ kg}) = 5.1 \text{ mg}$$

The prescribed dose will be 5.1 mg every 12 hours.

19. *Solution for problem 19.*

Compute modified dose for DT using linear pharmacokinetics:

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (6 \text{ μg/mL} / 4.5 \text{ μg/mL}) \ 5 \text{ mg} = 6.7 \text{ mg}$$

The new suggested dose would be 6.7 mg every 12 hours to be started at next scheduled dosing time.

2. Check steady-state trough concentration for new dosage regimen.

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration.

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (6.7 \text{ mg} / 5 \text{ mg})\ 0.9\ \mu\text{g/mL} = 1.2\ \mu\text{g/mL}$$

20. *Solution to problem 20* The initial gentamicin dose for patient UL would be calculated as follows:

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The pediatric CrCl equation from Chapter 3 can be used to estimate creatinine clearance (*Note: Height converted from inches to centimeters, 47 in · 2.54 cm/in = 119 cm*):

$$CrCl_{est} = (0.55 \cdot Ht) / S_{Cr} = (0.55 \cdot 119 \text{ cm}) / (0.5 \text{ mg/dL})$$

$$CrCl_{est} = 131 \text{ mL/min} / 1.73 \text{ m}^2$$

The patient has normal renal function, so typical initial doses can be used.

2. *Compute initial dose and dosage interval using literature-based recommended dosing for pediatric patients.*

The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatrics dosage recommendations given earlier in the chapter, a patient in this age and weight category should receive gentamicin 7.5 mg/kg/d given as divided doses every 8 hours.

$$\text{Dose} = 7.5 \text{ mg/kg/d}(24 \text{ kg}) = 180 \text{ mg/d}$$

$$(180 \text{ mg/d}) / (3 \text{ doses/d}) = 60 \text{ mg/dose}$$

The prescribed dose will be 60 mg every 8 hours.

21. Solution to problem 21 The revised gentamicin dose for patient UL would be calculated as follows:

1. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t' is considered to be the sum of the infusion and waiting times.)

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 4.5\ \mu\text{g/mL} - \ln 1.5\ \mu\text{g/mL}) / (3 \text{ h}) = 0.366 \text{ h}^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.366 \text{ h}^{-1} = 1.9 \text{ h}$$

Extrapolate measured concentrations to steady-state peak and trough values.

$$Css_{max} = C_1/(e^{-k_e t}) = (4.5\ \mu g/mL) / (e^{-(0.366\ h^{-1})(1\ h)}) = 6.5\ \mu g/mL$$

$$Css_{min} = C_2 e^{-k_e t} = (1.5\ \mu g/mL)(e^{-(0.366\ h^{-1})(3\ h)}) = 0.5\ \mu g/mL$$

Compute the patient's volume of distribution.

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(60\ mg/1\ h)\,[1 - e^{-(0.366\ h^{-1})(1\ h)}]}{0.366\ h^{-1}\{6.5\ mg/L - [0.5\ mg/L\ e^{-(0.366\ h^{-1})(1\ h)}]\}}$$

$$V = 8.2\ L$$

2. *Choose new steady-state peak and trough concentrations.* The desired steady-state peak and trough concentrations will be 9 μg/mL and 1 μg/mL, respectively.

3. *Determine the new dosage interval for the desired concentrations.* As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation using a one hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t' = [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL)/0.366\ h^{-1}] + 1\ h$$
$$= 7\ h, \text{ rounded to } 8\ h$$

4. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (9\ mg/L \cdot 0.366\ h^{-1} \cdot 8.2\ L)\{[1 - e^{-(0.366\ h^{-1})(8\ h)}] / [1 - e^{-(0.366\ h^{-1})(1\ h)}]\}$$
$$= 83\ mg, \text{ rounded to } 85\ mg$$

A dose of gentamicin 85 mg every 8 hours would be prescribed to begin approximately 8 hours after the last dose of the current regimen.

22. *Solution to problem 22.* The revised gentamicin dose for patient RD would be calculated as follows:

Steady-state Sawchuk-Zaske Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 59\ y)79\ kg] / (72 \cdot 1.5\ mg/L)$$

$$CrCl_{est} = 59\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(59\ mL/min) + 0.014 = 0.187\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.187\ h^{-1} = 3.7\ h$$

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state Sawchuk-Zaske method to compute a new dose.*

Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t′ is considered to be the sum of the infusion and waiting times.)

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 16.1\ \mu g/mL - \ln 2.5\ \mu g/mL) / (14\ h) = 0.133\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.133\ h^{-1} = 5.2\ h$$

Extrapolate measured concentrations to steady-state peak and trough values.

$$Css_{max} = C_1/(e^{-k_e t}) = (16.1\ \mu g/mL) / [e^{-(0.133\ h^{-1})(2\ h)}] = 21.0\ \mu g/mL$$

$$Css_{min} = C_2 e^{-k_e t} = (2.5\ \mu g/mL)[e^{-(0.133\ h^{-1})(7\ h)}] = 1.0\ \mu g/mL$$

Compute the patient's volume of distribution.

$$V = \frac{D/t'\ (1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(450\ mg/1\ h)\ [1 - e^{-(0.133\ h^{-1})(1\ h)}]}{0.133\ h^{-1}\{21\ mg/L - [1\ mg/L\ e^{-(0.133\ h^{-1})(1\ h)}]\}}$$

$$V = 20.9\ L$$

4. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 µg/mL and 0.3 µg/mL, respectively.

5. *Determine the new dosage interval for the desired concentrations.* The dosage interval (τ) is computed using the following equation using a 1 hour infusion time (t′):

$$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$$
$$= [(\ln 30\ \mu g/mL - \ln 0.3\ \mu g/mL) / 0.133\ h^{-1}] + 1\ h = 36\ h$$

6. *Determine the new dose for the desired concentrations.* The dose is computed using the one-compartment model intravenous infusion equation used in the initial dosing section of this chapter:

$$k_0 = Css_{max} k_e V[(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (30\ mg/L \cdot 0.133\ h^{-1} \cdot 20.9\ L)\{[1 - e^{-(0.133\ h^{-1})(36\ h)}] / [1 - e^{-(0.133\ h^{-1})(1\ h)}]\}$$
$$= 664\ mg, \text{ rounded to } 650\ mg$$

A dose of gentamicin 650 mg every 36 hours would be prescribed to begin after the last dose of the current regimen.

Bayesian Pharmacokinetic Computer Dosing Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 20.7 L, a half-life equal to 5.2 hours, and an elimination rate constant of 0.133 h^{-1}.

3. *Compute dose required to achieve desired aminoglycoside serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 650 mg every 36 hours will produce a steady-state peak concentration of 29.7 μg/mL and a steady-state trough concentration of 0.3 μg/mL.

23. *Solution to problem 23.* The revised tobramycin dose for patient KE would be calculated as follows:

1. *Estimate creatinine clearance*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 23\ y)67\ kg] / (72 \cdot 0.8\ mg/dL)$$

$$CrCl_{est} = 136\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The elimination rate constant versus creatinine clearance relationship is used to estimate the tobramycin elimination rate for this patient:

$$k_e = 0.00293(CrCl) + 0.014 = 0.00293(136\ mL/min) + 0.014 = 0.413\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.413\ h^{-1} = 1.7\ h$$

Because the patient has been receiving tobramycin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use Steady-state AUC method to compute a new dose.*

Compute the patient's actual elimination rate constant and half-life. (Note: For infusion times less than 1 hour, t' is considered to be the sum of the infusion and waiting times.)

$$k_e = (\ln C_1 - \ln C_2) / \Delta t = (\ln 9.6\ \mu g/mL - \ln 2.6\ \mu g/mL) / (4\ h) = 0.327\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.327\ h^{-1} = 2.1\ h$$

Extrapolate measured concentrations to steady-state peak and trough values.

$$Css_{max} = C_1 / (e^{-k_e t}) = (9.6\ \mu g/mL) / [e^{-(0.327\ h^{-1})(2\ h)}] = 18.5\ \mu g/mL$$

$$Css_{min} = C_2 e^{-k_e t} = (2.6\ \mu g/mL)[e^{-(0.327\ h^{-1})(17\ h)}] = 0.01\ \mu g/mL$$

Compute the patient's AUC_{ss}. (Note: mg/L = µg/mL and this substitution was made to aid the calculation.)

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left((0.065 \cdot \frac{Css_{max} - Css_{min}}{k_e} \right)$$

$$AUC_{ss} = \frac{18.5\ mg/L - 0.01\ mg/L}{0.327\ h^{-1}} + \left((0.065 \cdot \frac{18.5\ mg/L - 0.01\ mg/L}{0.327\ h^{-1}} \right)$$

$$AUC_{ss} = 60.2\ (mg \cdot h)/L$$

4. *Choose new target AUC_{ss}.* For the purposes of this example, a desired steady state of AUC of 81 (mg · h)/L was chosen.

5. *Determine the new dose for the desired AUC_{ss}.*

$$D_{new} = (AUC_{ss,new} / AUC_{ss,old})D_{old} = \{[81\ (mg \cdot h)/L] / [60.2\ (mg \cdot h)/L]\}350\ mg$$
$$= 471\ mg, \text{ rounded to } 475\ mg$$

6. *Determine the new steady-state peak and trough concentrations.*

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (475\ mg/350\ mg)\ 18.5\ \mu g/mL = 25.1\ \mu g/mL \text{ for the peak}$$

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (475\ mg/350\ mg)\ 0.01\ \mu g/mL = 0.01\ \mu g/mL \text{ for the trough}$$

These steady-state peak and trough concentrations are acceptable for the infection being treated and the new prescribed dose would be 475 mg every 24 hours.

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5

VANCOMYCIN

INTRODUCTION

Vancomycin is a glycopeptide antibiotic used to treat severe gram-positive infections due to organisms that are resistant to other antibiotics such as methicillin-resistant staphylococci and ampicillin-resistant enterococci. It is also used to treat infections caused by other sensitive gram-positive organisms in patients that are allergic to penicillins.

Vancomycin is bactericidal and exhibits time-dependent or concentration-independent bacterial killing.[1] Antibiotics with time-dependent killing characteristically kill bacteria most effectively when drug concentrations are a multiple (usually three to five times) of the minimum inhibitory concentration (MIC) for the bacteria.[1,2] The mechanism of action for vancomycin is inhibition of cell wall synthesis in susceptible bacteria by binding to the D-alanyl-D-alanine terminal end of cell wall precursor units.[3] Many strains of enterococcus have high MIC values for vancomycin, and for these bacteria vancomycin may only demonstrate bacteriostatic properties.

THERAPEUTIC AND TOXIC CONCENTRATIONS

Vancomycin is administered as a short-term (1-hour) intravenous infusion. Infusion rate related side effects have been noted when shorter infusion times (~30 minutes or less) have been used. Urticarial or erythematous reactions, intense flushing (known as the "red-man" or "red-neck" syndrome), tachycardia, and hypotension have all been reported and can be largely avoided with the longer infusion time. Even with a 1-hour infusion time, vancomycin serum concentrations exhibit a distribution phase so that drug in the blood and in the tissues are not yet in equilibrium (Figure 5-1). Because of this, a $^1/_2$–1 hour waiting period is allowed for distribution to finish before maximum or "peak" concentrations are measured. Since vancomycin exhibits time-dependent killing, microbiolgic or clinical cure

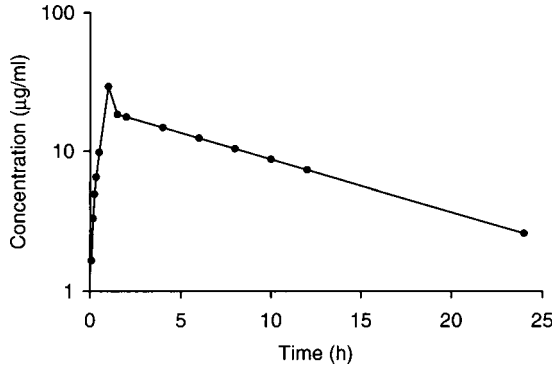

FIGURE 5-1 Concentration/time plot for vancomycin 1000 mg given as a 1-hour infusion *(circles with dashed line)*. When given as a 1-hour infusion, end of infusion concentrations are higher because the serum and tissues are not in equilibrium. A $^1/_2$- to 1-hour waiting time for vancomycin distribution to tissues is allowed before peak concentrations are measured.

rates are not closely associated with peak serum concentrations. However, ototoxicity has been reported when vancomycin serum concentrations exceed 80 µg/mL,[4,5] so the therapeutic range for steady-state peak concentrations is usually considered to be 20–40 µg/mL. Because vancomycin does not enter the central nervous system in appreciable amounts when given intravenously,[3] steady-state peak concentrations of 40–60 µg/mL or direct administration into the cerebral spinal fluid may be necessary.[6,7]

Vancomycin-associated ototoxicity is usually first noted by the appearance of tinnitus, dizziness, or high-frequency hearing loss (>4000 Hz).[4,7,8] Because the hearing loss is initially at high-frequencies, the auditory deficit can be challenging to detect unless audiometry is conducted at baseline before drug is administered and during vancomycin treatment. Since audiometry is difficult to conduct in seriously ill patients, it is rarely done in patients receiving ototoxic drugs so clinicians should monitor for signs and symptoms that may indicate ototoxicity is occurring in a patient (auditory: tinnitus, feeling of fullness or pressure in the ears, loss of hearing acuity in the conversational range; vestibular: loss of equilibrium, headache, nausea, vomiting, vertigo, dizziness, nystagmus, ataxia). Ototoxicity can be permanent if appropriate changes in vancomycin dosing are not made.[4,7–9] In some reports of vancomycin-induced ototoxicity, it is unclear when vancomycin serum concentrations were obtained during the dosage interval so the exact association between peak concentrations and ototoxicity is uncertain.

Trough concentrations (predose or minimum concentrations usually obtained within 30 minutes of the next dose) are usually related to therapeutic outcome for vancomycin because the antibiotic follows time-dependent bacterial killing.[1] Optimal bactericidal effects are found at concentrations three to five times the organism's MIC.[1,2] Because the average vancomycin MICs for *Staphylococcus aureus* and *Staphylococcus epidermidis* are 1–2 µg/mL, minimum predose or trough steady-state concentrations equal to 5–10 µg/mL are usually adequate to resolve infections with susceptible organisms. Methicillin-resistant *S. aureus* (MRSA) with MICs of 1.5–2 µg/mL may require higher steady-state trough concentrations to achieve a clinical cure.[10–12] The need for higher trough concentrations in institutions with antibiograms that include MRSA

with higher MIC values lead to the expansion of the therapeutic trough concentration range to 5–15 μg/mL. Vancomycin penetrates into lung tissue poorly (average serum: tissue ratio of 6:1) and pulmonary concentrations are highly variable among patients.[13,14] Based on these findings and reports of therapeutic failures, recent treatment guidelines for hospital-aquired pneumonia recommend vancomycin steady-state trough concentrations equal to 15–20 μg/mL.[15] Also, the selection of vancomycin intermediate-level resistant *S. aureus* (VISA) during therapy with vancomycin (known as heterogeneous resistance or hVISA) appears to be an important factor in treatment failures.[16,17]

Trough vancomycin steady-state concentrations above 15 μg/mL are related to an increased incidence of nephrotoxicity.[12,18,19] Many patients receiving vancomycin are critically ill, so other sources of renal dysfunction, such as hypotension or other nephrotoxic drug therapy (such as aminoglycosides, amphotericin B, or immunosupressants), should be ruled out before the diagnosis of vancomycin-induced renal damage is made in a patient. Compared to aminoglycoside antibiotics, vancomycin is usually considered to have less nephrotoxicity potential.[20] In contrast to ototoxicity, vancomycin-related nephrotoxicity is usually reversible with a low incidence of residual damage if the antibiotic is withdrawn or doses appropriately adjusted soon after renal function tests change. With adequate patient monitoring, the only result of vancomycin nephrotoxicity may be transient serum creatinine increases of 0.5–2.0 mg/dL. However, if kidney damage progresses to renal failure, the cost of maintaining the patient on dialysis until kidney function returns can exceed $50,000–$100,000 and, if the patient is critically ill, may contribute to his or her death.

Nephrotoxicity and ototoxicity cannot be completely avoided when using vancomycin by keeping serum concentrations within the suggested ranges. However, by adjusting vancomycin dosage regimens so that potentially toxic serum concentrations are avoided, drug concentration-related adverse effects should be held to the absolute minimum.

CLINICAL MONITORING PARAMETERS

Clinicians should always consult the patient's chart to confirm that antibiotic therapy is appropriate for current microbiologic cultures and sensitivities. Antibiograms should be consulted regularly to note changes in resistance patterns and minimum inhibitory concentrations for pathogens. Also, it should be confirmed that the patient is receiving other appropriate concurrent antibiotic therapy, such as aminoglycosides, when necessary to treat the infection. Patients with severe infections usually have elevated white blood cell counts and body temperatures. Measurement of serial white blood cell counts and body temperatures are useful to determine the efficacy of antibiotic therapy. A white blood cell count with a differential will identify the types of white blood cells that are elevated. A large number of neutrophils and immature neutrophils, clinically known as a "shift to the left," can also be observed in patients with severe bacterial infections. Favorable response to antibiotic treatment is usually indicated by high white blood cell counts decreasing toward the normal range, the trend of body temperatures (plotted as body temperature vs. time, also known as the "fever curve") approaching normal, and any specific infection site tests or procedures resolving. For instance, in pneumonia patients the chest x-ray should be resolving, in patients with infective endocarditis the size of the bacterial vegetation on

the heart valve should be decreasing, or in patients with a wound infection the wound should be less inflamed with less purulent discharge. Clinicians should also be aware that immunocompromised patients with a bacterial infection may not be able to mount a fever or elevated white blood cell count.

Vancomycin steady-state serum concentrations should be measured in 3–5 estimated half-lives. Methods to estimate this parameter are given in the initial dose calculation portion of this chapter. Since prolongation of the dosage interval is often used in patients with decreased elimination, a useful clinical rule is to measure serum concentrations after the third dose. If this approach is used, the dosage interval is increased in tandem with the increase in half-life so that 3–5 half-lives have elapsed by the time the third dose is administered. Additionally, the third dose typically occurs 1–3 days after dosing has commenced and this is a good time to also assess clinical efficacy of the treatment. Steady-state serum concentrations, in conjunction with clinical response, are used to adjust the antibiotic dose, if necessary. Methods to adjust vancomycin doses using serum concentrations are discussed later in this chapter. If the dosage is adjusted, vancomycin elimination changes or laboratory and clinical monitoring indicate that the infection is not resolving or worsening, clinicians should consider rechecking steady-state drug concentrations.

While some clinicians continue to monitor both steady-state peak and trough vancomycin serum concentrations, most individuals advocate the measurement of just a steady-state trough concentration.[11,12,15,21,22] The reasoning behind this approach is that vancomycin follows time-dependent bacterial killing, and the efficacy of the drug should be most closely related to the minimum serum concentration encountered over the dosage interval. Since nephrotoxicity is related to high trough concentrations, measurement of this value should ensure therapeutic, nonnephrotoxic drug concentrations. Vancomycin has a moderate sized volume of distribution (~0.7 L/kg), and does not significantly change for most disease states or conditions. Based on this, the argument has been made that if a patient has a therapeutic steady-state trough concentration (5–15 μg/mL) and the dose is in the usual range (500–1500 mg), it is difficult to produce a steady-state peak concentration that would be above the accepted toxic range (>80 μg/mL).[23] While these arguments are intellectually sound and appealing, one of the reasons to measure drug serum concentrations is pharmacokinetic variability. If a patient developed ototoxicity while receiving vancomycin, it could be difficult to prove that steady-state peak concentrations were in the acceptable range if no serum concentrations were obtained at that time. Clinicians should consider measuring peak concentrations when large doses are given (>1500 mg/dose) or for infections that require high peak concentrations (such as central nervous system infections).

Serial monitoring of serum creatinine concentrations should be used to detect nephrotoxicity. Ideally, a baseline serum creatinine concentration is obtained before vancomycin therapy is initiated and three times weekly during treatment. An increasing serum creatinine test on two or more consecutive measurement occasions indicates that more intensive monitoring of serum creatinine values, such as daily, is needed. If serum creatinine measurements increase more than 0.5 mg/dL over the baseline value (or >25–30% over baseline for serum creatinine values >2 mg/dL) and other causes of declining renal function have been ruled out (other nephrotoxic drugs or agents, hypotension, etc.), alternatives to vancomycin therapy or, if that option is not possible, intensive vancomycin serum concentration monitoring should be initiated to ensure that excessive amounts of vancomycin do not accumulate in the patient. In the clinical setting, audiometry is rarely

used to detect ototoxicity because it is difficult to accomplish in severely ill patients. Instead, clinical signs and symptoms of auditory (decreased hearing acuity in the conversational range, feeling of fullness or pressure in the ears, tinnitus) or vestibular (loss of equilibrium, headache, nausea, vomiting, vertigo, nystagmus, ataxia) ototoxicity are monitored at the same time intervals as serum creatinine determination. When high vancomycin concentrations are needed for therapeutic reasons (trough >15 μg/mL, peak >40 μg/mL), assessment of renal function and auditory/vestibular function should be conducted on a daily basis. Vancomycin can also cause allergic symptoms such as chills, fever, skin rashes, and anaphylactoid reactions.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Vancomycin is almost completely eliminated unchanged in the urine primarily by glomerular filtration (≥90%; Table 5-1).[24] This antibiotic is given by short-term (1 hour) intermittent intravenous infusion. Intramuscular administration is usually avoided because this route has been reported to cause tissue necrosis at the site of injection. Oral bioavailability is poor (<10%) so systemic infections cannot be treated by this route of administration.[5] However, patients with renal failure who have been given oral vancomycin for the treatment of antibiotic-associated colitis have accumulated therapeutic concentrations because gut wall inflammation increased vancomycin bioavailability and renal dysfunction decreased drug clearance.[25–28] Plasma protein binding is ~ 55%.[29] The recommended

TABLE 5-1 Disease States and Conditions That Alter Vancomycin Pharmacokinetics

DISEASE STATE/CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	8 hours (range: 7–9 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Usual dose 30 mg/kg/d in 2 divided doses
Adult, renal failure	130 hours (range: 120–140 hours)	0.7 L/kg (range: 0.5–1.0 L/kg)	Underhydration or overhydration does not effect the volume of distribution as much as with aminoglycosides
Burns	4 hour	0.7 L/kg	Because of shorter half-life, some patients may need every 6–8-hour dosage interval to maintain therapeutic trough concentrations
Obesity (>30% over IBW) with normal renal function	3–4 hours	V = 0.7 IBW*	Total daily doses are based on TBW*, V estimates based on IBW*. Because of shorter half-life, some patients may require every 8-hour dosage interval to maintain therapeutic trough concentrations

*IBW = ideal body weight,
TBW = total body weight

dose for vancomycin in patients with normal renal function is 30 mg/kg/d given as 2 or 4 divided daily doses. In normal weight adults, the dose is usually 2 g/d given as 1000 mg every 12 hours.

EFFECTS OF DISEASE STATES AND CONDITIONS ON VANCOMYCIN PHARMACOKINETICS AND DOSING

Nonobese adults with normal renal function (creatinine clearance >80 mL/min, Table 5-1) have an average vancomycin half-life of 8 hours (range = 7–9 hours), and the average volume of distribution for vancomycin is 0.7 L/kg (range 0.5–1.0 L/kg) in this population.[30,31] Because of the moderate size for volume of distribution, fluid balance (under- or overhydration) is less of an issue with vancomycin compared to the aminoglycoside antibiotics.

Since vancomycin is eliminated principally by glomerular filtration, renal dysfunction is the most important disease state that influences vancomycin pharmacokinetics.[32–34] Vancomycin total clearance decreases proportionally to decreases in creatinine clearance (Figure 5-2).[32] The relationship between renal function and vancomycin clearance forms the basis for initial dosage computation methods presented later in this chapter.

Major body burns (>30–40% body surface area) can cause large changes in vancomycin pharmacokinetics.[35] Forty-eight to seventy-two hours after a major burn, the basal metabolic rate of the patient increases to facilitate tissue repair. The increase in basal metabolic rate causes an increase in glomerular filtration rate which increases vancomycin clearance. Because of the increase in drug clearance, the average half-life for vancomycin in burn patients is 4 hours.

Obese individuals with normal serum creatinine concentrations have increased vancomycin clearance secondary to increased glomerular filtration rate and are best dosed with vancomycin using total body weight.[30,31,36,37] The reason for the increased drug clearance is kidney hypertrophy which results in larger creatinine clearance rates. Volume of distribution does not significantly change with obesity and is best estimated using

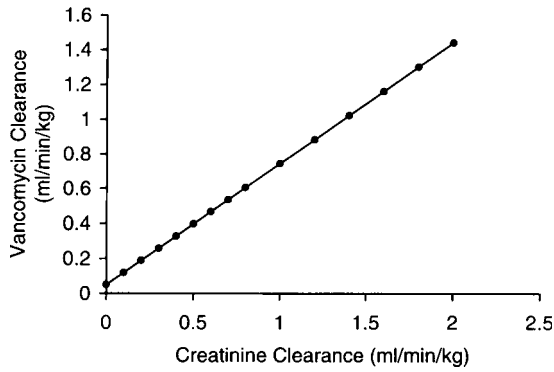

FIGURE 5-2 The clearance rate for vancomycin increases in proportion with creatinine clearance (CrCl). The equation for this relationship is Cl (in mL/min/kg) = 0.695(CrCl in mL/min/kg) + 0.05. This equation is used to estimate vancomycin clearance in patients for initial dosing purposes.

ideal body weight (IBW) in patients more than 30% overweight (>30% over IBW, V = 0.7 L/kg IBW).[30,31,37] Because the primary pharmacokinetic change for vancomycin in obesity is increased drug clearance with a negligible change in volume of distribution, average half-life decreases to 3.3 hours [$t_{1/2} = (0.693 \cdot V)/Cl$]. While the average dose in morbidly obese and normal weight patients with normal serum creatinine concentrations was ~30 mg/kg/d using total body weight in both populations, some morbidly obese patients required every-8-hour dosing to maintain vancomycin steady-state trough concentrations above 5 µg/mL.[30]

Premature infants (gestational age 32 weeks) have a larger amount of body water compared to adults. However, vancomycin volume of distribution (V = 0.7 L/kg) is not greatly affected by these greater amounts of body water as is the case with aminoglycoside antibiotics.[38] Kidneys are not completely developed at this early age so glomerular filtration and vancomycin clearance (15 mL/min) are decreased.[38] A lower clearance rate with about the same volume of distribution as adults results in a longer average half-life for vancomycin in premature babies (10 hours). Full-term neonates (gestational age ~40 weeks) have similar volumes of distribution for vancomycin compared to premature infants, but their vancomycin clearance rate is twice that found in infants born prematurely (30 mL/min). The increase in drug clearance is due to additional renal development that occurred *in utero*. The vancomycin half-life in full-term babies is about 7 hours. At about 3 months of age, vancomycin clearance has nearly doubled again (50 mL/min) resulting in a half-life of approximately 4 hours. The increase in vancomycin clearance continues through 4–8 years of age when clearance equals 130–160 mL/min while volume of distribution remains ~0.7 L/kg so that half-life is 2–3 hours. At that time, vancomycin clearance and half-life gradually approach adult values as puberty approaches in children (~12–14 years old).

Intravenous doses for neonates are based on birthweight and age.[39] Steady-state vancomycin serum concentrations are used to individualize doses:

	POSTNATAL AGE	
WEIGHT	**< 7 DAYS**	**≥ 7 DAYS**
<1.2 kg	15 mg/kg every 24 hours	15 mg/kg every 24 hours
1.2–2 kg	10–15 mg/kg every 12–18 hours	10–15 mg/kg every 8–12 hours
>2 kg	10–15 mg/kg every 8–12 hours	10–15 mg/kg every 6–8 hours

Intravenous doses for infants and children are 60 mg/kg/d given every 6 hours for central nervous system infections, 40–60 mg/kg/d given every 6 hours for severe infections, and 40 mg/kg/d given every 6–8 hours for other infections with a maximum of 1 g/dose.[39] Steady-state vancomycin serum concentrations are used to individualize doses.

The effect that hemodialysis has on vancomycin pharmacokinetics depends upon the type of artificial kidney used during the procedure. Vancomycin is a relatively large molecule with a moderate-sized volume of distribution and intermediate protein binding. These characteristics lead to poor hemodialysis removal from the body. The mean vancomycin half-life for

patients with renal failure is 120–140 hours.[34,40,41] Using traditional "low-flux" hemodialysis filters, an insignificant amount (<10%) of the total vancomycin body stores is removed during a 3- to 4-hour dialysis period.[33,34] When hemodialysis is performed with a "high-flux" filter, vancomycin serum concentrations decrease by $^1/_3$ during the dialysis period, but then slowly increase or "rebound" for the next 10–12 hours reaching nearly 90% of predialysis values.[42] Postdialysis vancomycin serum concentrations should be measured after the rebound period in patients receiving hemodialysis with a "high-flux" filter to determine if supplemental doses are needed.

Peritoneal dialysis removes only a negligible amount of vancomycin.[43–45] Patients who develop peritonitis while receiving peritoneal dialysis can be treated by placing vancomycin into the dialysis fluid. Over a 6-hour dwell time, approximately 50% of a vancomycin dose (1000 mg in 2 L dialysis fluid) is absorbed from the peritoneal cavity in renal failure patients without peritonitis.[43] Peritonitis causes inflammation of the peritoneal membrane, which facilitates absorption of vancomycin placed in the peritoneal dialysis fluid (up to 90% absorbed) and dialysis elimination of vancomycin from the body.[45]

Hemofiltration removes vancomycin from the body. The hemofiltration sieving coefficient for vancomycin is 0.80.[46,47] Recommended initial doses for critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration (CVVH) are a loading dose of 15–20 mg/kg followed by 250–500 mg every 12 hours.[48] For patients undergoing continuous ateriovenous hemofiltration (CAVH), the recommended initial dose is 500 mg every 24–48 hours.[49] Because of pharmacokinetic variability, vancomycin concentrations should be measured in hemofiltration patients.

DRUG INTERACTIONS

The most important drug interactions with vancomycin are pharmacodynamic, not pharmacokinetic, in nature. Coadministration of aminoglycoside antibiotics enhances the nephrotoxicity potential of vancomycin.[19,50,51] Aminoglycosides can cause nephrotoxicity when administered alone. When an aminoglycoside and vancomycin are administered concurrently, serum creatinine concentrations should be monitored on a daily basis. Additionally, serum concentrations of the aminoglycoside, as well as vancomycin, should be measured.

When vancomycin is administered to patients stabilized on warfarin therapy, the hypoprothrombinemic effect of the anticoagulant may be augmented.[52] The mechanism of this interaction is unknown, but resulted in a mean 45% increase in prothrombin time over baseline values when warfarin was given alone. Patients receiving warfarin therapy who require vancomycin treatment should have a baseline prothrombin time ratio (INR) measured before the antibiotic is administered and daily INR tests until it is certain that anticoagulation status is stable.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate vancomycin therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be

customized to reflect specific disease states and conditions present in the patient. However, it is computationally intensive.

Nomograms use the dosing concepts in the pharmacokinetic dosing method. But, in order to simplify calculations, they make simplifying assumptions. The *Moellering nomogram* is designed to achieve average steady-state concentrations equal to 15 μg/mL. Some clinicians find this approach confusing since target steady-state peak and trough concentrations are not stated by the nomogram. Since the computed dose provided by the nomogram is expressed in mg/kg/24 h, it can be difficult to determine the best dosage interval. However, once experience is gained with this approach, the Moellering nomogram computes doses similar, but not identical, to the pharmacokinetic dosing method. The *Matzke nomogram* is constructed to produce steady-state vancomycin peak and trough concentrations of 30 μg/mL and 7.5 μg/mL, respectively. When these target concentrations are acceptable, the Matzke nomogram computes doses that are very similar to those calculated by the pharmacokinetic dosing method. However, since the expected peak and trough concentrations are in the middle of their respective therapeutic ranges, the Matzke nomogram computes relatively large initial doses for patients.

Literature-based recommended dosing is a commonly used method to prescribe initial doses of vancomycin to pediatric patients. Doses are based on those that commonly produce steady-state concentrations within the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of vancomycin is to compute the best dose possible for the patient given their set of disease states and conditions that influence vancomycin pharmacokinetics and the site and severity of the infection. In order to do this, pharmacokinetic parameters for the patient will be estimated using mean parameters measured in other individuals with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Vancomycin is almost completely eliminated unchanged by the kidney, and there is a good relationship between creatinine clearance and vancomycin clearance (Figure 5-2).[32] This relationship permits the estimation of the vancomycin clearance for a patient which can be used to calculate an initial dose of the drug. Mathematically, the equation for the straight line shown in Figure 5-2 is: $Cl = 0.695(CrCl) + 0.05$, where Cl is vancomycin clearance in mL/min/kg and CrCl is creatinine clearance in mL/min/kg. Because each clearance value is normalized for the patient's weight, the estimated or measured creatinine clearance must be divided by the patient's weight in kilogram before using it in the equation, and the resulting vancomycin clearance must be multiplied by the patient's weight if the answer is needed in the units of mL/min. The weight factor that is used for all individuals, including obese patients, is total body weight (TBW).[30,31,34,36,37] It is not possible to simply enter a patient's creatinine clearance in mL/min and expect the resulting vancomycin clearance to have the units of mL/min with the idea that dividing the creatinine clearance by weight, then multiplying the vancomycin clearance by weight, mathematically cancels the weight factor out of the equation. The reason this does not work is that the y-intercept of the creatinine clearance/vancomycin clearance equation, which

represents nonrenal vancomycin clearance, is in terms of mL/min/kg so mathematical cancellation of the weight factor is not possible.

For example, the estimated vancomycin clearance for an individual with a creatinine clearance of 100 mL/min who weighs 70 kg is 1.04 mL/min/kg or 73 mL/min: Cl = 0.695[(100 mL/min)/70 kg] + 0.05 = 1.04 mL/min/kg or 1.04 mL/min/kg · 70 kg = 73 mL/min. Taking the patient's renal function into account when deriving an initial dose of vancomycin is the single most important characteristic to assess.

VOLUME OF DISTRIBUTION ESTIMATE

The average volume of distribution of vancomycin is 0.7 L/kg.[30,31] The weight factor that is used to calculate vancomycin volume of distribution for obese patients is ideal body weight (IBW).[30,31,37] Thus, for an 80-kg patient, the estimated vancomycin volume of distribution would be 56 L: V = 0.7 L/kg · 80 kg = 56 L. For a 150-kg obese patient with an ideal body weight of 60 kg, the estimated vancomycin volume of distribution is 42 L: V = 0.7 L/kg · 60 kg = 42 L.

ELIMINATION RATE CONSTANT AND HALF-LIFE ESTIMATES

The vancomycin elimination rate constant (k_e) is computed using the estimated clearance and volume of distribution values for the drug in the following equation: $k_e = Cl/V$. It is usually expressed using the unit of h^{-1}. For example, for a patient with a vancomycin clearance equal to 1.04 mL/min/kg and a vancomycin volume of distribution equal to 0.7 L/kg, the elimination rate constant (in h^{-1}) would be computed as follows: k_e = (1.04 mL/min/kg · 60 min/h)/(0.7 L/kg · 1000 mL/L) = 0.089 h^{-1}, where 60 min/h and 1000 mL/L are used as unit conversion factors for time and volume, respectively. Vancomycin half-life would be calculated using the equation that relates elimination rate constant and half-life: $t_{1/2} = 0.693/k_e = 0.693/0.089\ h^{-1} = 7.8$ h.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous infusion over an hour, vancomycin serum concentrations follow a two- or three-compartment pharmacokinetic model (Figure 5-1). After the end of infusion if a two-compartment model is followed, serum concentrations drop rapidly because of distribution of drug from blood to tissues (α or distribution phase). By about 30–60 minutes after the end of infusion, vancomycin serum concentrations decline more slowly, and the elimination rate constant for this portion of the concentration/time curve is one that varies with renal function (β or elimination phase). In patients whose vancomycin serum concentration/time curve follows a three-compartment model, an intermediate distribution phase is found between the α and β portions of the graph. While these models are important to understand conceptually, they cannot easily be used clinically because of their mathematical complexity. Because of this, the simpler one-compartment model is widely used and allows accurate dosage calculation when peak vancomycin serum concentrations are obtained after drug distribution is finished.[30,34]

Intravenously administered vancomycin is given over 1 hour as intermittent continuous infusions. Since the drug has a long half-life relative to the infusion time (1 hour) and waiting time (0.5–1 hour) necessary to allow for distribution to complete before peak concentrations are obtained, little of the drug is eliminated during this 1.5- to 2-hour time period. Intravenous infusion pharmacokinetic equations that take into account the loss of drug during the infusion time are not generally needed because so little vancomycin is

eliminated during the infusion and waiting time periods. So, although the antibiotic is given as an intravenous infusion, intravenous bolus equations accurately predict peak vancomycin concentrations and are mathematically simpler.[53] Because of these reasons, intravenous bolus equations are preferred by many clinicians to compute vancomycin doses (Table 5-2). Vancomycin steady-state peak (Css_{max}) and trough (Css_{min}) serum concentrations are chosen to treat the patient based upon the type, site, and severity of infection as well as the infecting organism. Steady-state versions of one-compartment model intravenous bolus equations are as follows (Table 5-2): $Css_{max} = (D/V)/(1 - e^{-k_e\tau})$, $Css_{min} = Css_{max}e^{-k_e\tau}$, where D is the antibiotic dose, V is the volume of distribution, k_e is the elimination rate constant, t is time, and τ is the dosage interval.

STEADY-STATE CONCENTRATION SELECTION

Vancomycin steady-state trough concentrations are selected based on site and severity of infection in addition to the infecting organism. A commonly used therapeutic range for this value is 5–15 μg/mL. For selected patients, such as those with hospital-acquired pneumonia in institutions with high MICs for methicillin-resistant *S. aureus* (MRSA), trough concentrations as high as 20 μg/mL may be needed to effect a cure.[15] There is far less clinical data available to aid in the selection of vancomycin serum concentrations compared to aminoglycoside serum concentrations. Severe, life-threatening infections should be treated with vancomycin trough steady-state concentrations in the

TABLE 5-2A One-Compartment Model Equations Used with Vancomycin

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval.

TABLE 5-2B Pharmacokinetic Constant Computations Utilizing a One-compartment Model Used with Vancomycin

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_{max}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_{max} - C_{min})$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(Css_{max} - Css_{min})$ $Cl = k_e V$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, C_{min} is the predose trough concentration, C_{max} is the postdose peak concentration.

TABLE 5-2C Equations Used to Compute Individualized Dosage Regimens for Vancomycin

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max}\, V(1 - e^{-k_e\tau})$ $LD = Css_{max}\, V$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, k_0 is the continuous infusion rate.

upper end of this range (10–15 μg/mL). Recent data suggests that steady-state trough concentrations as high as 15 μg/mL may pose no greater risk of vancomycin-induced nephrotoxicity than those within the traditional therapeutic range.[18] If a patient does not respond adequately to vancomycin therapy that provides trough serum concentrations within the usual range or for patients with sites of infection that are difficult for vancomycin to penetrate (such as the central nervous system), clinicians should consider prescribing an increased dose that produces a value as high as 20 μg/mL. Whenever vancomycin doses are used that exceed steady-state trough concentrations of 15 μg/mL, serum creatinine concentrations should be monitored daily to detect early signs of nephrotoxicity.

Steady-state peak vancomycin concentrations are chosen to provide adequate antibiotic penetration to the site of infection and to avoid adverse drug reactions. A commonly used therapeutic range for this value is 20–40 μg/mL. In severe, life-threatening infections of the central nervous system, peak vancomycin serum concentrations as high as 60 μg/mL may be necessary to facilitate drug penetration. Whenever doses of vancomycin are used that exceed steady-state peak concentrations of 40 μg/mL, the patient should be monitored daily for early signs of ototoxicity (decreased hearing acuity in the conversational range, feeling of fullness or pressure in the ears, tinnitus, loss of equilibrium, headache, nausea, vomiting, vertigo, nystagmus, ataxia).

DOSAGE COMPUTATION

The equations given in Table 5-2 are used to compute vancomycin doses.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

1. *Estimate the creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(97\ mL/min)/70kg] + 0.05 = 1.015\ mL/min/kg$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 70\ kg = 49\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (1.015\ mL/min/kg \cdot 60\ min/h)/(0.7\ L/kg \cdot 1000\ mL/L) = 0.087\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.087\ h^{-1} = 8\ h$$

5. *Choose desired steady-state serum concentrations.*

Patients with *S. aureus* wound infections need to be carefully assessed. This patient did not appear to be in acute distress, with a normal temperature and slightly elevated white blood cell count (WBC). The wound was warm and red with a slight amount of purulent discharge. Because the infection was localized to the wound area, a Css_{min} = 7 μg/mL and Css_{max} = 20 μg/mL were chosen.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 20\ \mu g/mL - \ln 7\ \mu g/mL)/0.087\ h^{-1} = 12.1\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 20\ mg/L \cdot 49\ L\ [1 - e^{-(0.087\ h^{-1})(12\ h)}] = 635\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 750 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 750 mg every 12 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 20\ mg/L \cdot 49\ L = 980\ mg$$

As noted, this patient has good renal function (CrCl ≥ 60 mL/min) so a loading dose wouldn't be prescribed for this patient.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(25\ mL/min)/70kg] + 0.05 = 0.298\ mL/min/kg$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 70\ kg = 49\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.298\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0256\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0256\ h^{-1} = 27\ h$$

5. *Choose desired steady-state serum concentrations.*

Patients with *S. aureus* wound infections need to be carefully assessed. This patient did not appear to be in acute distress, with a normal temperature and slightly elevated WBC. The wound was warm and red with a slight amount of purulent discharge. Because the infection was localized to the wound area, a $Css_{min} = 7\ \mu g/mL$ and $Css_{max} = 20\ \mu g/mL$ were chosen.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 20\ \mu g/mL - \ln 7\ \mu g/mL)/0.0256\ h^{-1} = 41\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 48 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 20\ mg/L \cdot 49\ L\ [1 - e^{-(0.0256\ h^{-1})(48\ h)}] = 693\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 750 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 750 mg every 48 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\, V = 20\ mg/L \cdot 49\ L = 980\ mg$$

As noted, this patient has poor renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.) The first maintenance dose would be given one dosage interval (48 hours) after the loading dose was administered.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an *Staphylococcus epidermidis* infection of a prosthetic knee joint. Her current serum creatinine is 0.7 mg/dL and is stable. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 0.7\ mg/dL)} = 184\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient. Since maintenance doses are based on total body weight (TBW), this weight factor is used to compute clearance:

Cl = 0.695(CrCl) + 0.05 = 0.695[(184 mL/min) / 150 kg] + 0.05 = 0.902 mL/min/kg TBW

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg and computed using the patient's ideal body weight because obesity does not significantly alter this parameter:

$$V = 0.7\ L/kg \cdot 57\ kg = 40\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

Note that in the case of obese individuals, different weight factors are needed for vancomycin clearance and volume of distribution, so these weights are included in the equation for elimination rate constant:

$$k_e = Cl/V = (0.902 \text{ mL/min/kg TBW} \cdot 150 \text{ kg TBW} \cdot 60 \text{ min/h}) / (0.7 \text{ L/kg IBW} \cdot 57 \text{ kg IBW} \cdot 1000 \text{ mL/L}) = 0.205 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.205 \text{ h}^{-1} = 3.4 \text{ h}$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 7.5 μg/mL and Css_{max} = 35 μg/mL were chosen for this patient with a. *S. epidermidis* prosthetic joint infection.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 35 \text{ μg/mL} - \ln 7.5 \text{ μg/mL})/0.205 \text{ h}^{-1} = 7.5 \text{ h}$$

Dosage intervals in obese individuals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 8 hours.

Calculate required dose (D):

$$D = Css_{max} V(1 - e^{-k_e\tau}) = 35 \text{ mg/L} \cdot 40 \text{ L} [1 - e^{-(0.205 \text{ h}^{-1})(8 \text{ h})}] = 1128 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1250 mg every 8 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max} V = 35 \text{ mg/L} \cdot 40 \text{ L} = 1400 \text{ mg}$$

As noted, this patient has good renal function (CrCl ≥ 60 mL/min) so a loading dose wouldn't be prescribed for this patient.

Example 4 JM is an 80-year-old, 80-kg (5 ft 8 in) male with Streptococcus viridans endocarditis and is allergic to penicillins and cephalosporins. His current serum creatinine is 1.5 mg/dL, and it has been stable. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {IBW_{males} = 50 + 2.3 (Ht − 60 in) = 50 + 2.3(68 − 60) = 68 kg; % overweight = [100(80kg − 68 kg)]/68kg = 18%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 80\ y)80\ kg]/(72 \cdot 1.5\ mg/dL)$$

$$CrCl_{est} = 44\ mL/min$$

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(44\ mL/min)/80\ kg] + 0.05 = 0.432\ mL/min/kg$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 80\ kg = 56\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.432\ mL/min/kg \cdot 60\ min/h)/(0.7\ L/kg \cdot 1000\ mL/L) = 0.0370\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0370\ h^{-1} = 18.7\ h$$

5. *Choose desired steady-state serum concentrations.*

Steady-state vancomycin serum concentrations of Css_{min} = 5 μg/mL and Css_{max} = 25 μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 25\ \mu g/mL - \ln 5\ \mu g/mL)/0.0370\ h^{-1} = 43\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 48 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 25\ mg/L \cdot 56\ L\ [1 - e^{-(0.0370\ h^{-1})(48\ h)}] = 1163\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1250 mg every 48 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are

given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 25\ mg/L \cdot 56\ L = 1400\ mg, \text{round to } 1500\ mg$$

As noted, this patient has poor renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100–250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required). The first maintenance dose would be given one dosage interval (48 hours) after the loading dose was administered.

Moellering Nomogram Method

Because the only two patient-specific factors that change when using the pharmacokinetic dosing method are patient weight and creatinine clearance, it is possible to make a simple nomogram to handle uncomplicated patients. The Moellering dosage nomogram was the first widely used approach that incorporated pharmacokinetic concepts to compute doses of vancomycin for patients with compromised renal function (Table 5-3).[32] The stated goal of the nomogram is to provide average steady-state vancomycin concentrations equal to 15 μg/mL (or 15 mg/L). In order to use the nomogram, the patient's creatinine clearance is computed and divided by their body weight so that the units for creatinine clearance are mL/min/kg. This value is converted to a vancomycin maintenance dose in terms of mg/kg/24 h. If the patient has renal impairment, a loading dose of 15 mg/kg is suggested. The nomogram does not provide a value for dosage interval.

The relationship between vancomycin clearance and creatinine clearance used in the pharmacokinetic dosing method is the one used to construct the Moellering nomogram. Hence, the dosage recommendations made by both these methods are generally similar although not identical because vancomycin peak and trough concentrations cannot be specified using the nomogram. A modification of the vancomycin clearance/creatinine clearance equation can be made that provides a direct calculation of the vancomycin maintenance dose.[54] Because the equation computes vancomycin clearance, it can be converted to the maintenance dose required to provide an average steady-state concentration of 15 mg/L by multiplying the equation by the concentration (MD = Css · Cl, where MD is maintenance dose) and appropriate unit conversion constants:

$$Cl\ (\text{in mL/min/kg}) = 0.695(\text{CrCl in mL/min/kg}) + 0.05$$

$$D\ (\text{in mg/h/kg}) = [(15\ mg/L \cdot 60\ min/h)/1000\ mL/L][0.695(\text{CrCl in mL/min/kg}) + 0.05]$$

$$D\ (\text{in mg/h/kg}) = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

The use of this modification is straightforward. The patient's creatinine clearance is estimated using an appropriate technique (Cockcroft-Gault method[55] for normal weight patients, Salazar-Corcoran method[56] for obese patients). The vancomycin maintenance dose is directly computed using the dosing equation and multiplied by the patient's weight to convert the answer into the units of mg/h. Guidance to the appropriate dosage interval (in hours) can be gained by dividing this dosage rate into a clinically acceptable

TABLE 5-3 Moellering Nomogram Vancomycin Dosage Chart

1. Compute patient's creatinine clearance (CrCl) using Cockcroft–Gault method for normal weight or Salazar-Corcoran method for obese patients.
2. Divide CrCl by patient's weight.
3. Compute 24-hour maintenance dose for CrCl value.
4. Loading dose of 15 mg/kg should be given in patients with significant renal function impairment.

CREATININE CLEARANCE (mL/min/kg)*	VANCOMYCIN DOSE (mg/kg/24 h)
2	30.9
1.9	29.3
1.8	27.8
1.7	26.3
1.6	24.7
1.5	23.2
1.4	21.6
1.3	20.1
1.2	18.5
1.1	17
1.0	15.4
0.9	13.9
0.8	12.4
0.7	10.8
0.6	9.3
0.5	7.7
0.4	6.2
0.3	4.6
0.2	3.1
0.1	1.5

* Dose for functionally anephric patients is 1.9 mg/kg/24 h
Adapted from Moellering et al.[32]

dose such as 1000 mg. To illustrate how this dosing approach is used, the same patient examples utilized in the previous section will be repeated for this dosage approach.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D\ (in\ mg/h/kg) = 0.626(CrCl\ in\ mL/min/kg) + 0.05$$

$$D = 0.626[(97\ mL/min)/70\ kg] + 0.05 = 0.918\ mg/h/kg$$

$$D = 0.918\ mg/h/kg \cdot 70\ kg = 64.2\ mg/h$$

Because the patient has good renal function, the typical dosage interval of 12 hours will be used:

$$D = 64.2\ mg/h \cdot 12\ h = 770\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 750 mg. The prescribed maintenance dose would be 750 mg every 12 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15\ mg/kg(70\ kg) = 1050\ mg$$

As noted, this patient has good renal function ($CrCl \geq 60$ mL/min) so a loading dose could optionally be prescribed for this patient.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D\ (in\ mg/h/kg) = 0.626(CrCl\ in\ mL/min/kg) + 0.05$$

$$D = 0.626[(25\ mL/min)/70\ kg] + 0.05 = 0.274\ mg/h/kg$$

$$D = 0.274\ mg/h/kg \cdot 70\ kg = 19.2\ mg/h$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000 \text{ mg} / (19.2 \text{ mg/h}) = 52 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 48 hours.

$$D = 19.2 \text{ mg/h} \cdot 48 \text{ h} = 922 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 48 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15 \text{ mg/kg}(70 \text{ kg}) = 1050 \text{ mg}$$

This patient has poor renal function (CrCl <60 mL/min) so a loading dose could be prescribed for this patient and given as the first dose. However, in this case, the loading dose is nearly identical to the maintenance dose, so the loading dose would not be given.

Example 3 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an *S. epidermidis* infection of a prosthetic knee joint. Her current serum creatinine is 0.7 mg/dL and is stable. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese ($IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg). The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - \text{age})[(0.287 \cdot \text{Wt}) + (9.74 \cdot \text{Ht}^2)]}{(60 \cdot \text{S}_{\text{Cr}})}$$

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - 35 \text{ y})\{(0.287 \cdot 150 \text{ kg}) + [9.74 \cdot (1.65 \text{ m})^2]\}}{(60 \cdot 0.7 \text{ mg/dL})} = 184 \text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D \text{ (in mg/h/kg)} = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

$$D = 0.626[(184 \text{ mL/min})/150 \text{ kg}] + 0.05 = 0.818 \text{ mg/h/kg}$$

$$D = 0.818 \text{ mg/h/kg} \cdot 150 \text{ kg} = 122.7 \text{ mg/h}$$

Because the patient has excellent renal function and is obese, a dosage interval equal to 8 hours will be used:

$$D = 122.7 \text{ mg/h} \cdot 8 \text{ h} = 981 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 8 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram. As noted, this patient has good renal function (CrCl ≥60 mL/min) so a loading dose would probably not be prescribed for this patient.

Example 4 JM is an 80-year-old, 80-kg (5 ft 8 in) male with S. viridans endocarditis and is allergic to penicillins and cephalosporins. His current serum creatinine is 1.5 mg/dL, and it has been stable. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {IBW_{males} = 50 + 2.3 (Ht − 60 in) = 50 + 2.3(68 − 60) = 68 kg; % overweight = [100(80kg − 68 kg)] / 68kg = 18%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 80\ y)80\ kg] / (72 \cdot 1.5\ mg/dL)$$

$$CrCl_{est} = 44\ mL/min$$

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D\ (in\ mg/h/kg) = 0.626(CrCl\ in\ mL/min/kg) + 0.05$$

$$D = 0.626[(44\ mL/min)/80\ kg] + 0.05 = 0.394\ mg/h/kg$$

$$D = 0.394\ mg/h/kg \cdot 80\ kg = 31.5\ mg/h$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000\ mg / (31.5\ mg/h) = 31.7\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 36 hours.

$$D = 31.5\ mg/h \cdot 36\ h = 1134\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. The prescribed maintenance dose would be 1250 mg every 36 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15\ mg/kg(80\ kg) = 1200\ mg$$

This patient has poor renal function (CrCl <60 mL/min) so a loading dose could be prescribed for this patient and given as the first dose. However, the computed loading dose is less than the maintenance dose, so would not be given.

Matzke Nomogram Method

The Matzke dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations (Table 5-4).[34] The nomogram has not been tested in obese subjects (>30% over ideal body weight) and should not be employed in this patient population. Additionally, the authors suggest that the nomogram should not be used in patients undergoing peritoneal dialysis.

The nomogram is constructed to produce steady-state vancomycin peak and trough concentrations of 30 μg/mL and 7.5 μg/mL, respectively. A loading dose of 25 mg/kg is given as the first dose, and subsequent maintenance doses of 19 mg/kg are given according to a dosage interval that varies by the patient's creatinine clearance. The dosage interval supplied by the nomogram is the time needed for 19 mg/kg of vancomycin to be eliminated from the body. By replacing the amount eliminated over the dosage interval with a maintenance dose of the same magnitude, the same peak and trough vancomycin concentration/time profile is reproduced after each dose. To illustrate how the nomogram is used, the same patient examples utilized in the previous section (omitting the obese patient case) will be repeated for this dosage approach. Since the nomogram uses slightly different estimates for volume of distribution and elimination rate constant as well as fixed steady-state peak and trough drug concentrations, differences in suggested doses are expected. While the Matzke nomogram has been shown to provide precise and unbiased dosage recommendations, it does supply relatively large doses because expected peak and trough concentrations are in the middle of their respective therapeutic ranges.

TABLE 5-4 Matzke Nomogram Vancomycin Dosage Chart

1. Compute patient's creatinine clearance (CrCl) using Cockcroft–Gault method: CrCl = [(140 − age)BW] / (Scr × 72). Multiply by 0.85 for females.
2. Nomogram not verified in obese individuals.
3. Dosage chart is designed to achieve peak serum concentrations of 30 μg/mL and trough concentrations of 7.5 μg/mL.
4. Compute loading dose of 25 mg/kg.
5. Compute maintenance dose of 19 mg/kg given at the dosage interval listed in the following chart for the patient's CrCl:

CrCl (mL/min)	DOSAGE INTERVAL (DAYS)
≥120	0.5
100	0.6
80	0.75
60	1.0
40	1.5
30	2.0
20	2.5
10	4.0
5	6.0
0	12.0

Adapted from Matzke et al.[34]

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25\ mg/kg(70\ kg) = 1750\ mg$$

3. *Determine dosage interval and maintenance dose.*

From the nomogram the dosage interval is 0.6 days, which would be rounded to every 12 hours. The maintenance dose would be 19 mg/kg · 70 kg = 1330 mg. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg and given one dosage interval (12 hours) after the loading dose.

The prescribed maintenance dose would be 1250 mg every 12 hours.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25\ mg/kg(70\ kg) = 1750\ mg$$

3. *Determine dosage interval and maintenance dose.*

After rounding creatinine clearance to 30 mL/min, the nomogram suggests a dosage interval of 2 days. The maintenance dose would be 19 mg/kg · 70 kg = 1330 mg. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg and given one dosage interval (2 days × 24 hours/day = 48 hours) after the loading dose.

The prescribed maintenance dose would be 1250 mg every 48 hours.

Example 3 JM is an 80-year-old, 80-kg (5 ft 8 in) male with S. viridans endocarditis and is allergic to penicillins and cephalosporins. His current serum creatinine is 1.5 mg/dL, and it has been stable. Compute a vancomycin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese {IBW_{males} = 50 + 2.3 (Ht − 60 in) = 50 + 2.3(68 − 60) = 68 kg; % overweight = [100(80kg − 68 kg)] / 68kg = 18%}. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 80\ y)80\ kg] / (72 \cdot 1.5\ mg/dL)$$

$$CrCl_{est} = 44\ mL/min$$

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25\ mg/kg(80\ kg) = 2000\ mg$$

3. *Determine dosage interval and maintenance dose.*

After rounding creatinine clearance to 40 mL/min, the nomogram suggests a dosage interval of 1.5 days. The maintenance dose would be 19 mg/kg · 80 kg = 1520 mg. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1500 mg and started 1 dosage interval (1.5 days × 24 hours/day = 36 hours) after the loading dose.

The prescribed maintenance dose would be 1500 mg every 36 hours.

Literature-based Recommended Dosing

Because of the large amount of variability in vancomycin pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard vancomycin doses for pediatric patients is warranted. The original computation of these doses was based on the pharmacokinetic dosing methods described in the previous section, and subsequently modified based on clinical experience. In general, the expected vancomycin steady-state serum concentrations used to compute these doses were similar to those for adults. Suggested initial vancomycin doses for various pediatric patients are listed in the *Effects of Disease States and Conditions on Vancomycin Pharmacokinetics and Dosing* section. Doses for neonates are usually rounded to the nearest milligram. If serum creatinine values are available, estimated creatinine clearance can be computed using equations that are specific for pediatric patients (age 0–1 year, $CrCl_{est}$ (in mL/min/1.73 m^2) = (0.45 · Ht)/S_{Cr}; age 1–20 years, $CrCl_{est}$ (in mL/min/1.73 m^2) = (0.55 · Ht) / S_{Cr}, where Ht is in cm and S_{Cr} is in mg/dL).[57]

Example 1 MM is a 3-day-old, 1015-g male with suspected methicillin-resistant *S. aureus* (MRSA) sepsis. His serum creatinine has not been measured, but it is assumed that it is typical for his age and weight. Compute an initial vancomycin dose for this patient.

1. *Compute initial dose and dosage interval.*

Often, serum creatinine measurements are not available for initial dosage computation in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatrics dosage recommendations given in earlier in this chapter, a patient in this age and weight category should receive vancomycin 15 mg/kg every 24 hours. (Note: Grams will be converted to kilograms before the computation is made).

$$\text{Dose} = 15 \text{ mg/kg}(1.015 \text{ kg}) = 15 \text{ mg}$$

The prescribed dose would be 15 mg every 24 hours.

USE OF VANCOMYCIN SERUM CONCENTRATIONS TO ALTER DOSAGES

Because of pharmacokinetic variability among patients, it is likely that doses calculated using patient population characteristics will not always produce vancomycin serum concentrations that are expected. Because of this, vancomycin serum concentrations are measured in many patients to ensure that therapeutic, nontoxic levels are present. However, not all patients may require serum concentration monitoring. For example, if it is expected that only a limited number of doses will be administered as is the case for surgical prophylaxis or an appropriate dose for the renal function and concurrent disease states of the patient is prescribed (e.g., 15 mg/kg every 12 hours for a patient with a creatinine clearance of 80–120 mL/min), vancomycin serum concentration monitoring may not be necessary. Whether or not vancomycin concentrations are measured, important patient parameters (fever curves, white blood cell counts, serum creatinine concentrations, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When vancomycin serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change vancomycin doses since these antibiotics follow *linear pharmacokinetics*. If only steady-state trough concentrations are being measured in a patient, a variant of linear pharmacokinetics can be used to perform *trough-only* dosage adjustments. Sometimes, it is not possible to simply change the dose, and the dosage interval must also be changed to achieve desired serum concentrations. In this case, it may be possible to use *pharmacokinetic concepts* to alter the vancomycin dose. In some situations, it may be necessary to compute the vancomycin pharmacokinetic parameters for the patient using the *one-compartment model parameter method* and utilize these to calculate the best drug dose. Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. If trough-only monitoring is being conducted for a patient, Bayesian computer programs can provide estimates for all vancomycin pharmacokinetic parameters even though only one serum concentration was measured.

Linear Pharmacokinetics Method

Because vancomycin antibiotics follow linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following

equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state peak or trough concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and it may not be possible to attain desired serum concentrations by only changing the dose.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 1000 mg every 12 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 35 μg/mL and 15 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and equaled 22 μg/mL and 10 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state trough of 15 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(97\ mL/min)/70\ kg] + 0.05 = 1.013\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 70\ kg = 49\ L$$

$$k_e = Cl/V = (1.013\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0868\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0868\ h^{-1} = 8\ h$$

Because the patient has been receiving vancomycin for ~3 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15\ \mu g/mL / 10\ \mu g/mL)\ 1000\ mg = 1500\ mg$$

The new suggested dose would be 1500 mg every 12 hours to be started at next scheduled dosing time.

4. *Check steady-state peak concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new}/D_{old})C_{ss,old} = (1500 \text{ mg}/1000 \text{ mg})\ 22\ \mu\text{g/mL} = 33\ \mu\text{g/mL}$$

This steady-state peak concentration should be safe and effective for the infection that is being treated.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an enterococcal endocarditis. Her current serum creatinine is 1.1 mg/dLand is stable. A vancomycin dose of 1000 mg every 12 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and 12 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 17 μg/mL and 6 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state trough of 12 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\text{ y})\{(0.287 \cdot 150\text{ kg}) + [9.74 \cdot (1.65\text{ m})^2]\}}{(60 \cdot 1.1\text{ mg/dL})} = 117\text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(117 \text{ mL/min}) / 150 \text{ kg}] + 0.05 = 0.592 \text{ mL/min/kg}$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7 \text{ L/kg} \cdot 57 \text{ kg} = 40 \text{ L}$$

$$k_e = Cl/V = (0.592 \text{ mL/min/kg} \cdot 150 \text{ kg} \cdot 60 \text{ min/h}) / (0.7 \text{ L/kg} \cdot 57 \text{ kg} \cdot 1000 \text{ mL/L}) = 0.134 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.134 \text{ h}^{-1} = 5.2 \text{ h}$$

Because the patient has been receiving vancomycin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12\ \mu g/mL / 6\ \mu g/mL)\ 1000\ mg = 2000\ mg$$

The new suggested dose would be 2000 mg every 12 hours to be started at next scheduled dosing time.

4. *Check steady-state peak concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new}/D_{old})C_{ss,old} = (2000\ mg/1000\ mg)\ 17\ \mu g/mL = 34\ \mu g/mL$$

This steady-state peak concentration should be safe and effective for the infection that is being treated.

Trough-only Method

Many clinicians adjust vancomycin doses based solely on a measurement of a steady-state trough concentration. When using this method, a typical dose of vancomycin is prescribed for the patient based on their pharmacokinetic and clinical characteristics, a steady-state trough concentration is measured, and the dosage interval is modified to attain the desired concentration. A straightforward way of accomplishing this is to use a simplified relationship between the steady-state trough concentration and the dosage interval:[58] $\tau_{new} = (C_{ss,old}/C_{ss,new})\tau_{old}$, where $C_{ss,old}$ and $C_{ss,new}$ are the original measured and new desired steady-state trough concentrations, respectively; and τ_{old} and τ_{new} are the original and new dosage intervals, respectively. New dosage intervals are rounded to clinically acceptable values (12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible), and the original dose is retained.

Because the dosage interval computation involves a simplification (e.g., steady-state concentrations vary according to the inverse of the dosage interval), the actual new steady-state trough concentration should be slightly higher than that calculated if a shorter dosage interval is used or slightly lower than that calculated if a longer dosage interval is used. However, this method produces steady-state trough concentrations that are usually within 1–2 μg/mL of those computed using more sophisticated Bayesian computer methods.[58]

Example 1 UI is a 55-year-old, 78-kg (height = 6 ft 1 in) male with a methicillin-resistant *S. aureus* (MRSA) pneumonia. His current serum creatinine is 1.5 mg/dL, and it has been stable over the last 3 days since admission. A vancomycin dose of 1000 mg every 24 hours was prescribed and expected to achieve a steady-state trough concentration equal to 15 μg/mL. After the second dose, the steady-state trough concentration equaled 7 μg/mL. Calculate a new vancomycin dose that would provide a steady-state trough of 15 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 55\ y)78\ kg] / (72 \cdot 1.5\ mg/dL)$$

$$CrCl_{est} = 61\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(61\ mL/min)/78\ kg] + 0.05 = 0.594\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 78\ kg = 55\ L$$

$$k_e = Cl/V = (0.594\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0509\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0509\ h^{-1} = 13.6\ h$$

Because the patient has been receiving vancomycin for >3 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dosage interval to achieve desired serum concentration.*

The new dosage interval to attain the desired concentration should be:

$$\tau_{new} = (C_{ss,old}/C_{ss,new})\tau_{old} = (7\ \mu g/mL / 15\ \mu g/mL)\ 24\ h = 11\ h, \text{ round to } 12\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours. The new suggested dose would be 1000 mg every 12 hours to be started 12 hours after the last dose.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in), 165-cm (65 in) female with an enterococcal endocarditis. Her current serum creatinine is 1.1 mg/dL and is stable. A vancomycin dose of 1250 mg every 12 hours was prescribed and expected to achieve a steady-state trough concentration equal to 10 µg/mL. After the third dose, a steady-state concentration was measured and equaled 6 µg/mL. Calculate a new vancomycin dose that would provide a steady-state trough of 10 µg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(117 \text{ mL/min}) / 150 \text{ kg}] + 0.05 = 0.592 \text{ mL/min/kg}$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7 \text{ L/kg} \cdot 57 \text{ kg} = 40 \text{ L}$$

$$k_e = Cl/V = (0.592 \text{ mL/min/kg} \cdot 150 \text{ kg} \cdot 60 \text{ min/h}) / (0.7 \text{ L/kg} \cdot 57 \text{ kg} \cdot 1000 \text{ mL/L}) = 0.134 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.134 \text{ h}^{-1} = 5.2 \text{ h}$$

Because the patient has been receiving vancomycin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dosage interval to achieve desired serum concentration.*

The new dosage interval to attain the desired concentration should be:

$$\tau_{new} = (C_{ss,old}/C_{ss,new})\tau_{old} = (6 \text{ µg/mL} / 10 \text{ µg/mL}) \ 12 \text{ h} = 7 \text{ h, round to 8 h}$$

The new suggested dose would be 1250 mg every 8 hours to be started 8 hours after the last dose. Note that a dosage interval less than 12 hours chosen because of the patient has an expected half-life that is very short.

Pharmacokinetic Concepts Method

As implied by the name, this technique derives alternate doses by estimating actual pharmacokinetic parameters or surrogates for pharmacokinetic parameters.[59] It is a very useful way to calculate drug doses when the linear pharmacokinetic method is not sufficient because a dosage change that will produce a proportional change in steady-state peak and trough concentrations is not appropriate. The only requirement is a steady-state peak and trough vancomycin serum concentration pair obtained before and after a dose (Figure 5-3). The following steps are used to compute new vancomycin doses:

1. *Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-3).*

2. *Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-3).*

3. *Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.* For example, a patient receives a vancomycin dose of 1000 mg given every 12 hours that produces a steady-state peak equal to 25 µg/mL and a steady-state trough equal to 13 µg/mL, and the dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-3).

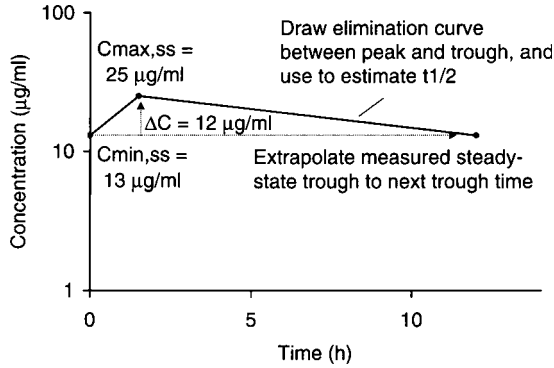

FIGURE 5-3 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

The time between the measured steady-state peak and the extrapolated trough concentration is 10.5 hours (the 12-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. Because the serum concentration declined by approximately half from the peak concentration to the trough concentration, the vancomycin half-life for this patient is approximately 10.5 hours. This information will be used to set the new dosage interval for the patient

4. *Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size.* In the current example, the patient is receiving a vancomycin dose equal to 1000 mg every 12 hours which produced steady-state peak and trough concentrations of 25 µg/mL and 13 µg/mL, respectively. The difference between the peak and trough values is 12 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

5. *Choose new steady-state peak and trough concentrations.* For the purposes of this example, the desired steady-state peak and trough concentrations will be approximately 30 µg/mL and 7 µg/mL, respectively.

6. *Determine the new dosage interval for the desired concentrations.* In this example, the patient has a desired peak concentration of 30 µg/mL. In 1 half-life, the serum concentration will decline to 15 µg/mL, and in an additional half-life the vancomycin concentration will decrease to 7.5 µg/mL (Figure 5-4). Since the approximate half-life is 10.5 hours and 2 half-lives are required for serum concentrations to decrease from the desired peak concentration to the desired trough concentration, the dosage interval should be 21 hours (10.5 hours × 2 half-lives). This value would be rounded off to the clinically acceptable value of 24 hours, and the actual trough concentration would be expected to be slightly lower than 7.5 µg/mL.

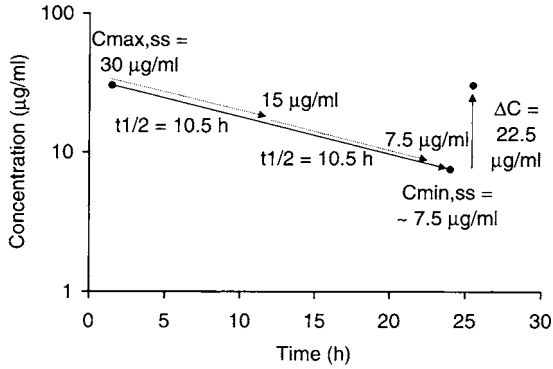

FIGURE 5-4 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

7. *Determine the new dose for the desired concentrations.* The desired peak concentration is 30 µg/mL, and the expected trough concentration is 7.5 µg/mL. The change in concentration between these values is 22.5 µg/mL. It is known from measured serum concentrations that administration of 1000 mg changes serum concentrations by 12 µg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. Therefore, a simple ratio will be used to compute the required dose: $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old}$, where D_{new} and D_{old} are the new and old doses, respectively; ΔC_{new} is the change in concentration between the peak and trough for the new dose; and ΔC_{old} is the change in concentration between the peak and trough for the old dose. (Note: This relationship is appropriate because doses are given into a fixed, constant volume of distribution; it is not because the drug follows linear pharmacokinetics so this method will work whether the agent follows nonlinear or linear pharmacokinetics.) For this example, D_{new} = (22.5 µg/mL / 12 µg/mL) 1000 mg = 1875 mg, which would be rounded to 1750 mg. Vancomycin 1750 mg every 24 hours would be started 24 hours after the last dose of the previous dosage regimen.

Once this method is mastered, it can be used without the need for a calculator. The following are examples that use the pharmacokinetic concepts method to change vancomycin doses.

Example 1 JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 800 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 20 µg/mL and 5 µg/mL, respectively. After the fourth dose, steady-state peak and trough concentrations were measured and equaled 25 µg/mL and 12 µg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 20 µg/mL and a trough of 5 µg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(25\ mL/min)/70\ kg] + 0.05 = 0.298\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 70\ kg = 49\ L$$

$$k_e = Cl/V = (0.298\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0255\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0255\ h^{-1} = 27\ h$$

Because the patient has been receiving vancomycin for ~3 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use pharmacokinetic concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-5).

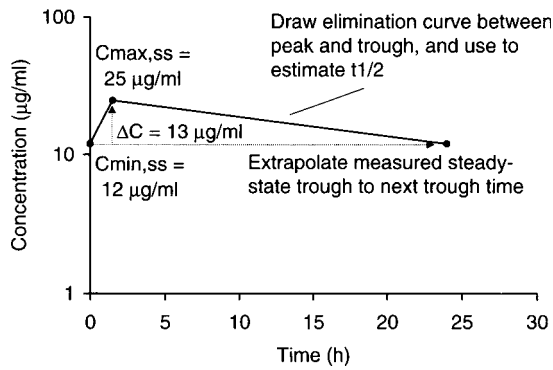

FIGURE 5-5 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-5).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving a vancomycin dose of 800 mg given every 24 hours that produces a steady-state peak equal to 25 μg/mL and a steady-state trough equal to 12 μg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-5). The time between the measured steady-state peak and the extrapolated trough concentration is 22.5 hours (the 24-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 25 μg/mL to 12.5 μg/mL. The concentration of 12 μg/mL is very close to the extrapolated trough value of 12.5 μg/mL. Therefore, 1 half-life expired during the 22.5-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 22.5 hours. This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example the patient is receiving a vancomycin dose equal to 800 mg every 24 hours which produced steady-state peak and trough concentrations of 25 μg/mL and 12 μg/mL, respectively. The difference between the peak and trough values is 13 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 20 μg/mL and 5 μg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations (Figure 5-6). Using the desired concentrations, it will take 1 half-life for the peak concentration of 20 μg/mL to decrease to 10 μg/mL, and an additional half-life for serum concentrations to decline from 10 μg/mL to 5 μg/mL. Therefore, the dosage interval will need to be

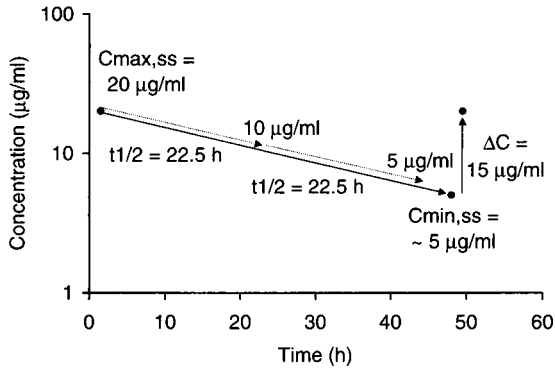

FIGURE 5-6 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

approximately 2 half-lives or 45 hours (22.5 hours × 2 half-lives = 45 hours). This dosage interval would be rounded off to 48 hours.

G. Determine the new dose for the desired concentrations (Figure 5-6). The desired peak concentration is 20 μg/mL, and the expected trough concentration is 5 μg/mL. The change in concentration between these values is 15 μg/mL. It is known from measured serum concentrations that administration of 800 mg changes serum concentrations by 13 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old}$ = (15 μg/mL / 13 μg/mL)800 mg = 923 mg, rounded to 1000 mg. Vancomycin 1000 mg every 48 hours would be started 48 hours after the last dose of the previous dosage regimen.

Example 2 ZW is a 35-year-old, 150 kg (5 ft 5 in) female with an *S. epidermidis* infection of a prosthetic knee joint. Her current serum creatinine is 1.1 mg/dL and is stable. A vancomycin dose of 2500 mg every 18 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and 10 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 40 μg/mL and 3 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 30 μg/mL and a steady-state trough 10 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(117\ mL/min)/150\ kg] + 0.05$$
$$= 0.592\ mL/min/kg\ TBW$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 57\ kg = 40\ L$$

$$k_e = Cl/V = (0.592\ mL/min/kg\ TBW \cdot 150\ kg \cdot 60\ min/h) / (0.7\ L/kg\ IBW \cdot 57\ kg \cdot 1000\ mL/L)$$
$$= 0.134\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.134\ h^{-1} = 5.2\ h$$

Because the patient has been receiving vancomycin for >5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use pharmacokinetic concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-7).

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-7).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving a vancomycin dose of 2500 mg given every 12 hours that produces a steady-state peak equal to 40 μg/mL and a steady-state trough equal to 3 μg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-7). The time between the measured steady-state peak and the extrapolated trough concentration is 16.5 hours (the 18-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 40 μg/mL to 20 μg/mL, another half-life to decrease from 20 μg/mL to 10 μg/mL, an additional half-life to decrease from 10 μg/mL to 5 μg/mL, and a final half-life to decrease from 5 μg/mL to 2.5 μg/mL. The concentration of 3 μg/mL is very close to the extrapolated trough value of 2.5 μg/mL. Therefore, 4 half-lives expired during the 16.5-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 4.1 hours (16.5 hours/4 half-lives = 4.1 h). This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example, the patient is receiving a vancomycin dose equal to 2500 mg

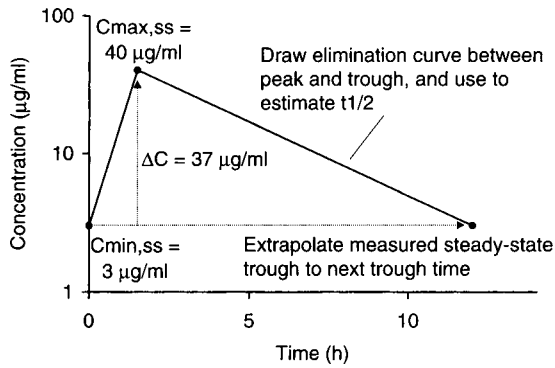

FIGURE 5-7 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The change in concentration after a dose is given (ΔC) is a surrogate measure of the volume of distribution and will be used to compute the new dose for the patient.

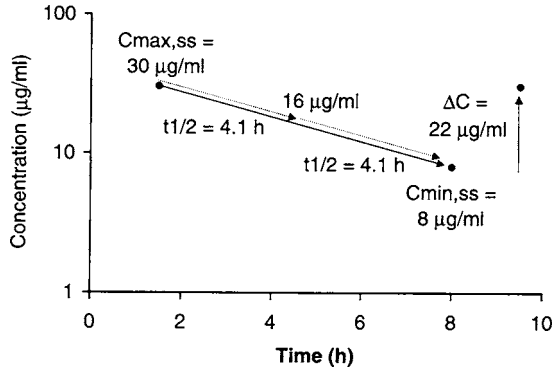

FIGURE 5-8 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

every 18 hours which produced steady-state peak and trough concentrations of 40 µg/mL and 3 µg/mL, respectively. The difference between the peak and trough values is 37 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 µg/mL and 10 µg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations (Figure 5-8). Using the desired concentrations, it will take 1 half-life for the peak concentration of 30 µg/mL to decrease to 15 µg/mL, and an additional half-life for serum concentrations to decline from 15 µg/mL to 8 µg/mL. This concentration is close to the desired trough concentration of 10 µg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 8.2 hours (4.1 hours × 2 half-lives = 8.2 hours). This dosage interval would be rounded off to 8 hours.

G. Determine the new dose for the desired concentrations (Figure 5-8). The desired peak concentration is 30 µg/mL, and the expected trough concentration is 8 µg/mL. The change in concentration between these values is 22 µg/mL. It is known from measured serum concentrations that administration of 2500 mg changes serum concentrations by 37 µg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case: $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old} = (22\ \mu g/mL/37\ \mu g/mL)2500\ mg = 1486\ mg$, rounded to 1500 mg. Vancomycin 1500 mg every 8 hours would be started 8 hours after the last dose of the previous dosage regimen.

One-Compartment Model Parameter Method

The one-compartment model parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations.[60] It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired vancomycin concentrations. The standard one-compartment model parameter method conducts a small pharmacokinetic experiment

using 3–4 vancomycin serum concentrations obtained during a dosage interval and does not require steady-state conditions. The steady-state one-compartment model parameter method assumes that steady state has been achieved and requires only a steady-state peak and trough concentration pair obtained before and after a dose. One-compartment model intravenous bolus equations are used successfully to dose drugs that are given by infusion when the infusion time is less than the drug half-life.[53]

STANDARD ONE-COMPARTMENT MODEL PARAMETER METHOD

The standard version of the one-compartment model parameter method does not require steady-state concentrations. A trough vancomycin concentration is obtained before a dose, a peak vancomycin concentration is obtained after the dose is infused ($^1/_2$–1 hour after a 1-hour infusion), and 1–2 additional postdose serum vancomycin concentrations are obtained (Figure 5-9). Ideally, the 1–2 postdose concentrations should be obtained at least 1 estimated half-life from each other to minimize the influence of assay error. The postdose serum concentrations are used to calculate the vancomycin elimination rate constant and half-life (Figure 5-9). The half-life can be computed by graphing the postdose concentrations on semilogarithmic paper, drawing the best straight line through the data points, and determining the time needed for serum concentrations to decline by one-half. Once the half-life is known, the elimination rate constant (k_e) can be computed: $k_e = 0.693/t_{1/2}$. Alternatively, the elimination rate constant can be directly calculated using the postdose serum concentrations [$k_e = (\ln C_1 - \ln C_2)/\Delta t$, where C_1 and C_2 are postdose serum concentrations and Δt is the time that expired between the times that C_1 and C_2 were obtained], and the half-life can be computed using the elimination rate constant ($t_{1/2} = 0.693/k_e$). The volume of distribution (V) is calculated using the following equation: $V = D/(C_{max} - C_{min})$ where D is the vancomycin dose, C_{max} is the peak concentration and C_{min} is the trough concentration. The elimination rate constant and volume

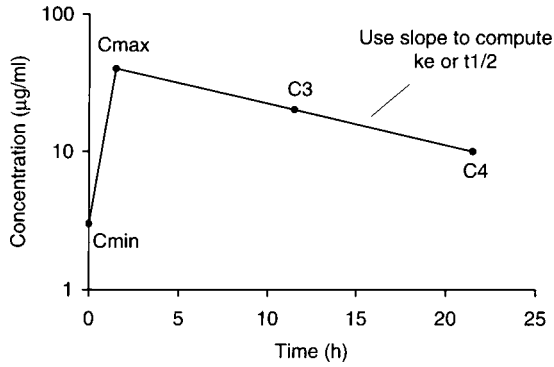

FIGURE 5-9 The one-compartment model parameter method for individualization of vancomycin doses uses a trough (C_{min}), peak (C_{max}), and 1–2 additional postdose concentrations (C_3, C_4) to compute a patient's own, unique pharmacokinetic parameters. This version of the one-compartment model parameter method does not require steady-state conditions. The peak and trough concentrations are used to calculate the volume of distribution, and the postdose concentrations (C_{max}, C_3, C_4) are used to compute half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired vancomycin concentrations.

of distribution measured in this fashion are the patient's own, unique vancomycin pharmacokinetic constants and can be used in one-compartment model intravenous bolus equations to compute the required dose to achieve any desired serum concentration.

STEADY-STATE ONE-COMPARTMENT MODEL PARAMETER METHOD

If a steady-state peak and trough vancomycin concentration pair is available for a patient, the one-compartment model parameter method can be used to compute patient pharmacokinetic parameters and vancomycin doses (Figure 5-10). Since the patient is at steady-state, the measured trough concentration obtained before the dose was given can be extrapolated to the next dosage time and used to compute the vancomycin elimination rate constant [$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t'$, where Css_{max} and Css_{min} are the steady-state peak and trough serum concentrations and t' and τ are the infusion time and dosage interval], and the half-life can be computed using the elimination rate constant ($t_{1/2} = 0.693/k_e$). The volume of distribution (V) is calculated using the following equation: $V = D / (Css_{max} - Css_{min})$ where D is the vancomycin dose, Css_{max} is the steady-state peak concentration and Css_{min} is the steady-state trough concentration. The elimination rate constant and volume of distribution measured in this way are the patient's own, unique vancomycin pharmacokinetic constants and can be used in one-compartment model intravenous bolus equations to compute the required dose to achieve any desired serum concentration. The dosage calculations are similar to those done in the initial dosage section of this chapter, except that the patient's real pharmacokinetic parameters are used in the equations instead of population pharmacokinetic estimates.

To illustrate the similarities and differences between the pharmacokinetic concepts and the one-compartment model parameter methods, some of the same cases used in the previous section will be used as examples here.

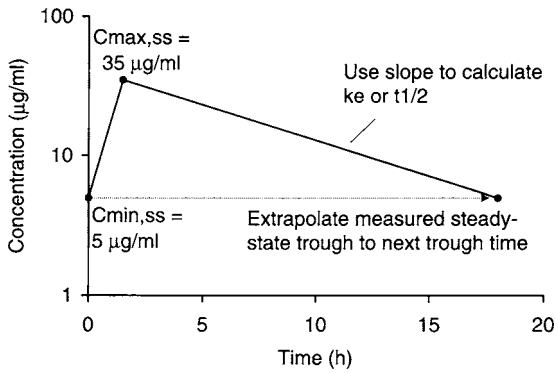

FIGURE 5-10 The steady-state version of the one-compartment model parameter method uses a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough concentration can be extrapolated to the next predose time. The steady-state peak and trough concentrations are used to calculate the volume of distribution and half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired vancomycin concentrations.

Example 1 JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 800 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 20 μg/mL and 5 μg/mL, respectively. After the fourth dose, steady-state peak and trough concentrations were measured and were 25 μg/mL and 12 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 20 μg/mL and a trough of 5 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(25\ mL/min)/70\ kg] + 0.05$$
$$= 0.298\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 70\ kg = 49\ L$$

$$k_e = Cl/V = (0.298\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0255\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0255\ h^{-1} = 27\ h$$

Because the patient has been receiving vancomycin for ~3 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use one-compartment model parameter method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: t' = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 25\ \mu g/mL - \ln 12\ \mu g/mL) / (24\ h - 1.5\ h)$$
$$= 0.0326\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0326\ h^{-1} = 21.2\ h$$

B. Compute the patient's volume of distribution.

$$V = D/(Css_{max} - Css_{min}) = 800\ mg/(25\ mg/L - 12\ mg/L) = 61.5\ L$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 20 μg/mL and 5 μg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 20\ \mu g/mL - \ln 5\ \mu g/mL)/0.0326\ h^{-1}$$
$$= 42\ h, \text{ rounded to } 48\ h$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$D = Css_{max}\, V(1 - e^{-k_e\tau}) = 20\ mg/L \cdot 61.5\ L\ [1 - e^{-(0.0326\ h^{-1})(48\ h)}]$$
$$= 974\ mg, \text{ rounded to } 1000\ mg$$

A dose of vancomycin 1000 mg every 48 hours would be prescribed to begin 48 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an *S. epidermidis* infection of a prosthetic knee joint. Her current serum creatinine is 1.1 mg/dL and is stable. A vancomycin dose of 2500 mg every 18 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and 10 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 40 μg/mL and 3 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 30 μg/mL and a steady-state trough 10 μg/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(117 \text{ mL/min})/150 \text{ kg}] + 0.05 = 0.592 \text{ mL/min/kg TBW}$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7 \text{ L/kg} \cdot 57 \text{ kg} = 40 \text{ L}$$

$$k_e = Cl/V = (0.592 \text{ mL/min/kg TBW} \cdot 150 \text{ kg} \cdot 60 \text{ min/h}) / (0.7 \text{ L/kg IBW} \cdot 57 \text{ kg} \cdot 1000 \text{ mL/L}) = 0.134 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.134 \text{ h}^{-1} = 5.2 \text{ h}$$

Because the patient has been receiving vancomycin for >5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Use one-compartment model parameter method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: assumed infusion time and waiting time are 1 hour and $^1/_2$ hour, respectively).

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 40 \text{ µg/mL} - \ln 3 \text{ µg/mL}) / (18 \text{ h} - 1.5 \text{ h}) = 0.157 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.157 \text{ h}^{-1} = 4.4 \text{ h}$$

B. Compute the patient's volume of distribution.

$$V = D / (Css_{max} - Css_{min}) = 2500 \text{ mg}/(40 \text{ mg/L} - 3 \text{ mg/L}) = 67.6 \text{ L}$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 µg/mL and 10 µg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 30 \text{ µg/mL} - \ln 10 \text{ µg/mL})/0.157 \text{ h}^{-1} = 7 \text{ h, rounded to 8 h}$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation used in the initial dosing section of this chapter:

$$D = Css_{max} V(1 - e^{-k_e\tau}) = 30 \text{ mg/L} \cdot 67.6 \text{ L} [1 - e^{-(0.157 \text{ h}^{-1})(8 \text{ h})}] = 1450 \text{ mg, rounded to 1500 mg}$$

A dose of vancomycin 1500 mg every 8 hours would be prescribed to begin 8 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Example 3 JH is a 24-year-old, 70-kg (height = 6 ft 0 in) male with methicillin-resistant *S. aureus* endocarditis. His current serum creatinine is 1.0 mg/dL, and it has been stable over the last 7 days since admission. A vancomycin dose of 1000 mg every 12 hours was prescribed. After the third dose, the following vancomycin serum concentrations were obtained:

TIME	VANCOMYCIN CONCENTRATION (μg/mL)
0800 H	2.0
0800–0900 H	Vancomycin 1000 mg
1000 H	18.0
1500 H	10.1
2000 H	5.7

Medication administration sheets were checked, and the previous dose was given 2 hours early (1800 H the previous day). Because of this, it is known that the patient is not at steady state. Calculate a new vancomycin dose that would provide a steady-state peak of 30 μg/mL and a trough of 10 μg/mL.

One-compartment Model Parameter Method to Compute a New Dose

A. Plot serum concentration/time data (Figure 5-11). Because serum concentrations decrease in a straight line, use any two postdose concentrations to compute the patient's elimination rate constant and half-life. Compute the patient's elimination rate constant and half-life.

$$k_e = (\ln C_{max} - \ln C_{min})/\Delta t = (\ln 18\ \mu g/mL - \ln 5.7\ \mu g/mL) / (10\ h) = 0.115\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.115\ h^{-1} = 6\ h$$

B. Compute the patient's volume of distribution.

$$V = D/(C_{max} - C_{min}) = 1000\ mg/(18\ mg/L - 2.0\ mg/L) = 62.5\ L$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 μg/mL and 10 μg/mL, respectively.

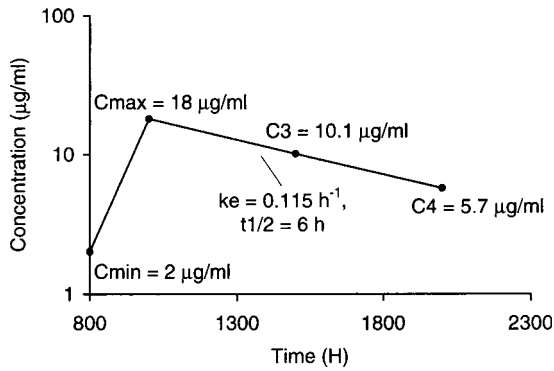

FIGURE 5-11 Graph of vancomycin serum concentrations used in one-compartment model parameter method example.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 30\ \mu g/mL - \ln 10\ \mu g/mL)/0.115\ h^{-1}$$
$$= 10\ h, \text{ rounded to } 12\ h$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation used in the initial dosing section of this chapter:

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 30\ mg/L \cdot 62.5\ L\ [1 - e^{-(0.115\ h^{-1})(12\ h)}]$$
$$= 1403\ mg, \text{ rounded to } 1500\ mg$$

A dose of vancomycin 1500 mg every 12 hours would be prescribed to begin 12 hours after the last dose of the previous regimen.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[61–63] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, renal function, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work

just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. When trough-only monitoring is used during vancomycin therapy, Bayesian pharmacokinetic computer programs can be used to compute a complete patient pharmacokinetic profile that includes clearance, volume of distribution, and half-life. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[64]

Example 1 JM is a 50-year-old, 70-kg (height = 5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A vancomycin dose of 800 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 20 μg/mL and 5 μg/mL, respectively. After the fourth dose, steady-state peak and trough concentrations were measured and were 25 μg/mL and 12 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 20 μg/mL and a trough of 5 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 57.4 L, a half-life equal to 24.2 hours, and an elimination rate constant of 0.0286 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1000 mg every 48 hours will produce a steady-state peak concentration of 23 μg/mL and a steady-state trough concentration of 6 μg/mL. Using either the pharmacokinetic concepts or the one-compartment model parameter methods previously described in this chapter produced the same answer for this patient.

Example 2 ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an *S. epidermidis* infection of a prosthetic knee joint. Her current serum creatinine is 1.1 mg/dL and is stable. A vancomycin dose of 2500 mg every 18 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 30 μg/mL and 10 μg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 40 μg/mL and 3 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state peak of 30 μg/mL and a steady-state trough 10 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 55.9 L, a half-life equal to 4.4 hours, and an elimination rate constant of 0.158 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1500 mg every 8 hours will produce a steady-state peak concentration of 34.6 μg/mL and a steady-state trough concentration of 11.5 μg/mL. Using either the pharmacokinetic concepts or the one-compartment model parameter methods previously described in this chapter produced the same answer for this patient.

Example 3 KU is an 80-year-old, 65-kg (height = 5 ft 8 in) male with S. viridans endocarditis and is allergic to penicillins and cephalosporins. His current serum creatinine is 1.9 mg/dL, and it has been stable. A vancomycin dose of 1000 mg every 12 hours was prescribed with the expectation that it would produce steady-state peak and trough concentrations of 30 μg/mL and 10 μg/mL, respectively. After the third dose, a trough concentration was measured and equaled 17.5 μg/mL. Calculate a new vancomycin dose that would provide a steady-state peak of 30 μg/mL and a steady-state trough 10 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program* In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 74.8 L, a half-life equal to 33.6 hours, and an elimination rate constant of 0.0206 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1250 mg every 48 hours will produce a steady-state peak concentration of 26 μg/mL and a steady-state trough concentration of 10 μg/mL.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 5-5.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that antibiotic therapy is appropriate for current microbiologic

TABLE 5-5 Dosing Strategies

DOSING APPROACH/PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	One-compartment model parameter method
Nomogram/concepts	Moellering or Matzke nomogram (adults) or Literature-based recommended dosing (pediatrics)	Trough-only method (1 concentration) or Pharmacokinetic concepts method (≥2 concentrations)
Computerized	Bayesian computer program	Bayesian computer program

cultures and sensitivities. Also, it should be confirmed that the patient is receiving other appropriate concurrent antibiotic therapy, such as aminoglycoside antibiotics, when necessary to treat the infection.

1. KI is a 75-year-old, 62-kg (height = 5 ft 9 in) male with *S. epidermidis* sepsis. His current serum creatinine is 1.3 mg/dL, and it has been stable since admission. Compute a vancomycin dose for this patient to provide a steady-state peak concentration of 30 μg/mL and a steady-state trough concentration of 10 μg/mL using conventional dosing.

2. Patient KI (please see problem 1) was prescribed vancomycin 1000 mg every 36 hours. Steady-state vancomycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a 1-hour infusion of vancomycin) was 34 μg/mL while the trough concentration (obtained immediately before dosage administration) was 2.5 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state peak concentration of 30 μg/mL and a steady-state trough concentration of 7 μg/mL.

3. HT is a 35-year-old, 75-kg (height = 5 ft 7 in) female with a methicillin-resistant *S. aureus* wound infection and chronic renal failure. Her current serum creatinine is 3.7 mg/dL, and it has been stable since admission. Compute a vancomycin dose for this patient to provide a steady-state peak concentration of 25 μg/mL and a steady-state trough concentration of 5 μg/mL using conventional dosing.

4. Patient HT (please see problem 3) was prescribed vancomycin 1200 mg every 48 hours. Steady-state vancomycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a 1-hour infusion of vancomycin) was 55 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 18 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state peak concentration of 25 μg/mL and a steady-state trough concentration of 5 μg/mL.

5. LK is a 55-year-old, 140-kg (height = 5 ft 8 in) male with a penicillin-resistant enterococcal endocarditis. His current serum creatinine is 0.9 mg/dL, and it has been stable since admission. Compute a vancomycin dose for this patient to provide a

steady-state peak concentration of 40 μg/mL and a steady-state trough concentration of 10 μg/mL.

6. Patient LK (please see problem 5) was prescribed vancomycin 1000 mg every 8 hours. Steady-state vancomycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a 1-hour infusion of vancomycin) was 42 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 18 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state peak concentration of 40 μg/mL and a steady-state trough concentration of 10 μg/mL.

7. AF is a 45-year-old, 140-kg (5 ft 2 in) female with an S. viridans endocarditits who is allergic to penicillins and cephalosporins. Her current serum creatinine is 2.4 mg/dL and is stable. Compute a vancomycin dose for this patient to provide a steady-state peak concentration of 25 μg/mL, and a steady-state trough concentration of 7 μg/mL.

8. Patient AF (please see problem 7) was prescribed 1300 mg every 24 hours. Steady-state vancomycin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained $^1/_2$ hour after a 1-hour infusion of vancomycin) was 30 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 2.5 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state peak concentration of 25 μg/mL and a steady-state trough concentration of 7 μg/mL.

9. DG is a 66-year-old, 65 kg (5 ft 5 in) female with a methicillin-resistant *S. aureus* sternal osteomyelitis secondary to coronary artery bypass graft (CABG) surgery. While in the hospital, she developed ascites due to hepatorenal syndrome and her current weight is 72 kg. Her current serum creatinine is 1.4 mg/dL and stable. Compute a vancomycin dose for this patient to provide a steady-state peak concentration of 30 μg/mL, and a steady-state trough concentration of 7 μg/mL.

10. Patient DG (please see problem 9) was prescribed 1200 mg every 36 hours. Steady-state vancomycin concentrations were obtained before and after the fifth dose, and the peak concentration (obtained $^1/_2$ hour after a 1-hour infusion of vancomycin) was 17 μg/mL while the trough concentration (obtained within $^1/_2$ hour before dosage administration) was 4 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state peak concentration of 30 μg/mL and a steady-state trough concentration of 7 μg/mL.

11. GG is a 27-year-old, 85-kg (6 ft 2 in) male trauma patient with a penicillin-resistant enterococcal pneumonia and is currently on a respirator. He sustained multiple injuries secondary to a motor vehicle accident 2 weeks ago and lost a large amount of blood at the accident site. He developed acute renal failure due to prolonged hypotension and poor perfusion of his kidneys (current postdialysis serum creatinine is 5.3 mg/dL). He is currently receiving hemodialysis on Mondays, Wednesdays, and Fridays from 0800 H to 1200 H using a low-flux dialysis filter. Recommend a vancomycin dosage regimen that will achieve peak concentrations of 40 μg/mL and trough concentrations of 10 μg/mL. The first dose of the regimen will be given immediately after hemodialysis is finished on Wednesday at 1200 H.

12. Patient GG (please see problem 11) was prescribed 1600 mg loading dose on Wednesday at 1200 H and following serum concentrations were obtained:

DATE/TIME	DESCRIPTION	CONCENTRATION
Friday at 0800 H	Predialysis	20 μg/mL
Monday at 0800 H	Predialysis	12.1 μg/mL

Use these serum concentrations to compute the patient's own pharmacokinetic parameters for vancomycin and a new dosage schedule that will achieve peak concentrations of 40 μg/mL and trough concentrations of 10 μg/mL.

13. FD is a 67-year-old, 60-kg (5 ft 2 in) female with a serum creatinine equal to 1.8 mg/dL placed on vancomycin for a postsurgical brain abcess. The prescribed dose was vancomycin 900 mg every 12 hours (infused over 1 hour) and 2 doses have been given at 0800 and 2000 hours. A trough concentration of 20 μg/mL was obtained at 0730 H the next morning ($^1/_2$ hour before the third dose). Compute the dose to give Css_{max} = 40 μg/mL and Css_{min} = 15 μg/mL.

14. OI is a 52-year-old, 87-kg (6 ft 2 in) male with postoperative *S. epidermidis* septic arthritis. His current serum creatinine is 1.4 mg/dL and stable. Nine hours after the second dose of vancomycin 1000 mg every 12 hours, a vancomycin serum concentration equal to 5 μg/mL is measured. Compute a revised vancomycin dose for this patient to provide steady-state peak concentrations equal to 30 μg/mL and steady-state trough concentrations of 7 μg/mL.

15. HY is a 45-year-old, 65-kg (5 ft 4 in) female bone marrow transplant recipient who develops methicillin-resistant *S. aureus* sepsis. Her current serum creatinine is 1.1 mg/dL. She is administered vancomycin 750 mg every 12 hours. A vancomycin serum concentration was obtained 5 hours after the first dose and equaled 15 μg/mL. Compute a revised vancomycin dose for this patient to provide steady-state peak concentrations equal to 40 μg/mL and steady-state trough concentrations of 13 μg/mL.

16. OF is a 9-day-old, 1550-g female with a wound infection. Her serum creatinine has not been measured, but it is assumed that it is typical for her age and weight. Compute an initial vancomycin dose for this patient.

17. Patient OF (please see problem 16) was prescribed vancomycin 20 mg every 12 hours. Steady-state vancomycin concentrations were obtained, and the peak concentration was 16 μg/mL while the trough concentration was 4 μg/mL. Compute a revised vancomycin dose for this patient to provide a steady-state trough concentration of 7 μg/mL.

18. UL is a 7-year-old, 24-kg (3-ft 11-in) male with methicillin-resistant *S. aureus* (MRSA) sepsis. His serum creatinine is 0.5 mg/dL, and it has been stable for the last 2 days. Compute an initial vancomycin dose for this patient.

19. Patient UL (please see problem 18) was prescribed vancomycin 250 mg every 6 hours and was expected to achieve steady-state peak and trough concentrations equal to 25 μg/mL and 10 μg/mL, respectively. Steady-state peak and trough concentrations were measured and were 15 μg/mL and 7 μg/mL, respectively. Calculate a new vancomycin dose that would provide a steady-state trough of 10 μg/mL.

20. TK is a 75-year-old, 66-kg (height = 5 ft 5 in) female with a methicillin-resistant *S. aureus* (MRSA) pneumonia. Her current serum creatinine is 1.8 mg/dL, and it has been stable over the last 3 days since admission. A vancomycin dose of 1000 mg every 24 hours was prescribed and expected to achieve a steady-state trough concentration equal to 15 μg/mL. After the third dose, the steady-state trough concentration equaled 25 μg/mL. Calculate a new vancomycin dose that would provide a steady-state trough of 15 μg/mL.

21. VY is a 48-year-old, 170-kg (height = 5 ft 7 in) female with septic arthritis due to methicillin-resistant *S. aureus* (MRSA). Her current serum creatinine is 1.3 mg/dL and is stable. A vancomycin dose of 1000 mg every 24 hours was prescribed and expected to achieve a steady-state trough concentration equal to 12 μg/mL. After the third dose, a steady-state concentration was measured and equaled 8 μg/mL. Calculate a new vancomycin dose that would provide a steady-state trough of 12 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial vancomycin dose for patient KI would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(43\ mL/min)/62kg] + 0.05 = 0.533\ mL/min/kg$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 62\ kg = 43.4\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.533\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0457\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.0457\ h^{-1} = 15.2\ h$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 10 μg/mL and Css_{max} = 30 μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e = (\ln 30\ \mu g/mL - \ln 10\ \mu g/mL) / 0.0457\ h^{-1} = 24.1\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 24 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 30\ mg/L \cdot 43.4\ L\ [1 - e^{-(0.0457\ h^{-1})(24\ h)}] = 867\ mg$$

Vancomycin doses should be rounded to the nearest 100 – 250 mg. This dose would be rounded to 1000 mg because the patient has sepsis. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1000 mg every 24 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 30\ mg/L \cdot 43.4\ L = 1302\ mg$$

As noted, this patient has poor renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.) The first maintenance dose would be given one dosage interval (24 hours) after the loading dose was administered.

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D \text{ (in mg/h/kg)} = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

$$D = 0.626[(43 \text{ mL/min}) / 62 \text{ kg}] + 0.05 = 0.484 \text{ mg/h/kg}$$

$$D = 0.484 \text{ mg/h/kg} \cdot 62 \text{ kg} = 30 \text{ mg/h}$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000 \text{ mg}/(30 \text{ mg/h}) = 33 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 36 hours.

$$D = 30 \text{ mg/h} \cdot 36 \text{ h} = 1080 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 36 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15 \text{ mg/kg}(62 \text{ kg}) = 930 \text{ mg}$$

This loading dose is less than the suggested maintenance dose, so would not be prescribed.

Matzke Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 75 \text{ y})62 \text{ kg}] / (72 \cdot 1.3 \text{ mg/dL})$$

$$CrCl_{est} = 43 \text{ mL/min}$$

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25 \text{ mg/kg}(62 \text{ kg}) = 1550 \text{ mg, rounded to } 1500 \text{ mg}$$

3. *Determine dosage interval and maintenance dose.*

From the nomogram the dosage interval is 1.5 days or 36 hours. The maintenance dose would be 19 mg/kg · 62 kg = 1178 mg. Vancomycin doses should be rounded to

the nearest 100–250 mg. This dose would be rounded to 1250 mg and given one dosage interval (36 hours) after the loading dose.

The prescribed maintenance dose would be 1250 mg every 36 hours.

2. *Solution to problem 2* The revised vancomycin dose for patient KI would be calculated as follows:

Pharmacokinetic Concepts Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(43\ mL/min) / 62\ kg] + 0.05$$
$$= 0.533\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 62\ kg = 43.4\ L$$

$$k_e = Cl/V = (0.533\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L)$$
$$= 0.0457\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0457\ h^{-1} = 15.2\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use pharmacokinetic concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-12).

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-12).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving a vancomycin dose of 1000 mg given every 36 hours that produces a steady-state peak equal to 34 µg/mL and a steady-state trough equal to 2.5 µg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later

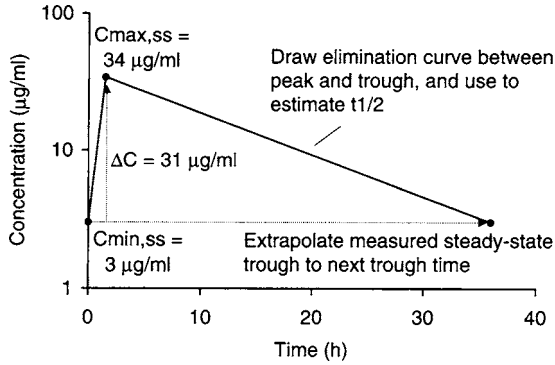

FIGURE 5-12 Solution to problem 2 using pharmacokinetic concepts method.

(Figure 5-12). The time between the measured steady-state peak and the extrapolated trough concentration is 34.5 hours (the 36-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 34 µg/mL to 17 µg/mL, another half-life for concentrations to decrease from 17 µg/mL to 8.5 µg/mL, an additional half-life for concentrations to drop from ~ 8 µg/mL to 4 µg/mL, and a final half-life for the concentration to decrease to 2 µg/mL. The concentration of 2 µg/mL is very close to the extrapolated trough value of 2.5 µg/mL. Therefore, 4 half-lives expired during the 34.5-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is 9 hours (34.5 h / 4 half-lives = ~ 9 h). This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example the patient is receiving a vancomycin dose equal to 1000 mg every 36 hours which produced steady-state peak and trough concentrations of 34 µg/mL and 2.5 µg/mL, respectively. The difference between the peak and trough values is 31.5 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 µg/mL and 7 µg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations. Using the desired concentrations, it will take 1 half-life for the peak concentration of 30 µg/mL to decrease to 15 µg/mL, and an additional half-life for serum concentrations to decline from 15 µg/mL to 7.5 µg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 18 hours (9 hours × 2 half-lives = 18 hours).

G. Determine the new dose for the desired concentrations. The desired peak concentration is 30 µg/mL, and the expected trough concentration is 7 µg/mL. The change in concentration between these values is 23 µg/mL. It is known from measured serum

concentrations that administration of 1000 mg changes serum concentrations by 31.5 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case, $D_{new} = (\Delta C_{new} / \Delta C_{old}) D_{old} =$ (23 μg / mL / 31.5 μg/mL)1000 mg = 730 mg, rounded to 750 mg. Vancomycin 750 mg every 18 hours would be started 18 hours after the last dose of the previous dosage regimen.

One-Compartment Model Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(43\ mL/min)/62\ kg] + 0.05 = 0.533\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 62\ kg = 43.4\ L$$

$$k_e = Cl/V = (0.533\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0457\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.0457\ h^{-1} = 15.2\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use One-Compartment Model Parameter Method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: t′ = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 34\ \mu g/mL - \ln 2.5\ \mu g/mL) / (36\ h - 1.5\ h)$$
$$= 0.0757\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.0757\ h^{-1} = 9.2\ h$$

B. Compute the patient's volume of distribution.

$$V = D/(Css_{max} - Css_{min}) = 1000\ mg/(34\ mg/L - 2.5\ mg/L) = 31.7\ L$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 30 μg/mL and 7 μg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 30\ \mu g/mL - \ln 7\ \mu g/mL)/0.0757\ h^{-1}$$
$$= 19\ h, \text{ rounded to } 18\ h$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 30\ mg/L \cdot 31.7\ L\ [1 - e^{-(0.0757\ h^{-1})(18\ h)}]$$
$$= 708\ mg, \text{ rounded to } 750\ mg$$

A dose of vancomycin 750 mg every 18 hours would be prescribed to begin 18 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 33.5 L, a half-life equal to 9.6 hours, and an elimination rate constant of $0.0720\ h^{-1}$.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 750 mg every 18 hours will produce a steady-state peak concentration of 29.7 µg/mL and a steady-state trough concentration of 8.7 µg/mL. Using the pharmacokinetic concepts method or the one-compartment model parameter method produced the same result.

3. *Solution to problem 3* The initial vancomycin dose for patient HT would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot S_{Cr})\}0.85$$
$$= \{[(140 - 35\ y)75\ kg]/(72 \cdot 3.7\ mg/dL)\}0.85$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(25\ mL/min)/75\ kg] + 0.05 \\ &= 0.283\ mL/min/kg \end{aligned}$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 75\ kg = 52.5\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.283\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0242\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.0242\ h^{-1} = 28.6\ h$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 5 µg/mL and Css_{max} = 25 µg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 25\ \mu g/mL - \ln 5\ \mu g/mL)/0.0242\ h^{-1} = 66\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 72 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 25\ mg/L \cdot 52.5\ L\ [1 - e^{-(0.0242\ h^{-1})(72\ h)}] = 1083\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. (Note: µg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1000 mg every 72 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 25\ mg/L \cdot 52.5\ L = 1313\ mg$$

As noted, this patient has poor renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.) The first maintenance dose would be given one dosage interval (72 hours) after the loading dose was administered.

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85 \end{aligned}$$

$$CrCl_{est} = 25\ mL/min$$

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D\ (in\ mg/h/kg) = 0.626(CrCl\ in\ mL/min/kg) + 0.05$$

$$D = 0.626[(25\ mL/min)/75\ kg] + 0.05 = 0.260\ mg/h/kg$$

$$D = 0.260\ mg/h/kg \cdot 75\ kg = 19.5\ mg/h$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000\ mg / (19.5\ mg/h) = 51\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 48 hours.

$$D = 19.5\ mg/h \cdot 48\ h = 935\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 48 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15\ mg/kg(75\ kg) = 1125\ mg$$

This loading dose would be rounded off to 1250 mg and given as the first dose. The first maintenance dose would be given one dosage interval (48 hours) after the loading dose.

Matzke Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85 \end{aligned}$$

$$CrCl_{est} = 25\ mL/min$$

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25\ mg/kg(75\ kg) = 1875\ mg, \text{ rounded to } 1750\ mg$$

3. *Determine dosage interval and maintenance dose.*

Round the creatinine clearance value to 30 mL/min. From the nomogram the dosage interval is 2 days or 48 hours. The maintenance dose would be:

$$19\ mg/kg \cdot 75\ kg = 1425\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1500 mg and given one dosage interval (48 hours) after the loading dose.

The prescribed maintenance dose would be 1500 mg every 48 hours.

4. *Solution to problem 4* The revised vancomycin dose for patient HT would be calculated as follows:

Pharmacokinetic Concepts Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85 \end{aligned}$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(25\ mL/min)/75\ kg] + 0.05 = 0.283\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 75\ kg = 52.5\ L$$

$$k_e = Cl/V = (0.283\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0242\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0242\ h^{-1} = 28.6\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use pharmacokinetic concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-13).

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-13).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving an vancomycin dose of 1200 mg given every 48 hours that produces a steady-state peak equal to 55 μg/mL and a steady-state trough equal to 18 μg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-13). The time between the measured steady-state peak and the extrapolated trough concentration is 46.5 hours (the 48-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 55 μg/mL to 28 μg/mL, and an additional half-life for concentrations to drop from 28 μg/mL to 14 μg/mL. The concentration of 18 μg/mL is close to the extrapolated trough value of 14 μg/mL. Therefore, ~1.5 half-lives expired during the 46.5-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is ~31 hours (46.5 h / 1.5 half-lives = ~31 h). This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example the patient is receiving a vancomycin

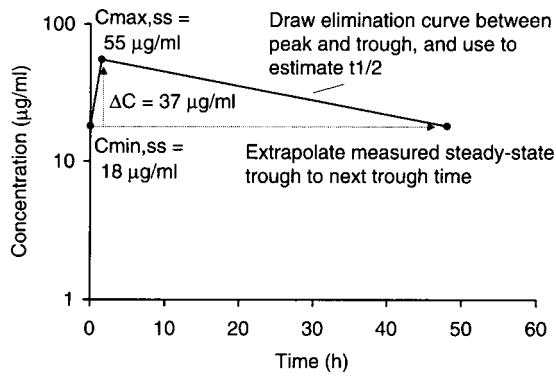

FIGURE 5-13 Solution to problem 4 using pharmacokinetic concepts method.

dose equal to 1200 mg every 48 hours which produced steady-state peak and trough concentrations of 55 μg/mL and 18 μg/mL, respectively. The difference between the peak and trough values is 37 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 25 μg/mL and 5 μg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations. Using the desired concentrations, it will take 1 half-life for the peak concentration of 25 μg/mL to decrease to 12.5 μg/mL, and an additional half-life for serum concentrations to decline from 12.5 μg/mL to 6 μg/mL. A concentration of 6 μg/mL is close to the desired concentration of 5 μg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 72 hours (31 hours × 2 half-lives = 62 h, round to 72 h).

G. Determine the new dose for the desired concentrations. The desired peak concentration is 25 μg/mL, and the expected trough concentration is 6 μg/mL. The change in concentration between these values is 19 μg/mL. It is known from measured serum concentrations that administration of 1200 mg changes serum concentrations by 37 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case, $D_{new} = (\Delta C_{new} / \Delta C_{old}) D_{old}$ = (19 μg/mL / 37 μg/mL)1200 mg = 616 mg, rounded to 750 mg (dose rounded up because of MRSA infection). Vancomycin 750 mg every 72 hours would be started 72 hours after the last dose of the previous dosage regimen.

One-Compartment Model Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - \text{age})BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ \text{y})75\ \text{kg}] / (72 \cdot 3.7\ \text{mg/dL})\}0.85 \end{aligned}$$

$$CrCl_{est} = 25\ \text{mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(25\ \text{mL/min})/75\ \text{kg}] + 0.05 = 0.283\ \text{mL/min/kg}$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ \text{L/kg} \cdot 75\ \text{kg} = 52.5\ \text{L}$$

$$k_e = Cl/V = (0.283\ \text{mL/min/kg} \cdot 60\ \text{min/h}) / (0.7\ \text{L/kg} \cdot 1000\ \text{mL/L}) = 0.0242\ \text{h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0242\ \text{h}^{-1} = 28.6\ \text{h}$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use one-compartment model parameter method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: t′ = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 55\ \mu g/mL - \ln 18\ \mu g/mL)/(48\ h - 1.5\ h) = 0.0240\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0240\ h^{-1} = 28.9\ h$$

B. Compute the patient's volume of distribution.

$$V = D/(Css_{max} - Css_{min}) = 1200\ mg/(55\ mg/L - 18\ mg/L) = 32.4\ L$$

C. Choose new steady-state peak and trough concentrations. For the purpose of this example, the desired steady-state peak and trough concentrations will be 25 μg/mL and 5 μg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 25\ \mu g/mL - \ln 5\ \mu g/mL)/0.0240\ h^{-1} = 67\ h, \text{ rounded to } 72\ h$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 25\ mg/L \cdot 32.4\ L\ [1 - e^{-(0.0240\ h^{-1})(72\ h)}] = 667\ mg, \text{ rounded to } 750\ mg$$

A dose of vancomycin 750 mg every 72 hours would be prescribed to begin 72 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 33.8 L, a half-life equal to 31.3 hours, and an elimination rate constant of 0.0221 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 750 mg every 72 hours will produce a steady-state peak concentration of 27.7 μg/mL and a steady-state trough concentration of 5.8 μg/mL. Using the pharmacokinetic concepts method or the one-compartment model parameter method gives identical answers.

5. *Solution to problem 5* The initial vancomycin dose for patient LK would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3 (Ht − 60) = 50 + 2.3(68 in − 60) = 68.4 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{(51 \cdot 0.9\ mg/dL)} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(136\ mL/min)/140\ kg] + 0.05$$
$$= 0.724\ mL/min/kg\ TBW$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 68.4\ kg = 47.9\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.724\ mL/min/kg\ TBW \cdot 140\ kg \cdot 60\ min/h) / (0.7\ L/kg\ IBW \cdot 68.4\ kg \cdot 1000\ mL/L) = 0.127\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.127\ h^{-1} = 5.5\ h$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 10 μg/mL and Css_{max} = 40 μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 40\ \mu g/mL - \ln 10\ \mu g/mL)/0.127\ h^{-1} = 11\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 40\ mg/L \cdot 47.9\ L\ [1 - e^{-(0.127\ h^{-1})(12\ h)}] = 1498\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1500 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be: 1500 mg every 12 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 40\ mg/L \cdot 47.9\ L = 1915\ mg$$

As noted, this patient has good renal function (CrCl ≥ 60 mL/min) so a loading dose would not be necessary for this patient. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3 (Ht − 60) = 50 + 2.3(68 in − 60) = 68.4 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{(51 \cdot 0.9\ mg/dL)} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D \text{ (in mg/h/kg)} = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

$$D = 0.626[(136 \text{ mL/min})/140 \text{ kg}] + 0.05 = 0.657 \text{ mg/h/kg TBW}$$

$$D = 0.657 \text{ mg/h/kg} \cdot 140 \text{ kg} = 92 \text{ mg/h}$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000 \text{ mg}/(92 \text{ mg/h}) = 11 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 hours.

$$D = 92 \text{ mg/h} \cdot 12 \text{ h} = 1103 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 12 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg IBW is suggested by the Moellering nomogram:

$$LD = 15 \text{ mg/kg}(68.4 \text{ kg}) = 1026 \text{ mg}$$

This loading dose is smaller than the maintenance dose and would not be given.

6. *Solution to problem 6* The revised vancomycin dose for patient LK would be calculated as follows:

Pharmacokinetic Concepts Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3 (Ht − 60) = 50 + 2.3(68 in − 60) = 68.4 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est(males)}} = \frac{(137 - \text{age})[(0.285 \cdot \text{Wt}) + (12.1 \cdot \text{Ht}^2)]}{(51 \cdot \text{S}_{\text{Cr}})}$$

$$\text{CrCl}_{\text{est(males)}} = \frac{(137 - 55 \text{ y})\{(0.285 \cdot 140 \text{ kg}) + [12.1 \cdot (1.73 \text{ m})^2]\}}{(51 \cdot 0.9 \text{ mg/dL})} = 136 \text{ mL/min}$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(136\ mL/min)/140\ kg] + 0.05 \\ &= 0.724\ mL/min/kg\ TBW \end{aligned}$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 68.4\ kg = 47.9\ L$$

$$\begin{aligned} k_e = Cl/V &= (0.724\ mL/min/kg\ TBW \cdot 140\ kg \cdot 60\ min/h)\ / \\ &\quad (0.7\ L/kg \cdot 68.4\ kg\ IBW \cdot 1000\ mL/L) = 0.127\ h^{-1} \end{aligned}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.127\ h^{-1} = 5.5\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use pharmacokinetic concepts method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-14).

B. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time (Figure 5-14).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient is receiving a vancomycin dose of 1000 mg given every 8 hours that produces a steady-state peak equal to 42 µg/mL and a steady-state trough equal to 18 µg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-14). The time between the measured steady-state peak and the extrapolated trough concentration is 6.5 hours (the 8-hour dosage interval minus the 1.5 hours combined infusion and waiting time). The definition of half-life is the time needed

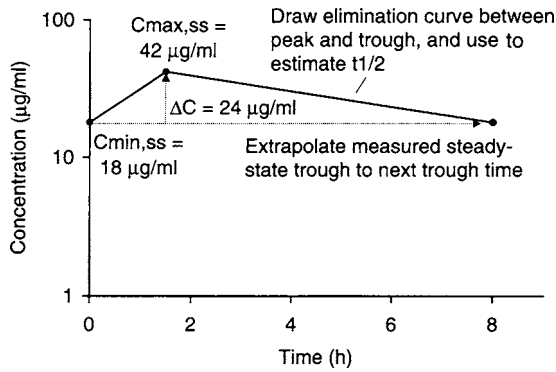

FIGURE 5-14 Solution to problem 6 using pharmacokinetic concepts method.

for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 42 μg/mL to 21 μg/mL. The concentration of 18 μg/mL is just slightly below 21 μg/mL. Therefore, ~1.25 half-lives expired during the 6.5-hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is ~5 hours (6.5 h/1.25 half-lives = ~5 h). This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example, the patient is receiving a vancomycin dose equal to 1000 mg every 8 hours which produced steady-state peak and trough concentrations of 42 μg/mL and 18 μg/mL, respectively. The difference between the peak and trough values is 24 μg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 40 μg/mL and 10 μg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations. Using the desired concentrations, it will take 1 half-life for the peak concentration of 40 μg/mL to decrease to 20 μg/mL, and an additional half-life for serum concentrations to decline from 20 μg/mL to 10 μg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 12 hours (5 hours × 2 half-lives = 10 h, round to 12 h).

G. Determine the new dose for the desired concentrations. The desired peak concentration is 40 μg/mL, and the expected trough concentration is 10 μg/mL. The change in concentration between these values is 30 μg/mL. It is known from measured serum concentrations that administration of 1000 mg changes serum concentrations by 24 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case, $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old}$ = (30 μg/mL / 24 μg/mL)1000 mg = 1250 mg. Vancomycin 1250 mg every 12 hours would be started 12 hours after the last dose of the previous dosage regimen.

One-Compartment Model Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3 (Ht – 60) = 50 + 2.3(68 in – 60) = 68.4 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{(51 \cdot 0.9\ mg/dL)} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in) / (100 cm/m) = 1.73 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(136 \text{ mL/min})/140 \text{ kg}] + 0.05 \\ &= 0.724 \text{ mL/min/kg TBW} \end{aligned}$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7 \text{ L/kg} \cdot 68.4 \text{ kg} = 47.9 \text{ L}$$

$$\begin{aligned} k_e = Cl/V &= (0.724 \text{ mL/min/kg TBW} \cdot 140 \text{ kg} \cdot 60 \text{ min/h}) / \\ &\quad (0.7 \text{ L/kg IBW} \cdot 68.4 \text{ kg} \cdot 1000 \text{ mL/L}) = 0.127 \text{ h}^{-1} \end{aligned}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.127 \text{ h}^{-1} = 5.5 \text{ h}$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use one-compartment model parameter method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: t′ = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$\begin{aligned} k_e &= (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 42 \text{ µg/mL} - \ln 18 \text{ µg/mL}) / (8 \text{ h} - 1.5 \text{ h}) \\ &= 0.130 \text{ h}^{-1} \end{aligned}$$

$$t_{1/2} = 0.693/k_e = 0.693 / 0.130 \text{ h}^{-1} = 5.3 \text{ h}$$

B. Compute the patient's volume of distribution.

$$V = D/(Css_{max} - Css_{min}) = 1000 \text{ mg}/(42 \text{ mg/L} - 18 \text{ mg/L}) = 41.7 \text{ L}$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 40 µg/mL and 10 µg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\begin{aligned} \tau &= (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 40 \text{ µg/mL} - \ln 10 \text{ µg/mL})/0.130 \text{ h}^{-1} \\ &= 11 \text{ h, rounded to } 12 \text{ h} \end{aligned}$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$\begin{aligned} D &= Css_{max} V(1 - e^{-k_e\tau}) = 40 \text{ mg/L} \cdot 41.7 \text{ L} [1 - e^{-(0.130 \text{ h}^{-1})(12 \text{ h})}] \\ &= 1318 \text{ mg, rounded to } 1250 \text{ mg} \end{aligned}$$

A dose of vancomycin 1250 mg every 12 hours would be prescribed to begin 12 hours after the last dose of the previous regimen. This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 68.4 L, a half-life equal to 12.6 hours, and an elimination rate constant of 0.0551 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1750 mg every 24 hours will produce a steady-state peak concentration of 34 μg/mL and a steady-state trough concentration of 9.7 μg/mL. Using the pharmacokinetic concepts method or the one-compartment model parameter method produced the same answer of 1250 mg every 12 hours. The Bayesian computer program suggests a longer dosage interval and larger dose because of the population pharmacokinetic parameter influence for volume of distribution on the dosing algorithm. If additional concentrations are input into the program, the effect of the population parameters will diminish and eventually produce the same answer as the other two methods.

7. *Solution to problem 7* The initial vancomycin dose for patient AF would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(62 in − 60) = 49.6 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - \mathrm{age})[(0.287 \cdot \mathrm{Wt}) + (9.74 \cdot \mathrm{Ht}^2)]}{(60 \cdot \mathrm{S_{Cr}})}$$

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - 45\ \mathrm{y})\{(0.287 \cdot 140\ \mathrm{kg}) + [9.74 \cdot (1.57\ \mathrm{m})^2]\}}{(60 \cdot 2.4\ \mathrm{mg/dL})} = 45\ \mathrm{mL/min}$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$\mathrm{Cl} = 0.695(\mathrm{CrCl}) + 0.05 = 0.695[(45\ \mathrm{mL/min})/140\ \mathrm{kg}] + 0.05$$
$$= 0.274\ \mathrm{mL/min/kg\ TBW}$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7 \text{ L/kg} \cdot 49.6 \text{ kg} = 34.7 \text{ L}$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.274 \text{ mL/min/kg TBW} \cdot 140 \text{ kg} \cdot 60 \text{ min/h}) / (0.7 \text{ L/kg IBW} \cdot 49.6 \text{ kg} \cdot 1000 \text{ mL/L}) = 0.0663 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0663 \text{ h}^{-1} = 10.5 \text{ h}$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 7 μg/mL and Css_{max} = 25 μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 25 \text{ μg/mL} - \ln 7 \text{ μg/mL})/0.0663 \text{ h}^{-1} = 19.2 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 18 hours.

Calculate required dose (D):

$$D = Css_{max} V(1 - e^{-k_e \tau}) = 25 \text{ mg/L} \cdot 34.7 \text{ L} [1 - e^{-(0.0663 \text{ h}^{-1})(18 \text{ h})}] = 605 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 500 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 500 mg every 18 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max} V = 25 \text{ mg/L} \cdot 34.7 \text{ L} = 868 \text{ mg}$$

As noted, this patient has moderate renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient. The loading dose would be rounded to 750 mg and given as the first dose. Maintenance doses would begin one dosage interval after the loading dose was administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required).

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(62 in − 60) = 49.6 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 45\ y)\{(0.287 \cdot 140\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 2.4\ mg/dL)} = 45\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D\ (in\ mg/h/kg) = 0.626(CrCl\ in\ mL/min/kg) + 0.05$$

$$D = 0.626[(45\ mL/min)/140\ kg] + 0.05 = 0.252\ mg/h/kg\ TBW$$

$$D = 0.252\ mg/h/kg \cdot 140\ kg = 35.2\ mg/h$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000\ mg/(35.2\ mg/h) = 28.4\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 24 hours.

$$D = 35.2\ mg/h \cdot 24\ h = 846\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 750 mg. The prescribed maintenance dose would be 750 mg every 24 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg IBW is suggested by the Moellering nomogram:

$$LD = 15\ mg/kg(49.6\ kg) = 744\ mg$$

This loading is smaller than the maintenance dose and would not be given.

8. *Solution to problem 8* The revised vancomycin dose for patient AF would be calculated as follows:

Pharmacokinetic Concepts Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(62 in − 60) = 49.6 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 45\ y)\{(0.287 \cdot 140\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 2.4\ mg/dL)} = 45\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(45\ mL/min)/140\ kg] + 0.05$$
$$= 0.274\ mL/min/kg\ TBW$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 49.6\ kg = 34.7\ L$$

$$k_e = Cl/V = (0.\ 274\ mL/min/kg\ TBW \cdot 140\ kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 49.6\ kg \cdot 1000\ mL/L) = 0.0663\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0663\ h^{-1} = 10.5\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use Pharmacokinetic Concepts Method to compute a new dose.*

A. Draw a rough sketch of the serum log concentration/time curve by hand, keeping tract of the relative time between the serum concentrations (Figure 5-15).

B. Since the patient is at steady-state, the trough concentration can be extrapolated to the next trough value time (Figure 5-15).

C. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life. The patient

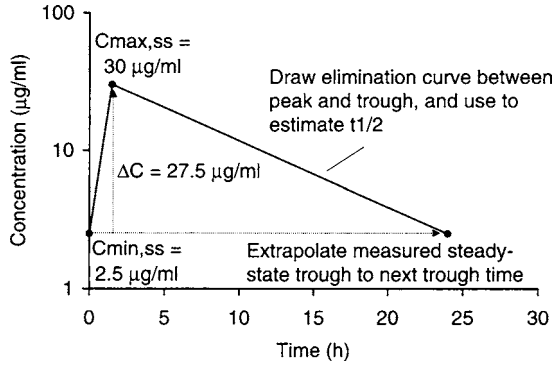

FIGURE 5-15 Solution to Problem 8 using pharmacokinetic concepts method.

is receiving a vancomycin dose of 1300 mg given every 24 hours that produces a steady-state peak equal to 30 µg/mL and a steady-state trough equal to 2.5 µg/mL. The dose is infused over 1 hour and the peak concentration is drawn $^1/_2$ hour later (Figure 5-15). The time between the measured steady-state peak and the extrapolated trough concentration is 22.5 hours (the 24-hour dosage interval minus the 1.5-hour combined infusion and waiting time). The definition of half-life is the time needed for serum concentrations to decrease by half. It would take 1 half-life for the peak serum concentration to decline from 30 µg/mL to 15 µg/mL, an additional half-life for the concentration to decrease from 15 µg/mL to 7.5 µg/mL, another half-life for the concentration to decline from 7.5 µg/mL to 4 µg/mL, and a final half-life for the concentration to reach 2 µg/mL. The concentration of 2 µg/mL is just slightly below 2.5 µg/mL. Therefore, 4 half-lives expired during the 22.5 hour time period between the peak concentration and extrapolated trough concentration, and the estimated half-life is ~ 6 hours (22.5 h / 4 half-lives = ~ 6 h). This information will be used to set the new dosage interval for the patient.

D. Determine the difference in concentration between the steady-state peak and trough concentrations. The difference in concentration will change proportionally with the dose size. In the current example the patient is receiving a vancomycin dose equal to 1300 mg every 24 hours which produced steady-state peak and trough concentrations of 30 µg/mL and 2.5 µg/mL, respectively. The difference between the peak and trough values is 27.5 µg/mL. The change in serum concentration is proportional to the dose, and this information will be used to set a new dose for the patient.

E. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 25 µg/mL and 7 µg/mL, respectively.

F. Determine the new dosage interval for the desired concentrations. Using the desired concentrations, it will take 1 half-life for the peak concentration of 25 µg/mL to decrease to 12.5 µg/mL, and an additional half-life for serum concentrations to decline from 12.5 µg/mL to 6 µg/mL. Therefore, the dosage interval will need to be approximately 2 half-lives or 12 hours (6 hours × 2 half-lives = 12 hours).

G. Determine the new dose for the desired concentrations. The desired peak concentration is 25 μg/mL, and the expected trough concentration is 6 μg/mL. The change in concentration between these values is 19 μg/mL. It is known from measured serum concentrations that administration of 1300 mg changes serum concentrations by 27.5 μg/mL and that the change in serum concentration between the peak and trough values is proportional to the size of the dose. In this case, $D_{new} = (\Delta C_{new}/\Delta C_{old})D_{old} = (19\ \mu g/mL/27.5\ \mu g/mL)1300\ mg = 898\ mg$, rounded to 1000 mg. Vancomycin 1000 mg every 12 hours would be started 12 hours after the last dose of the previous dosage regimen.

One-Compartment Model Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(62 in − 60) = 49.6 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 45\ y)\{(0.287 \cdot 140\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 2.4\ mg/dL)} = 45\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(45\ mL/min)/140\ kg] + 0.05$$
$$= 0.274\ mL/min/kg\ TBW$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 49.6\ kg = 34.7\ L$$

$$k_e = Cl/V = (0.274\ mL/min/kg\ TBW \cdot 140\ kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 49.6\ kg \cdot 1000\ mL/L) = 0.0663\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0663\ h^{-1} = 10.5\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are close to steady-state values. This steady-state concentration pair can be used to compute the patient's own unique pharmacokinetic parameters which can be utilized to calculate individualized doses.

3. *Use one-compartment model parameter method to compute a new dose.*

A. Compute the patient's elimination rate constant and half-life. (Note: t′ = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$k_e = (\ln Css_{max} - \ln Css_{min})/\tau - t' = (\ln 30\ \mu g/mL - \ln 2.5\ \mu g/mL) / (24\ h - 1.5\ h) = 0.110\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.110\ h^{-1} = 6.3\ h$$

B. Compute the patient's volume of distribution.

$$V = D/(Css_{max} - Css_{min}) = 1300\ mg/(30\ mg/L - 2.5\ mg/L) = 47.3\ L$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 25 μg/mL and 7 μg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 25\ \mu g/mL - \ln 7\ \mu g/mL)/0.110\ h^{-1} = 12\ h$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 25\ mg/L \cdot 47.3\ L\ [1 - e^{-(0.110\ h^{-1})(12\ h)}] = 868\ mg, \text{ rounded to } 1000\ mg$$

A dose of vancomycin 1000 mg every 12 hours would be prescribed to begin 12 hours after the last dose of the previous regimen (dose rounded up because patient is being treated for endocarditis). This dose is identical to that derived for the patient using the pharmacokinetic concepts method.

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 41.4 L, a half-life equal to 6.3 hours, and an elimination rate constant of $0.110\ h^{-1}$.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 750 mg every 12 hours will produce a steady-state peak concentration of 23.4 μg/mL and a steady-state trough concentration

of 7 μg/mL. Using the pharmacokinetic concepts method or the one-compartment model parameter method produced similar results.

9. *Solution to problem 9* The initial vancomycin dose for patient DG would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW]/(72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 66\ y)65\ kg]/(72 \cdot 1.4\ mg/dL)\}0.85 \end{aligned}$$

$$CrCl_{est} = 41\ mL/min$$

(Note: The patient's weight before ascites developed was used to compute $CrCl_{est}$, but the weight after ascites developed was used in the drug dose calculations since the extra ascitic fluid will contribute to the volume of distribution.)

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(41\ mL/min)/72\ kg] + 0.05 \\ &= 0.446\ mL/min/kg \end{aligned}$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 72\ kg = 50.4\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.446\ mL/min/kg \cdot 60\ min/h)/(0.7\ L/kg \cdot 1000\ mL/L) = 0.0382\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0382\ h^{-1} = 18.1\ h$$

5. *Choose desired steady-state serum concentrations.*

A $Css_{min} = 7$ μg/mL and $Css_{max} = 30$ μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 30\ \mu g/mL - \ln 7\ \mu g/mL)/0.0382\ h^{-1} = 38.1\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 36 hours.

Calculate required dose (D):

$$D = Css_{max}\, V(1 - e^{-k_e\tau}) = 30 \text{ mg/L} \cdot 50.4 \text{ L}\,[1 - e^{-(0.0382 \text{ h}^{-1})(36 \text{ h})}] = 1130 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1250 mg every 36 hours.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\, V = 30 \text{ mg/L} \cdot 50.4 \text{ L} = 1512 \text{ mg}$$

As noted, this patient has moderate renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100 – 250 mg. This dose would be rounded to 1500 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.) The first maintenance dose would be given one dosage interval (36 hours) after the loading dose was administered.

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - \text{age})BW]/(72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 66 \text{ y})65 \text{ kg}]/(72 \cdot 1.4 \text{ mg/dL})\}0.85 \end{aligned}$$

$$CrCl_{est} = 41 \text{ mL/min}$$

(Note: The patient's weight before ascites developed was used to compute $CrCl_{est}$, but the weight after ascites developed was used in the drug dose calculations since the extra ascitic fluid will contribute to the volume of distribution.)

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the modified vancomycin dosing equation:

$$D \text{ (in mg/h/kg)} = 0.626(\text{CrCl in mL/min/kg}) + 0.05$$

$$D = 0.626[(41 \text{ mL/min})/72 \text{ kg}] + 0.05 = 0.407 \text{ mg/h/kg}$$

$$D = 0.407 \text{ mg/h/kg} \cdot 72 \text{ kg} = 29.3 \text{ mg/h}$$

The standard dose of 1000 mg can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = 1000 \text{ mg}/(29.3 \text{ mg/h}) = 34.1 \text{ h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 36 hours.

$$D = 29.3 \text{ mg/h} \cdot 36 \text{ h} = 1055 \text{ mg}$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1000 mg. The prescribed maintenance dose would be 1000 mg every 36 hours.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$LD = 15 \text{ mg/kg}(72 \text{ kg}) = 1080 \text{ mg}$$

This loading dose is similar to the suggested maintenance dose, so would not be prescribed.

Matzke Nomogram Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - \text{age})BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 66 \text{ y})65 \text{ kg}] / (72 \cdot 1.4 \text{ mg/dL})\}0.85 \end{aligned}$$

$$CrCl_{est} = 41 \text{ mL/min}$$

(Note: The patient's weight before ascitis developed was used to compute $CrCl_{est}$, but the weight after ascites developed was used in the drug dose calculations since the extra ascitic fluid will contribute to the volume of distribution.)

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$LD = 25 \text{ mg/kg}(72 \text{ kg}) = 1800 \text{ mg, round to } 1750 \text{ mg}$$

3. *Determine dosage interval and maintenance dose.*

From the nomogram the dosage interval is 1.5 days or 36 hours. The maintenance dose would be 19 mg/kg · 72 kg = 1368 mg. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1250 mg and given one dosage interval (36 hours) after the loading dose.

The prescribed maintenance dose would be 1250 mg every 36 hours.

10. *Solution to problem 10* The revised vancomycin dose for patient DG would be calculated as follows:

Linear Pharmacokinetics Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 = \{[(140 - 66\ y)65\ kg] / (72 \cdot 1.4\ mg/dL)\}0.85$$

$$CrCl_{est} = 41\ mL/min$$

(Note: The patient's weight before ascites developed was used to compute $CrCl_{est}$, but the weight after ascites developed was used in the drug dose calculations since the extra ascitic fluid will contribute to the volume of distribution.)

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(41\ mL/min) / 72\ kg] + 0.05 = 0.446\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 72\ kg = 50.4\ L$$

$$k_e = Cl/V = (0.446\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0382\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0382\ h^{-1} = 18.1\ h$$

Because the patient has been receiving vancomycin for >3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (7\ \mu g/mL / 4\ \mu g/mL)\ 1200\ mg$$
$$= 2100\ mg, \text{ round to } 2000\ mg$$

The new suggested dose would be 2000 mg every 36 hours to be started at next scheduled dosing time.

4. *Check steady-state peak concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new}/D_{old})C_{ss,old} = (2000\ mg/1200\ mg)\ 17\ \mu g/mL = 28\ \mu g/mL$$

This steady-state peak concentration should be safe and effective for the infection that is being treated.

11. *Solution to problem 11* The initial vancomycin dose for patient GG would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient is not obese. The patient is in acute renal failure and receiving hemodialysis. Because dialysis removes creatinine, the serum creatinine cannot be used to estimate creatinine clearance for the patient. Since the patient's renal function is poor enough to require dialysis, the creatinine clearance will be assumed to equal zero.

2. *Estimate vancomycin clearance.*

The vancomycin clearance versus creatinine clearance relationship is used to estimate the vancomycin clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(0\ mL/min)/85kg] + 0.05 \\ &= 0.05\ mL/min/kg \end{aligned}$$

3. *Estimate vancomycin volume of distribution.*

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ L/kg \cdot 85\ kg = 59.5\ L$$

4. *Estimate vancomycin elimination rate constant (k_e) and half-life ($t_{1/2}$).*

$$k_e = Cl/V = (0.05\ mL/min/kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 1000\ mL/L) = 0.0043\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0043\ h^{-1} = 161\ h$$

5. *Choose desired steady-state serum concentrations.*

A Css_{min} = 10 μg/mL and Css_{max} = 40 μg/mL were chosen to treat this patient.

6. *Use intravenous bolus equations to compute dose (Table 5-2).*

Calculate required dosage interval (τ):

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 40\ \mu g/mL - \ln 10\ \mu g/mL)/0.0043\ h^{-1} = 322\ h$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 312 hours or 13 days.

Calculate required dose (D):

$$D = Css_{max}\ V(1 - e^{-k_e\tau}) = 40\ mg/L \cdot 59.5\ L\ [1 - e^{-(0.0043\ h^{-1})(312\ h)}] = 1759\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1750 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 1750 mg every 13 days.

7. *Compute loading dose (LD), if needed.*

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only *estimated* values and not *actual* values, the patient's own parameters may be much different from the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

$$LD = Css_{max}\ V = 40\ mg/L \cdot 59.5\ L = 2380\ mg$$

As noted, this patient has poor renal function (CrCl <60 mL/min) so a loading dose would be prescribed for this patient and given as the first dose. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 2500 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css_{max} so that unnecessary unit conversion was not required.) The first maintenance dose would be given one dosage interval (13 days) after the loading dose was administered. In this patient's case, it is possible that only one dose will need to be given if the infection resolves before a maintenance dose is due.

Moellering Nomogram Method

1. *Estimate creatinine clearance.*

This patient is not obese. The patient is in acute renal failure and receiving hemodialysis. Because dialysis removes creatinine, the serum creatinine cannot be used to estimate creatinine clearance for the patient. Since the patient's renal function is poor enough to require dialysis, the creatinine clearance will be assumed to equal zero.

2. *Determine dosage interval and maintenance dose.*

The maintenance dose is calculated using the nomogram suggested dose for functionally anephric patients:

$$D = 1.9\ mg/kg/24\ h \cdot Weight$$

$$D = 1.9\ mg/kg/24h \cdot 85\ kg = 162\ mg/24\ h$$

The standard dose of 2000 mg/24 h in patients with normal renal function can be used to gain an approximation for an acceptable dosage interval (τ):

$$\tau = (2000\ mg) / (162\ mg/d) = 12.3\ d$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval would be rounded to 12 days.

$$D = 162\ mg/d \cdot 12\ d = 1944\ mg$$

Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 2000 mg. The prescribed maintenance dose would be 2000 mg every 12 days.

3. *Compute loading dose.*

A loading dose (LD) of 15 mg/kg is suggested by the Moellering nomogram:

$$\text{LD} = 15 \text{ mg/kg}(85 \text{ kg}) = 1275 \text{ mg}$$

This loading dose is less than the suggested maintenance dose, so would not be prescribed.

Matzke Nomogram Method

1. *Estimate creatinine clearance.*

This patient is not obese. The patient is in acute renal failure and receiving hemodialysis. Because dialysis removes creatinine, the serum creatinine cannot be used to estimate creatinine clearance for the patient. Since the patient's renal function is poor enough to require dialysis, the creatinine clearance will be assumed to equal zero.

2. *Compute loading dose (Table 5-4).*

A loading dose (LD) of 25 mg/kg will provide a peak concentration of 30 μg/mL.

$$\text{LD} = 25 \text{ mg/kg}(85 \text{ kg}) = 2125 \text{ mg, round to } 2000 \text{ mg}$$

3. *Determine dosage interval and maintenance dose.*

From the nomogram the dosage interval is 12 days. The maintenance dose would be 19 mg/kg · 85 kg = 1615 mg. Vancomycin doses should be rounded to the nearest 100–250 mg. This dose would be rounded to 1500 mg and given one dosage interval (12 days) after the loading dose. In this patient's case, it is possible that only one dose will need to be given if the infection resolves before a maintenance dose is due.

The prescribed maintenance dose would be 1500 mg every 12 days.

12. *Solution to problem 12* The revised vancomycin dose for patient GG would be calculated as follows:

After the first dose, this patient is not at steady state so none of the steady-state dosing methods are valid. Also, hemodialysis with a low-flux filter will not effect the elimination of the drug and is not a factor in calculating the drug dose.

One-Compartment Model Parameter Method

A. Compute the patient's elimination rate constant and half-life (Table 5-2, single dose equations. Note: t' = infusion time + waiting time of 1 hour and $^1/_2$ hour, respectively.)

$$k_e = (\ln C_1 - \ln C_2)/\Delta t = (\ln 20 \text{ μg/mL} - \ln 12.1 \text{ μg/mL}) / (72 \text{ h}) = 0.0070 \text{ h}^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.0070 \text{ h}^{-1} = 99.2 \text{ h}$$

B. Compute the patient's volume of distribution.

The vancomycin serum concentration needs to be extrapolated to the immediate postdose time 42.5 hours (accounting for infusion and waiting times) previous

to the first measured concentration before the volume of distribution can be calculated:

$$C_{max} = C/e^{-k_e t} = (20\ \mu g/mL)/e^{-(0.0070\ h^{-1})(42.5\ h)} = 26.9\ \mu g/mL$$

$$V = D/C_{max} = 1600\ mg/(26.9\ mg/L) = 59.5\ L$$

C. Choose new steady-state peak and trough concentrations. For the purposes of this example, the desired steady-state peak and trough concentrations will be 40 μg/mL and 10 μg/mL, respectively.

D. Determine the new dosage interval for the desired concentrations. As in the initial dosage section of this chapter, the dosage interval (τ) is computed using the following equation:

$$\tau = (\ln Css_{max} - \ln Css_{min})/k_e = (\ln 40\ \mu g/mL - \ln 10\ \mu g/mL)/0.0070\ h^{-1}$$
$$= 198\ h, \text{ round to } 192\ h \text{ or } 8\ d$$

E. Determine the new dose for the desired concentrations. The dose is computed using the one-compartment model intravenous bolus equation utilized in the initial dosing section of this chapter:

$$D = Css_{max}\ V(1 - e^{-k_e \tau}) = 40\ mg/L \cdot 59.5\ L\ [1 - e^{-(0.0070\ h^{-1})(192\ h)}]$$
$$= 1759\ mg, \text{ rounded to } 1750\ mg$$

A dose of vancomycin 1750 mg every 8 days would be prescribed to begin 8 days after the last dose of the previous regimen. In this patient's case, it may not be necessary to administer a maintenance dose if the infection resolves before the next dose is due.

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 60.9 L, a half-life equal to 108 hours, and an elimination rate constant of $0.0064\ h^{-1}$.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1250 mg every 7 days will produce a steady-state peak concentration of 31 μg/mL and a steady-state trough concentration of 10 μg/mL.

13. *Solution to problem 13* The revised vancomycin dose for patient FD would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

After the second dose, this patient is not at steady-state so none of the steady-state dosing methods are valid.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 63.1 L, a half-life equal to 38.1 hours, and an elimination rate constant of 0.0182 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1250 mg every 48 hours will produce a steady-state peak concentration of 34 μg/mL and a steady-state trough concentration of 14 μg/mL.

14. *Solution to problem 14* The revised vancomycin dose for patient OI would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

After the second dose, this patient is not at steady state so none of the steady-state dosing methods are valid.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 38 L, a half-life equal to 3.4 hours, and an elimination rate constant of 0.203 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1000 mg every 8 hours will produce a steady-state peak concentration of 30 μg/mL and a steady-state trough concentration of 7.2 μg/mL.

15. *Solution to problem 15* The revised vancomycin dose for patient HY would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

After the first dose, this patient is not at steady state so none of the steady-state dosing methods are valid.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 40.2 L, a half-life equal to 13.4 hours, and an elimination rate constant of 0.0517 h^{-1}.

3. *Compute dose required to achieve desired vancomycin serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 1250 mg every 24 hours will produce a steady-state peak concentration of 42 μg/mL and a steady-state trough concentration of 13 μg/mL.

16. *Solution to problem 16* The initial vancomycin dose for patient of would be calculated as follows:

Literature-Based Recommended Dosing

1. *Compute initial dose and dosage interval.*

Often, serum creatinine measurements are not available for initial dosage computation in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatrics dosage recommendations given earlier in this chapter, a patient in this age and weight category should receive vancomycin 10–15 mg/kg every 8–12 hours. For a wound infection, an intermediate dose of 15 mg/kg every 12 hours is chosen. (Note: grams will be converted to kilograms before the computation is made.)

$$\text{Dose} = 15 \text{ mg/kg}(1.550 \text{ kg}) = 23 \text{ mg}$$

The prescribed dose would be 23 mg every 12 hours.

17. *Solution to problem 17* The revised vancomycin dose for patient of would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (*Note: the assumption that steady state was attained should be verified by checking the medication administration record.*):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (7 \text{ μg/mL}/4 \text{ μg/mL})\ 20 \text{ mg} = 35 \text{ mg}$$

The new suggested dose would be 35 mg every 12 hours to be started at next scheduled dosing time.

2. *Check steady-state peak concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new}/D_{old})C_{ss,old} = (35 \text{ mg}/20 \text{ mg})\ 16 \text{ μg/mL} = 28 \text{ μg/mL}$$

This steady-state peak concentration should be safe and effective for the infection that is being treated.

18. *Solution to problem 18* The initial vancomycin dose for patient UL would be calculated as follows:

Literature-Based Recommended Dosing

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The pediatric CrCl equation from Chapter 3 can be used to estimate creatinine clearance (*Note: Height converted from inches to centimeters, 47 in · 2.54 cm/in = 119 cm.*):

$$CrCl_{est} = (0.55 \cdot Ht)/S_{Cr} = (0.55 \cdot 119\ cm)/(0.5\ mg/dL)$$

$$CrCl_{est} = 131\ mL/min/1.73\ m^2$$

The patient has normal renal function, so typical initial doses can be used.

2. *Compute initial dose and dosage interval using literature-based recommended dosing for pediatric patients.*

The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

From the pediatrics dosage recommendations given earlier in the chapter, a patient in this age and weight category should receive vancomycin 40-60 mg/kg/d given as divided doses every 6 hours for a severe infection. Because the patient is being treated for sepsis, the highest dose is selected.

$$Dose = 60\ mg/kg/d(24\ kg) = 1440\ mg/d$$

$$(1440\ mg/d)/(4\ doses/d) = 360\ mg/dose, round\ to\ 350\ mg$$

The prescribed dose will be 350 mg every 6 hours.

19. *Solution to problem 19* The revised vancomycin dose for patient UL would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (*Note: The assumption that steady-state was attained should be verified by checking the medication administration record.*):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (10\ \mu g/mL/7\ \mu g/mL)\ 250\ mg$$
$$= 357\ mg, rounded\ to\ 350\ mg$$

The new suggested dose would be 350 mg every 6 hours to be started at next scheduled dosing time.

2. *Check steady-state peak concentration for new dosage regimen.*

Using linear pharmacokinetics, the new steady-state concentration can be estimated and should be proportional to the old dose that produced the measured concentration:

$$C_{ss,new} = (D_{new}/D_{old})C_{ss,old} = (350 \text{ mg}/250 \text{ mg})\ 15\ \mu\text{g/mL} = 21\ \mu\text{g/mL}$$

This steady-state peak concentration should be safe and effective for the infection that is being treated.

20. *Solution to problem 20* The revised vancomycin dose for patient TK would be calculated as follows:

Trough-only Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - \text{age})BW]0.85\} / (72 \cdot S_{Cr}) \\ &= \{[(140 - 75\ \text{y})66\ \text{kg}]0.85\} / (72 \cdot 1.8\ \text{mg/dL}) \end{aligned}$$

$$CrCl_{est} = 28\ \text{mL/min}$$

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$\begin{aligned} Cl &= 0.695(CrCl) + 0.05 = 0.695[(28\ \text{mL/min})/66\ \text{kg}] + 0.05 \\ &= 0.345\ \text{mL/min/kg} \end{aligned}$$

The average volume of distribution for vancomycin is 0.7 L/kg:

$$V = 0.7\ \text{L/kg} \cdot 66\ \text{kg} = 46\ \text{L}$$

$$\begin{aligned} k_e &= Cl/V = (0.345\ \text{mL/min/kg} \cdot 60\ \text{min/h}) / (0.7\ \text{L/kg} \cdot 1000\ \text{mL/L}) \\ &= 0.0296\ \text{h}^{-1} \end{aligned}$$

$$t_{1/2} = 0.693 / k_e = 0.693 / 0.0296\ \text{h}^{-1} = 23\ \text{h}$$

Because the patient has been receiving vancomycin for >3 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dosage interval to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$\begin{aligned} \tau_{new} &= (C_{ss,old}/C_{ss,new})\tau_{old} = (25\ \mu\text{g/mL}/15\ \mu\text{g/mL})\ 24\ \text{h} \\ &= 40\ \text{h, round to } 36\ \text{h} \end{aligned}$$

Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter,

whenever possible. In this case, the dosage interval would be rounded to 36 hours. The new suggested dose would be 1000 mg every 36 hours to be started 36 hours after the last dose.

21. *Solution to problem 21* The revised vancomycin dose for patient VY would be calculated as follows:

Trough-only Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3 (Ht − 60) = 45 + 2.3(67 in − 60) = 61 kg]. The Salazar-Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 48\ y)\{(0.287 \cdot 170\ kg) + [9.74 \cdot (1.70\ m)^2]\}}{(60 \cdot 1.3\ mg/dL)} = 97\ mL/min$$

Note: Height is converted from inches to meters: Ht = (67 in · 2.54 cm/in) / (100 cm/m) = 1.70 m.

2. *Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).*

The vancomycin clearance versus creatinine clearance relationship is used to estimate drug clearance for this patient:

$$Cl = 0.695(CrCl) + 0.05 = 0.695[(97\ mL/min)/170\ kg] + 0.05$$
$$= 0.447\ mL/min/kg$$

The average volume of distribution for vancomycin is 0.7 L/kg IBW:

$$V = 0.7\ L/kg \cdot 61\ kg = 43\ L$$

$$k_e = Cl/V = (0.447\ mL/min/kg \cdot 170\ kg \cdot 60\ min/h) / (0.7\ L/kg \cdot 61\ kg \cdot 1000\ mL/L)$$
$$= 0.107\ h^{-1}$$

$$t_{1/2} = 0.693/k_e = 0.693/0.107\ h^{-1} = 6.5\ h$$

Because the patient has been receiving vancomycin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. *Compute new dosage interval to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$\tau_{new} = (C_{ss,old}/C_{ss,new})\tau_{old} = (8\ \mu g/mL/12\ \mu g/mL)\ 24\ h = 16\ h, \text{ round to } 18\ h$$

The new suggested dose would be 1000 mg every 18 hours to be started 18 hours after the last dose.

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Part III

CARDIOVASCULAR AGENTS

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6

DIGOXIN

INTRODUCTION

Digoxin is the primary cardiac glycoside in clinical use. Digoxin is used for the treatment of congestive heart failure (CHF) because of its inotropic effects on the myocardium and for the treatment of atrial fibrillation because of its chronotropic effects on the electrophysiological system of the heart. The role of digoxin in the treatment of each of these disease states has changed in recent years as a better understanding of the pathophysiology of these conditions has been gained and new drug therapies have been developed.[1,2] For the treatment of chronic CHF, angiotensin I converting enzyme inhibitors (ACE inhibitors) and diuretics are the primary pharmacotherapeutic agents with angiotensin II receptor antagonists, spironolactone, and β-blockers playing key roles.[3] For the treatment of acute or severe heart failure, agents that decrease cardiac preload (diuretics, nitrates) or afterload (vasodilators) and ACE inhibitors (decreases both preload and afterload) are used in conjunction with potent intravenously administered inotropic agents (dobutamine, dopamine, adrenergic agonists) to balance the current cardiovascular status of the patient.[3] In either the acute or severe heart failure situations, digoxin can be used when a mild inotropic or oral agent is needed.

If a patient presents with severe cardiovascular symptoms due to atrial fibrillation, direct-current cardioversion is a treatment option.[4] For the treatment of atrial fibrillation with mild or no cardiovasuclar symptoms, many clinicians prefer to prescribe intravenous calcium channel blockers (diltiazem or verapamil) for the control ventricular rate.[4] If atrial fibrillation is due to excessive adrenergic tone, intravenous β-blockers can also be used. Digoxin continues to be prescribed for the control of ventricular rate in patients with atrial fibrillation with no accessory pathway and can be an excellent choice if the patient is sedentary or has heart failure or left ventricular dysfunction. It is also possible to use digoxin in combination with a β-blocker or a calcium channel blocker to treat atrial fibrillation.[5] Once ventricular rate is controlled, the patient's heart may spontaneously revert to normal sinus rhythm, or electrical or pharmacologic cardioversion of atrial fibrillation may be necessary.

The positive inotropic effect of digoxin is caused by binding to sodium- and potassium-activated adenosine triphosphatase, also known as Na,K-ATPase or the sodium pump.[6] Digoxin-induced inhibition of Na,K-ATPase leads to decreased transport of sodium out of myocardial cells and increased intracellular sodium concentrations that aid calcium entry and decrease calcium elimination via the sodium-calcium exchanger. The increased intracellular calcium is stored in the endoplasmic reticulum so that action potential–induced calcium release is augmented causing enhanced myocardial contractility. The chronotropic effects of digoxin are mediated via increased parasympathetic activity and vagal tone.

THERAPEUTIC AND TOXIC CONCENTRATIONS

When given as oral or intravenous doses, the serum digoxin concentration–time curve follows a two-compartment model and exhibits a long and large distribution phase of 8–12 hours (Figure 6-1).[7–9] During the distribution phase, digoxin in the serum is not in equilibrium with digoxin in the tissues, so digoxin serum concentrations should not be measured until the distribution phase is finished. When drug distribution is complete, digoxin serum and tissue concentrations will be proportional to each other so that digoxin serum concentrations reflect concentrations at the site of action. When a

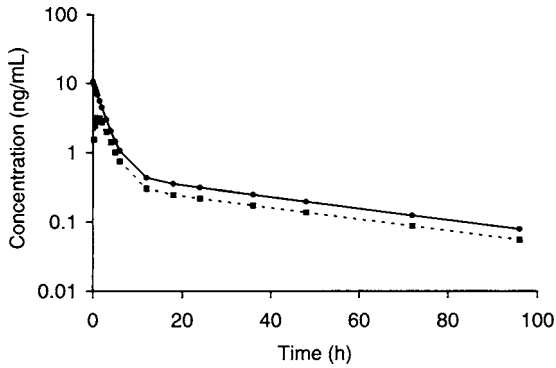

FIGURE 6-1 Digoxin serum concentrations after 250-µg doses given intravenously *(circles and solid line)* and orally as a tablet *(squares with dashed line).* After an intravenous dose, digoxin serum concentrations are very high because all of the drug is initially contained in the blood. During the distribution phase, digoxin begins to move out of the vascular system into the tissues. It is also cleared from the body during this phase. Digoxin serum concentrations decline relatively rapidly over an 8- to 12-hour time period until the blood and tissues are in psuedoequilibrium with each other. During the elmininationphase, digoxin serum concentrations in patients with good renal function (creatinine clearance >80 mL/min) decline with a half-life of about 36 hours. After oral tablet administration, about 70% of a digoxin dose is absorbed from the gastrointestinal tract. Maximum, or peak, concentrations occur about 1.5–2 hours after oral dosing with tablets, and the distribution phase still lasts 8–12 hours. During the elimination phase, intravenous and oral digoxin have the same terminal half-life.

digoxin serum concentration is very high but the patient is not exhibiting signs or symptoms of digitalis overdose, clinicians should consider the possibility that the blood sample for the determination of a digoxin serum concentration was obtained during the distribution phase, is too high because digoxin has not had the opportinunity to diffuse out of the bloodstream into the myocardium, and is not reflective of myocardial tissue concentrations.

There is a great deal of inter- and intrapatient variability in the pharmacodynamic responses to digoxin. Clinically beneficial inotropic effects of digoxin are generally achieved at steady-state serum concentrations of 0.5–1 ng/mL.[10,11] Increasing steady-state serum concentrations to 1.2–1.5 ng/mL may provide some minor, additional inotropic effect.[10,11] Chronotropic effects usually require higher digoxin steady-state serum concentrations of 0.8–1.5 ng/mL.[12,13] Additional chronotropic effects may be observed at digoxin steady-state serum concentrations as high as 2 ng/mL. Because of pharmacodynamic variability, clinicians should consider these ranges as initial guidelines and rely heavily on patient response to monitor digoxin therapy.

Steady-state digoxin serum concentrations above 2 ng/mL are associated with an increased incidence of adverse drug reactions. At digoxin concentrations of 2.5 ng/mL or above ~50% of all patients will exhibit some form of digoxin toxicity.[14] Most digoxin side effects involve the gastointestinal tract, central nervous system, or cardiovascular system.[15] Gastrointestinal-related adverse effects include anorexia, nausea, vomiting, diarrhea, abdominal pain, or constipation. Central nervous system side effects are headache, fatigue, insomnia, confusion, or vertigo. Visual disturbances can also occur and are manifested as blurred vision and changes in color vision or colored halos around objects often times involving the yellow-green spectrum. As can be appreicated, most of the gastrointestinal and central nervous system side effects of digoxin are nonspecific and could be caused by many different things. Because of this, clinicians should pay close attention to any new symptoms reported by patients receiving cardiac glycosides. Cardiac side effects commonly include second or third degree atrioventricular block, atrioventricular dissociation, bradycardia, premature ventricular contractions, or ventricular tachycardia. Rarely, almost every cardiac arrhythmia has been reported to occur due to digoxin toxicity. If a patient develops a new arrhythimia while receiving digoxin treatment, consideration should be given to possibility that it is digoxin induced. Also, it should be noted that relatively minor adverse effects such as nausea, headache, or changes in color vision may not occur in a patient before major cardiovascular side effects are found. In the case of life-threatening digoxin overdose, digoxin antigen binding fragments or digoxin immune Fab (Digibind) are portions of digoxin-specific antibodies that can be used to rapidly reverse the adverse symptoms (please see Special Dosing Considerations section).

CLINICAL MONITORING PARAMETERS

In patients receving digoxin for heart failure, the common signs and symptoms of CHF should be routinuely monitored; left-sided failure—dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, tachypnea, cough, hemoptysis, pulmonary rales/edema, S3 gallop, pleural effusion, Cheyne-Stokes respiration; right-sided failure—abdominal pain, anorexia, nausea, bloating, constipation, ascites, peripheral edema, jugular venous

distention, hepatojugular reflux, hepatomegaly; general symptoms—fatigue, weakness, nocturia, CNS symptoms, tachycardia, pallor, digital cyanosis, cardiomegaly.[3] A very useful functional classification for heart failure patients proposed by the New York Heart Association is given in Table 6-1.

When used for the treatment of atrial fibrillation, digoxin will not stop the atrial arrhythmia but is used to decrease, or control, the ventricular rate to an acceptable value (usually <100 beats/min).[4] The patient's pulse or ventricular rate should be monitored, and an electrocardiogram can also be useful to clinicians able to interpret the output. Atrial fibrillation is characterized by 400–600 nonuniform atrial beats/min. Sinus rhythum will not be restored with the use of digoxin alone although atrial fibrillation can spontaneously remit. Depending on the symptomatology experienced by the patient, cardioversion can be attempted by using direct electrical current or by the use of an antiarrhythmic agent such as flecainide, dofetilide, propafenone, amiodarone, or ibutilide. Adequate anticoagulation to prevent thromboembolism is needed before cardioversion if atrial fibrillation has occurred for longer than 48 hours.

Patients with severe heart disease such as cornary artery disease (angina, myocardial infarction) can have increased pharmacodynamic sensitivity to cardiac glycosides, and patients receiving these drugs should be monitored closely for adverse drug effects.[14,16] Also, augmented pharmacologic responses to digitalis derivatives occur with serum electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypercalcemia even though steady-state digoxin serum concentrations are in the therapeutic range.[6] Serum potassium concentrations should be routinely monitored in patients receiving digoxin and potassium-wasting diuretics. Potassium supplimentation may be necessary in some of these patients. Also, many patients receiving digoxin and diuretics will be receiving angiotensin I converting enzyme (ACE) inhibitors which can cause potassium retention. When receiving all three drugs, it can be difficult to reasonably ascertain what the patient's serum potassium status is without measuring it.

As an adjunct to the patient's clinical response, postdistribution (8–12 hours postdose) steady-state digoxin serum concentrations can be measured 3–5 half-lives after a stable

TABLE 6-1 New York Heart Association (NYHA) Functional Classification for Heart Failure[3]

NYHA HEART FAILURE CLASS	DESCRIPTION
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitations of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

dose is initiated. Digoxin is primarily eliminated unchanged by the kidney (~75%) so its clearance is predominately influenced by renal function.[8,9] Once stable, therapeutic steady-state digoxin serum concentrations and dosage levels have been established, serum creatinine measurements can be used to detect changes in renal function which may result in digoxin clearance and concentration alterations. Hospitalized patients with severe or acute heart failure may need to have serum creatinine determinations 2–3 times weekly to monitor renal function, while ambulatory patients with stable heart failure may only need yearly serum creatinine measurements.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

The primary route of digoxin elimination from the body is by the kidney via glomerular filtration and active tubular secretion of unchanged drug (~75%).[8,9] The remainder of a digoxin dose (~25%) is removed by hepatic metabolism or biliary excretion. The primary transporter involved in active tubular secretion and biliary excretion is p-glycoprotein (PGP).[17,18] Enterohepatic recirculaton (reabsorption of drug from the gastrointestinal tract after elimination in the bile) of digoxin occurs.[19] Digoxin is given as an intravenous injection or orally as a tablet, capsule, or elixir. When given intravenously, doses should be infused over at least 5–10 minutes. Average bioavailability constants (F) for the tablet, capsule, and elixir are 0.7, 0.9, and 0.8.[20–25] Digoxin is not usually administered intramuscularly due to erratic absorption and severe pain at the injection site. Plasma protein binding is ~25% for digoxin.[26,27] Usual digoxin doses for adults are 250 μg/d (range: 125–500 μg/d) in patients with good renal function (creatinine clearance ≥80 mL/min) and 125 μg every 2–3 days in patients with renal dysfunction (creatinine clearnace ≤15 mL/min).

EFFECTS OF DISEASE STATES AND CONDITIONS ON DIGOXIN PHARMACOKINETICS AND DOSING

Adults with normal renal function (creatinine clearance ≥80 mL/min, Table 6-2) have an average digoxin half-life of 36 hours (range: 24–48 hours) and volume of distribution of 7 L/kg (range: 5–9 L/kg).[28,29] The volume of distribution is large due to the extensive tissue binding of digoxin in the body. Digoxin pharmacokinetics are not effected by obesity (>30% over ideal body weight), so volume of distribution and dosage estimates should be based on ideal body weight.[30,31]

Because digoxin is principally eliminated by the kidney, renal dysfunction is the most important disease state that effects digoxin pharmacokinetics.[9] The digoxin clearance rate decreases in proportion to creatinine clearance, and this relationship will be utilized to aid in the computation of initial doses later in this chapter (Figure 6-2). The equation that estimates digoxin clearance from creatinine clearance is: $Cl = 1.303\ (CrCl) + Cl_{NR}$, where Cl is digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and Cl_{NR} is digoxin clearance by nonrenal routes of elimination which equals 40 mL/min in patients with no or mild heart failure (NYHA CHF class I or II, Table 6-1).[9] Digoxin volume of distribution, in addition to clearance, decreases with declining renal function.[7,32] While

TABLE 6-2 Disease States and Conditions that Alter Digoxin Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	36 hours or 1.5 days (range: 24–48 hours)	7 L/kg (range: 5–9 L/kg)	Usual dose 250 µg/d (range: 125–500 µg/d) resulting in total body stores of 8–12 µg/kg for heart failure or 13–15 µg/kg for atrial fibrillaton. Digoxin is eliminated ~75% unchanged renally/~25% nonrenally.
Adult, renal failure	120 hours or 5 days	4.5 L/kg $V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right) \times (Wt / 70)$ where V is digoxin volume of distribution in L/70 kg, Wt is body weight in kg (use ideal body weight if >30% overweight) and CrCl is creatinine clearance in mL/min.	Renal failure patients have decreased digoxin clearance and volume of distribution. As a result, half-life is not as long as might be expected [$t_{1/2}$ = (0.693V) / Cl]. Digoxin total body stores decrease to 6–10 µg/kg because of reduced volume of distribution.
Moderate/severe heart failure	See comments	7 L/kg	Heart failure patients (NYHA III–IV) have decreased cardiac output, which causes decreased liver blood flow and digoxin hepatic clearance. In patients with good renal function (creatinine clearance >80 mL/min), the effect on digoxin total clearance is negligable. But in patients with poor renal function, (creatinine clearance <30 mL/min) nonrenal clearance is a primary elimination pathway.
Obesity (>30% over IBW) with normal renal function	36 hours or 1.5 days	7 L/kg IBW	Digoxin does not distribute to adipose tissue, so volume of distribution calculations should be conducted with ideal body weight (IBW).
Hyperthyroidism with normal renal function	24 hours or 1 day	7 L/kg	Hyperthyroid patients are hypermetabolic and have higher digoxin renal and nonrenal clearances.

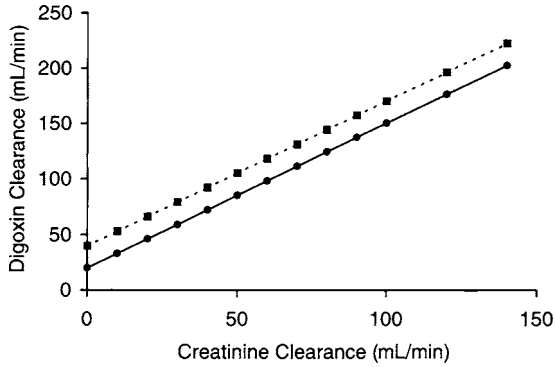

FIGURE 6-2 Digoxin clearance is proportional to creatinine clearance for patients with [*circles with solid line:* Cl = 1.303(CrCl) + 20] and without [*squares with dashed line:* Cl = 1.303(CrCl) + 40] moderate-severe (NYHA class III or IV) heart failure. Nonrenal clearance (denoted by the y-intercept) is lower for patients with moderate-severe heart failure because reduced cardiac output results in decreased liver blood flow and digoxin hepatic clearance.

the mechanism for this change is not as well understood, it is likely that digoxin is diplaced from tissue binding sites by an unknown substance or substances present in patients with renal dysfunction so that drug which would have been bound to tissues becomes unbound. Unbound digoxin molecules displaced from tissue binding sites move into the blood causing the decreased volume of distribution [$\downarrow V = V_b + (f_b / \uparrow f_t)\ V_t$, where V is digoxin volume of distribution, V_b is blood volume, V_t is tissue volume, f_b is the unbound fraction of digoxin in the blood, and f_t is the unbound fraction of digoxin in the tissues]. The equation that estimates digoxin volume of distribution using creatinine clearance is:

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt / 70)$$

where V is digoxin volume of distribution in L/70 kg, Wt is body weight in kilogram (use ideal body weight if >30% overweight) and CrCl is creatinine clearance in mL/min.[32] Because digoxin volume of distribution and clearance decrease simultaneously in patients with renal failure, the average half-life for digoxin of 5 days is shorter than what might be expected if clearance alone decreased [$t_{1/2} = (0.693 \cdot V) / Cl$].

Digoxin is not significantly eliminated by hemodialysis or peritoneal dialysis.[28,29] Hemofiltration does remove digoxin with a typical sieving coefficient of 0.7.[33,34] In many cases, a sufficient amount of digoxin will not be removed to warrant an increased maintenance dose. However, due to pharmacokinetic variability, some patients may need a periodic booster dose to increase digoxin concentrations (see Special Dosing Consideration section at end of chapter).[34]

Heart failure decreases cardiac output which in turn decreases liver blood flow. Liver blood flow is an important factor in the determination of hepatic clearance for drugs because it is the vehicle that delivers drug molecules to the liver for possible elimination. Moderate-severe heart failure (NYHA CHF class III or IV, Table 6-1) decreases the

hepatic clearance of digoxin by this mechanism.[9] When estimating digoxin clearance for the purpose of computing initial drug doses, it is necessary to decrease the nonrenal clearance (Cl_{NR}) factor to 20 mL/min in the equation to compansate for decreased hepatic clearance: Cl = 1.303 (CrCl) + 20, where Cl is digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and 20 is digoxin nonrenal clearance Cl_{NR} in mL/min.

Thyroid homone regulates basal metabolic rate, and thyroid status will influence every major organ system in the body including the heart (heart rate and cardiac output), liver (liver blood flow and microsomal drug-metabolizing enzyme function), and kidney (renal blood flow and glomerular filtration rate). Patients who are hypothyroid will have slower metabolic rates and eliminate digoxin more slowly than euthryoid patients ($t_{1/2}$ = 48 hours with normal renal function).[28,29,35–37] Hyperthyroid patients have faster metabolic rates and elminate digoxin faster than euthyroid patients ($t_{1/2}$ = 24 hours with normal renal function).[28,29,35–37] Hyperthyroid patients can present with atrial fibrillation which may be treated with digoxin. Generally, these patients require higher digoxin doses to control ventricular rate because of the increase in digoxin clearance.

Similar to other drugs, digoxin clearance is lower in neonates and premature infants because renal and hepatic function are not completely developed.[38,39] Premature infants and neonates have average digoxin half-lives equal to 60 hours and 45 hours, respectively. In older babies and young children (6 months to 8 years old) renal and hepatic function are fully developed and half-lives can be as short as 18 hours. Older children (≥12 years old) have mean digoxin half-lives ($t_{1/2}$ = 36 hours) that are similar to those found in adults. Also, volume of distribution is larger in infants and children compared to adults as is found with many other drugs. Pediatric loading and maintenance doses are given in Table 6-3.

Malabsorption of oral digoxin has been reported in patients with severe diarrhea, radiation treatments to the abdomen and gastrointestinal hypermotility.[35,40–44] In these cases, steady-state digoxin serum concentrations decrease due to poor bioavailability of the drug.

TABLE 6-3 Initial Pediatric Doses of Digoxin for Patients with Normal Renal Function (CrCl > 50 mL/min)[93]

	LOADING DOSE (μg/kg)*		MAINTENANCE (μg/kg/d)†,‡	
AGE	PO	IV/IM	PO	IV/IM
Premature	20	15	5	3–4
Full term	30	20	8–10	6–8
<2 yr	40–50	30–40	10–12	7.5–9
2–10 yr	30–40	20–30	8–10	6–8
>10 yr and <100 kg	10–15	8–12	2.5–5	2–3

*Administer 1/2 dose initially, then 1/4 dose at 8–18 hour intervals; obtain ECG after each dose to assess effect and toxicity

†*<10 yr:* Divide daily dose in half and give twice daily, *≥10 yr:* Give once daily

‡For CrCl = 10–50 mL/min give 25–75% of daily dose every 24 hours or give total dose every 36 hours, for CrCl <10 mL/min give 10–25% of daily dose every 24 hours or give total dose every 48 hours

DRUG INTERACTIONS

Digoxin has an extensive list of drug interactions with other agents. Because of this, only the most common and severe drug interactions will be discussed. Inhibition of P-glycoprotein, a drug efflux pump which is found in the kidney, liver, and intestine, appears to be involved in the majority of digoxin interactions.[17,18,45] Clinicians should consult a current drug interaction reference when other medications are prescribed to patients receiving digoxin therapy.[46]

Quinidine decreases both the renal and nonrenal clearance of digoxin and also decreases the volume of distribution of digoxin.[47–52] Inhibition of P-glycoprotein may be involved in this interaction.[45] The result of this complex interaction is that concurrent quindine therapy increases the average steady-state digoxin concentration by 30–70%.

Verapamil, diltiazem, and bepridil inhibit digoxin clearance and increase mean digoxin steady-state concentrations by various degrees.[52–58] Of these calcium channel blockers, verapamil is the most potent inhibitor of digoxin clearance, and increases digoxin steady-state serum concentrations up to 70%. Diltiazem and bepridil therapy each increase average digoxin steady-state serum concentrations by about 30%.

Amiodarone[59–62] and propafenone[63–65] are antiarrhythmic agents that decrease digoxin clearance. In addition to this drug interaction mechanism, aminodarone also simultaneously increases digoxin oral bioavailability, and it is likely that P-glycoprotein inhibition is involved in the drug interaction between these two drugs.[66] Digoxin steady-state serum concentrations increase 2–3 times over baseline values with concommittant amiodarone therapy. Because amiodarone has a very long half-life (~50 hours), the onset of the drug interaction with digoxin can be very long. As serum concentrations of aminodarone slowly increase and approach steady-state values, digoxin clearance and bioavailability are simultaneously slowly changing. The incidious nature of the amiodarone-digoxin drug interaction can make it difficult to detect in patients. Propafenone therapy increases mean digoxin steady-state concentrations by 30–60% in a dose-dependent fashion with propafenone doses of 450 mg/d causing digoxin concentration changes in the lower end of the range and propafenone doses of 900 mg/d causing digoxin concentration changes in the upper end of the range.

Cyclosporine therapy has been reported to increase average steady-state digoxin concentrations up to 50%.[67] P-glycoprotein inhibition by cyclosporine is the primary mechanism for this drug interaction.[17]

About 10% of patients receiving digoxin therapy have significant amounts of *Eubacterium letum* in their gastrointestinal tract that metabolizes orally administered digoxin before it can be absorbed.[68,69] Erythromycin, clarithromycin, and tetracycline are antibiotics that can kill this bacteria.[70–75] Digoxin steady-state serum concentrations increase an average of 30% in these select patients when one of these three antibiotics have been prescribed. P-glycoprotein inhibition may be one of the mechanisms involved with this interaction involving macrolide antibiotics.[75]

The absorption of oral digoxin from the gastrointestinal tract is influenced by many different compounds. Aluminum-containing antacids and kaolin-pectin physically adsorb digoxin rending it unabsorbable.[76] These compounds should be administered no closer than 2 hours to an oral digoxin dose. Similarly, cholestyramine also reduces digoxin oral bioavailability by binding it in the gastrointestinal tract and should be given no closer than 8 hours to a digoxin oral dose.[77,78] Sulfasalazine and neomycin each decrease digoxin oral bioavailability by unknown mechanisms.[79,80] Propantheline increases oral digoxin

bioavailability by prolonging gastrointestinal transit time, while metoclopramide and cisapride decreases oral digoxin bioavailability by decreasing gastrointestinal transit time.[78,81,82]

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate digoxin therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. However, it is computationally intensive.

The *Jelliffe method* is similar to the pharmacokinetic dosing method, except a target total body store is selected based on specific disease states and conditions present in the patient. It is also computationally intensive.

Nomograms that use the dosing concepts in the Jelliffe dosing method are available. But, in order to make calculations easier, they make simplifying assumptions. The nomograms are for adults only, and separate versions are needed for intravenous injection (Table 6-4A), tablet (Table 6-4B), and capsule (Table 6-4C) because of bioavailability

TABLE 6-4A Jelliffe Nomogram for Intravenous Digoxin (in μg) in Adult Patients with Heart Failure to Provide Total Body Stores of 10 μg/kg[94]

	LEAN BODY WEIGHT							NUMBER OF DAYS BEFORE
CORRECTED CrCL (mL/min per 70 kg)*	KG LB	50 110	60 132	70 154	80 176	90 198	100 220	STEADY STATE ACHIEVED†
0		75‡	75	100	100	125	150	22
10		75	100	100	125	150	150	19
20		100	100	125	150	150	175	16
30		100	125	150	150	175	200	14
40		100	125	150	175	200	225	13
50		125	150	175	200	225	250	12
60		125	150	175	200	225	250	11
70		150	175	200	225	250	275	10
80		150	175	200	250	275	300	9
90		150	200	225	250	300	325	8
100		175	200	250	275	300	350	7

*Daily maintenance doses have been rounded to the nearest 25-mcg increment.
†CrCL is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults,* if only serum creatinine concentrations (Scr) are available, a CrCL (corrected to 70 kg body weight) may be estimated in men as (140 – Age) / Scr. For women, this result should be multiplied by 0.85. *Note: This equation cannot be used for estimating creatinine clearance in infants or children.*
‡If no loading dose administered.

TABLE 6-4B Jelliffe Nomogram for Oral Digoxin Tablets (in μg) in Adult Patients with Heart Failure to Provide Total Body Stores of 10 μg/kg[94]

CORRECTED CrCL (mL/min per 70 kg)*	LEAN BODY WEIGHT KG / LB	50 / 110	60 / 132	70 / 154	80 / 176	90 / 198	100 / 220	NUMBER OF DAYS BEFORE STEADY STATE ACHIEVED†
0		62.5‡	125	125	125	187.5	187.5	22
10		125	125	125	187.5	187.5	187.5	19
20		125	125	187.5	187.5	187.5	250	16
30		125	187.5	187.5	187.5	250	250	14
40		125	187.5	187.5	250	250	250	13
50		187.5	187.5	250	250	250	250	12
60		187.5	187.5	250	250	250	375	11
70		187.5	250	250	250	250	375	10
80		187.5	250	250	250	375	375	9
90		187.5	250	250	250	375	500	8
100		250	250	250	375	375	500	7

*Daily maintenance doses have been rounded to the nearest 25-mcg increment.
†CrCL is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults,* if only serum creatinine concentrations (Scr) are available, a CrCL (corrected to 70 kg body weight) may be estimated in men as (140 – Age) / Scr. For women, this result should be multiplied by 0.85. *Note:* This equation cannot be used for estimating creatinine clearance in infants or children.
‡If no loading dose administered.

differences among dosage forms. All three nomograms assume that digoxin total body stores of 10 μg/kg are adequate, so are limited to heart failure patients requiring this dose.

Recommended initial doses for pediatric patients are given in Table 6-3.

PHARMACOKINETIC DOSING METHOD

The goal of initial dosing of digoxin is to compute the best dose possible for the patient given their set of disease states and conditions that influence digoxin pharmacokinetics and the cardiovascular disorder being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles. This approach is also known as the Jusko-Koup method for digoxin dosing.[9,32]

CLEARANCE ESTIMATE

Digoxin is predominately eliminated unchanged in the urine, and there is a good relationship between creatinine clearance and digoxin clearance (Figure 6-2). This relationship allows the estimation of the digoxin clearance for a patient which can be used to

TABLE 6-4C Jelliffe Nomogram for Oral Digoxin capsules (in μg) in Adult Patients with Heart Failure to Provide Total Body Stores of 10 μg/kg[94]

	LEAN BODY WEIGHT						NUMBER OF DAYS BEFORE
CORRECTED CrCL (mL/min per 70 kg)*	KG 50	60	70	80	90	100	STEADY STATE ACHIEVED†
	LB 110	132	154	176	198	220	
0	50‡	100	100	100	150	150	22
10	100	100	100	150	150	150	19
20	100	100	150	150	150	200	16
30	100	150	150	150	200	200	14
40	100	150	150	200	200	250	13
50	150	150	200	200	250	250	12
60	150	150	200	200	250	300	11
70	150	200	200	250	250	300	10
80	150	200	200	250	300	300	9
90	150	200	250	250	300	350	8
100	200	200	250	300	300	350	7

*Daily maintenance doses have been rounded to the nearest 25-mcg increment.
†CrCL is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults,* if only serum creatinine concentrations (Scr) are available, a CrCL (corrected to 70 kg body weight) may be estimated in men as (140 – Age)/Scr. For women, this result should be multiplied by 0.85. *Note: This equation cannot be used for estimating creatinine clearance in infants or children.*
‡If no loading dose administered.

compute an initial dose of the cardiac glycoside. Mathematically, the equation for the straight line shown in Figure 6-2 is: Cl = 1.303(CrCl) + Cl_{NR}, where Cl is the digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and Cl_{NR} is digoxin nonrenal clearance.[9] A digoxin nonrenal clearance value of 40 mL/min is used for patients without heart failure or who have only mild signs and symptoms of heart failure (NYHA CHF classes I or II). Patients with moderate or severe heart failure (NYHA CHF classes III or IV) have significant decreases in cardiac output which leads to a reduction in liver blood flow and digoxin hepatic clearance. In these cases, digoxin nonrenal clearance is set to equal 20 mL/min in the equation. For example, the estimated digoxin clearance for an individual with a creatinine clearance of 10 mL/min is 53 mL/min if the patient has no or mild symptoms of heart failure [Cl = 1.303(10 mL/min) + 40 = 53 mL/min] or 33 mL/min if the patient has moderate-to-severe symptoms of heart failure [Cl = 1.303 (10 mL/min) + 20 = 33 mL/min]. Taking the patient's renal function into account when deriving initial doses of digoxin is the single most important characteristic to assess.

VOLUME OF DISTRIBUTION ESTIMATE

The average volume of distribution for patients without disease states and conditions that change this parameter is 7 L/kg.[28,29] Because obesity does not change digoxin volume of distribution, the weight factor used in this calculation is ideal body weight (IBW)

for patients that are significantly overweight (>30% over IBW).[30,31] Thus, for a 70-kg patient with good renal function, the estimated volume of distribution would be 490 L (V = 7 L/kg · 70 kg = 490 L). If a patient weights less than their ideal body weight, actual body weight is used to estimate volume of distribution. For patients whose weight is between their ideal body weight and 30% over ideal weight, actual body weight can be used to compute estimated volume of distribution, although some clinicians prefer to use ideal body weight for these individuals. In patients who are more than 30% above their ideal body weight, volume of distribution (V) estimates should be based on ideal body weight. For an obese patient with normal renal function whose ideal body weight is 55 kg and total body weight is 95 kg, the estimated volume of distribution would be 385 L: V = 7 L/kg · IBW = 7 L/kg (55 kg) = 385 L.

For patients with renal dysfunction (creatinine clearance ≤30 mL/min), creatinine clearance should be used to provide an improved volume of distribution estimate (V in L) using the following formula:

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt / 70)$$

where CrCl is the patient's creatinine clearance in mL/min.[32] For example, a 70-kg patient with significant renal dysfunction (CrCl = 10 mL/min) is to receive a loading dose of digoxin and an estimate of digoxin volume of distribution is needed. The estimated volume of distribution for this patient would be 302 L:

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt / 70) = \left(226 + \frac{298 \cdot 10\ mL / min}{29.1 + 10\ mL / min}\right)(70\ kg / 70) = 302\ L$$

In patients who are more than 30% above their ideal body weight, volume of distribution (V) estimates should be based on ideal body weight, so the weight factor used in the equation would be IBW.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous injection or orally, digoxin follows a two-compartment pharmacokinetic model (Figure 6-1). After the end of intravenous infusion or after peak concentration has been reached after an oral dose, serum concentrations drop over an 8–12 hour time period because of distribution of drug from blood to tissues (α or distribution phase). After distribution of digoxin is complete, drug concentrations decline more slowly, and the elimination rate constant for this segment of the concentration/time curve is the one that varies with renal function (β or elimination phase). While this model is the most correct from a strict pharmacokinetic viewpoint, it cannot easily be used clinically because of its mathematical complexity. During the elimination phase of the concentration/time curve, digoxin serum concentrations drop very slowly due to the long elimination half life (36 hours with normal renal function, 5 days with end-stage renal disease). Because of this, a very simple pharmcokinetic equation that computes the average digoxin steady-state serum concentration (Css in ng/mL = μg/L) is widely used and allows maintenence dosage calculation: $Css = [F(D/\tau)] / Cl$ or $D/\tau = (Css \cdot Cl) / F$, where F is the bioavailability fraction for the oral dosage form (F = 1 for intravenous digoxin), D is the digoxin dose in μg, τ is the dosage interval in days, and Cl is digoxin clearance in L/d.[9,32]

The equation used to calculate loading dose (LD in μg) is based on a simple one-compartment model: LD = (Css · V) / F, where Css is the desired digoxin steady-state concentration in μg/L which is equivalent to ng/mL, V is the digoxin volume of distribution, and F is the bioavailability fraction for the oral dosage form (F = 1 for intravenous digoxin). When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). A portion of the loading dose can be withheld if the patient is experiencing any digoxin adverse effects such as a low pulse rate. This technique is used to allow the assessment of clinical response before additional digoxin is given in order to avoid accidental overdosage.

STEADY-STATE CONCENTRATION SELECTION

Digoxin steady-state concentrations are selected based on the cardiovascular disease being treated. For heart failure, steady-state serum concentrations of 0.5–1 ng/mL are usually effective.[10,11] For initial dosing purposes, a target digoxin concentration equal to 0.8 ng/mL is reasonable. For patients with atrial fibrillation, steady-state serum concentrations of 0.8–1.5 ng/mL are usually needed to control the ventricular rate to 100 beats/min or less.[12,29] An initial target digoxin concentration of 1.2 ng/mL is reasonable for patients with this disease state.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an intravenous digoxin dose for this patient to control ventricular rate.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 40 mL/min since the patient does not have moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(97\ mL/min) + 40\ mL/min = 167\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL. A serum concentration equal to 1.2 ng/mL will be chosen for this patient, and intravenous digoxin will be used (F = 1). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl) / F = (1.2\ \mu g/L \cdot 167\ mL/min \cdot 1440\ min/d) / (1 \cdot 1000\ mL/L)$$
$$= 288\ \mu g/d, \text{ round to } 250\ \mu g/d$$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has good renal function and is nonobese. Therefore, a volume of distribution equal to 7 L/kg and actual body weight can be used to compute the digoxin loading dose. An intravenous loading dose (F = 1) could be used in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used and concentrations allowed to accumulate over 3–5 half-lives.

$$V = 7 \text{ L/kg} \cdot 70 \text{ kg} = 490 \text{ L}$$

$$LD = (Css \cdot V) / F = (1.2 \text{ μg/L} \cdot 490 \text{ L}) / 1 = 588 \text{ μg rounded to } 500 \text{ μg}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 250 μg would be given initially, followed by two additional intravenous doses of 125 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 50 \text{ y})70 \text{ kg}] / (72 \cdot 3.5 \text{ mg/dL})$$

$$CrCl_{est} = 25 \text{ mL/min}$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 40 mL/min since the patient does not have moderate-to-severe heart failure):

$$Cl = 1.303 \text{ (CrCl)} + Cl_{NR} = 1.303(25 \text{ mL/min}) + 40 \text{ mL/min} = 73 \text{ mL/min}$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation the desired digoxin concentration would be 0.8 – 1.5 ng/mL. A serum concentration equal to 1.2 ng/mL will be chosen for this patient, and intravenous digoxin will be used (F = 1). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl) / F = (1.2 \text{ μg/L} \cdot 73 \text{ mL/min} \cdot 1440 \text{ min/d}) / (1 \cdot 1000 \text{ mL/L}) = 125 \text{ μg/d}$$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has poor renal function and is nonobese. Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction can be used to

compute the digoxin loading dose. An intravenous loading dose (F = 1) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used to allow concentrations to accumulate over 3–5 half-lives.

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt / 70) = \left(226 + \frac{298 \cdot 25 \text{ mL/min}}{29.1 + 25 \text{ mL/min}}\right)(70 \text{ kg} / 70) = 364 \text{ L}$$

$$LD = (Css \cdot V)/F = (1.2 \text{ μg/L} \cdot 364 \text{ L})/1 = 437 \text{ μg rounded to } 400 \text{ μg}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 200 μg would be given initially, followed by two additional intravenous doses of 100 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Example 3 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment. Additionally, the patient is being treated for NYHA class III moderate heart failure, not atrial fibrillation. Compute an oral digoxin tablet maintenance dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW]/(72 \cdot S_{Cr}) = [(140 - 50 \text{ y})70 \text{ kg}]/(72 \cdot 3.5 \text{ mg/dL})$$

$$CrCl_{est} = 25 \text{ mL/min}$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 20 mL/min since the patient has moderate heart failure):

$$Cl = 1.303 \text{ (CrCl)} + Cl_{NR} = 1.303(25 \text{ mL/min}) + 20 \text{ mL/min} = 53 \text{ mL/min}$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with heart failure the desired digoxin concentration would be 0.5–1 ng/mL. A serum concentration equal to 0.8 ng/mL will be chosen for this patient, and oral digoxin will be used (F = 0.7). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (0.8 \text{ μg/L} \cdot 53 \text{ mL/min} \cdot 1440 \text{ min/d})/(0.7 \cdot 1000 \text{ mL/L})$$
$$= 87 \text{ μg/d, or } 174 \text{ μg every 2 days } (87 \text{ μg/d} \cdot 2 \text{ d} = 174 \text{ μg every 2 days})$$

This oral tablet dose would be rounded to 125 μg every other day.

Example 4 OI is a 65-year-old, 170-kg (5 ft 5 in) female with NYHA class III moderate heart failure. Her current serum creatinine is 4.7 mg/dL and is stable. Compute an intravenous digoxin loading and maintenance dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 65\ y)\{(0.287 \cdot 170\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 4.7\ mg/dL)} = 22\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 20 mL/min since the patient has moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(22\ mL/min) + 20\ mL/min = 48\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with heart failure the desired digoxin concentration would be 0.5–1 ng/mL. A serum concentration equal to 0.8 ng/mL will be chosen for this patient, and intravenous digoxin will be used (F = 1). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (0.8\ \mu g/L \cdot 48\ mL/min \cdot 1440\ min/d)/(1 \cdot 1000\ mL/L)$$
$$= 56\ \mu g/d, \text{ or } 112\ \mu g \text{ every 2 days } (56\ \mu g/d \cdot 2\ d = 112\ \mu g \text{ every 2 days})$$

This intravenous dose would be rounded to 125 μg every other day.

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has poor renal function and is obese. Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction can be used to compute the digoxin loading dose, and ideal body weight will be used as the weight factor. An intravenous loading dose (F = 1) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used to allow concentrations to accumulate over 3–5 half-lives.

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt/70) = \left(226 + \frac{298 \cdot 22\ mL/min}{29.1 + 22\ mL/min}\right)(57\ kg/70) = 288\ L$$

$$LD = (Css \cdot V)/F = (0.8\ \mu g/L \cdot 288\ L)/1 = 230\ \mu g \text{ rounded to } 250\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 125 μg would be given initially, followed by two additional intravenous doses of 62.5 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesireable digoxin adverse effects were noted.

Jelliffe Method

Another approach to derive initial doses of digoxin is to compute an appropriate loading dose which provides an amount of the drug in the body that evokes the appropriate pharmacologic response.[83,84] The amount of digoxin in the body that produces the desired effect is known at the total body stores (TBS) of digoxin. The percent of drug that is lost on a daily basis (%lost/d) is related to renal function according to the following equation: %lost/d = 14% + 0.20(CrCl), where 14% is the percent of digoxin eliminated per day by nonrenal routes and CrCl is creatinine clearance in mL/min.[84] Because the goal of therapy is to provide the total body stores of digoxin that causes the appropriate inotropic or chronotropic effect, the maintenance dose (D in μg/d) is the amount of digoxin eliminated on a daily basis: $D = [TBS \cdot (\%lost/d)]/F$, where TBS is total body stores in μg/d, %lost/d is the percent of digoxin TBS lost per day, F is the bioavailability factor for the dosage form, and 100 is a conversion factor to convert the percentage to a fraction. Combining the two equations produces the initial digoxin maintenance dose: $D = \{TBS \cdot [14\% + 0.20(CrCl)]\}/(F \cdot 100)$.

For patients with creatinine clearance values over 30 mL/min, digoxin total body stores of 8–12 μg/kg are usually required to cause inotropic effects while 13–15 μg/kg are generally needed to cause chronotropic effects.[85,86] Since renal disease (creatinine clearance <30 mL/min) decreases digoxin volume of distribution, initial digoxin total body stores of 6–10 μg/kg are recommended for patients with poor renal function.[85] Because obesity does not change digoxin volume of distribution, the weight factor used in this calculation is ideal body weight (IBW) for patients that are significantly overweight (>30% over IBW).[30,31] If a patient weighs less than their ideal body weight, actual body weight is used to calculate total body stores. For patients whose weight is between their ideal body weight and 30% over ideal weight, actual body weight can be used to compute total body stores, although some clinicians prefer to use ideal body weight for these individuals. If a loading dose is required, the total body store (TBS in μg) is calculated and used to compute the loading dose (LD in μg) after correction for dosage form bioavailability (F): $LD = TBS/F$.[83,84]

Nomograms that use the dosing concepts in the Jelliffe dosing method are available. But, in order to make calculations easier, they make simplifying assumptions. The nomograms are for adults only, and separate versions are needed for intravenous injection (Table 6-4A), tablet (Table 6-4B), and capsule (Table 6-4C) because of bioavailability differences among dosage forms. All three nomograms assume that digoxin total body stores of 10 μg/kg are adequate, so are limited to heart failure patients requiring this dose.

To contrast the Jelliffe dosage method with the Jusko-Koup dosage method, the same patient cases will be used as examples for this section.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over

the last 5 days since admission. Compute an intravenous digoxin dose for this patient to control ventricular rate.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has good renal function and is nonobese. Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 14 μg/kg is chosen for this patient.

$$TBS = 14\ \mu g/kg \cdot 70\ kg = 980\ \mu g$$

$$\begin{aligned} D &= \{TBS \cdot [14\% + 0.20(CrCl)]\}/(F \cdot 100) \\ &= \{980\ \mu g \cdot [14\% + 0.20(97\ mL/min)]\}/(1 \cdot 100) \\ &= 328\ \mu g/d, \text{ round to } 375\ \mu g/d \end{aligned}$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$LD = TBS/F = 980\ \mu g/1 = 980\ \mu g, \text{ round to } 1000\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 500 μg would be given initially, followed by two additional intravenous doses of 250 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats/min or other undesireable digoxin adverse effects were noted.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is nonobese. Digoxin total body stores of 6–10 μg/kg are recommended for patients with renal dysfunction. A digoxin dose of 8 μg/kg is chosen for this patient.

$$\text{TBS} = 8\ \mu\text{g/kg} \cdot 70\ \text{kg} = 560\ \mu\text{g}$$

$$\begin{aligned} \text{D} &= \{\text{TBS} \cdot [14\% + 0.20(\text{CrCl})]\} / (\text{F} \cdot 100) \\ &= \{560\ \mu\text{g} \cdot [14\% + 0.20(25\ \text{mL/min})]\} / (1 \cdot 100) \\ &= 106\ \mu\text{g/d, round to } 125\ \mu\text{g/d} \end{aligned}$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$\text{LD} = \text{TBS} / \text{F} = 560\ \mu\text{g} / 1 = 560\ \mu\text{g, round to } 500\ \mu\text{g}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 250 µg would be given initially, followed by two additional intravenous doses of 125 µg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesireable digoxin adverse effects were noted.

Example 3 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment. Additionally, the patient is being treated for NYHA class III moderate heart failure, not atrial fibrillation. Compute an oral digoxin tablet maintenance dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est}} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{S}_{\text{Cr}}) = [(140 - 50\ \text{y})70\ \text{kg}] / (72 \cdot 3.5\ \text{mg/dL})$$

$$\text{CrCl}_{\text{est}} = 25\ \text{mL/min}$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is nonobese. Digoxin total body stores of 6–10 µg/kg are recommended for patients with renal dysfunction. A digoxin dose of 8 µg/kg is chosen for this patient.

$$\text{TBS} = 8\ \mu\text{g/kg} \cdot 70\ \text{kg} = 560\ \mu\text{g}$$

$$\begin{aligned} \text{D} &= \{\text{TBS} \cdot [14\% + 0.20(\text{CrCl})]\} / (\text{F} \cdot 100) \\ &= \{560\ \mu\text{g} \cdot [14\% + 0.20(25\ \text{mL/min})]\} / (0.7 \cdot 100) \\ &= 152\ \mu\text{g/d, round to } 125\ \mu\text{g/d} \end{aligned}$$

Example 4 OI is a 65-year-old, 170-kg (5 ft 5 in) female with NYHA class III moderate heart failure. Her current serum creatinine is 4.7 mg/dL and is stable. Compute an intravenous digoxin loading and maintenance dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$\text{IBW}_{\text{females}}$ (in kg) = 45 + 2.3(Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - \mathrm{age})[(0.287 \cdot \mathrm{Wt}) + (9.74 \cdot \mathrm{Ht}^2)]}{(60 \cdot \mathrm{S_{Cr}})}$$

$$\mathrm{CrCl}_{\mathrm{est(females)}} = \frac{(146 - 65\ \mathrm{y})\{(0.287 \cdot 170\ \mathrm{kg}) + [9.74 \cdot (1.65\ \mathrm{m})^2]\}}{(60 \cdot 4.7\ \mathrm{mg/dL})} = 22\ \mathrm{mL/min}$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in)/(100 cm/m) = 1.65 m.

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is obese. Digoxin total body stores of 6–10 μg/kg are recommended for patients with renal dysfunction, and ideal body weight (IBW) should be used in the computation. A digoxin dose of 8 μg/kg is chosen for this patient.

$$\mathrm{TBS} = 8\ \mu\mathrm{g/kg} \cdot 57\ \mathrm{kg} = 456\ \mu\mathrm{g}$$

$$\begin{aligned} \mathrm{D} &= \{\mathrm{TBS} \cdot [14\% + 0.20(\mathrm{CrCl})]\} / (\mathrm{F} \cdot 100) \\ &= \{456\ \mu\mathrm{g} \cdot [14\% + 0.20(22\ \mathrm{mL/min})]\}/(1 \cdot 100) \\ &= 83\ \mu\mathrm{g/d}, \text{ or } 166\ \mu\mathrm{g} \text{ every 2 days } (83\ \mu\mathrm{g/d} \cdot 2 \text{ days} \\ &= 166\ \mu\mathrm{g} \text{ every 2 days}) \end{aligned}$$

This intravenous dose would be rounded to 150 μg every other day.

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$\mathrm{LD} = \mathrm{TBS}/\mathrm{F} = 456\ \mu\mathrm{g}/1 = 456\ \mu\mathrm{g}, \text{ round to } 500\ \mu\mathrm{g}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 250 μg would be given initially, followed by two additional intravenous doses of 125 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

USE OF DIGOXIN SERUM CONCENTRATIONS TO ALTER DOSAGES

Because of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce digoxin serum concentrations that are expected. Because of this, digoxin serum concentrations are measured in many patients to ensure that therapeutic, nontoxic levels are present and to check for compliance to dosage regimens. However, not all patients may require serum concentration monitoring. For example, if an appropriate dose for the renal function and concurrent disease states of the patient is prescribed (e.g., 250 μg/d in a patient with a creatinine

clearance of 80–100 mL/min for heart failure) and the desired clinical effect is achieved without adverse effects, digoxin serum concentration monitoring may not be necessary. Whether or not digoxin concentrations are measured, important patient parameters (dyspnea, orthopnea, tachypnea, cough, pulmonary rales/edema, S3 gallop, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When digoxin serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change digoxin doses since digoxin follows *linear pharmacokinetics*. Sometimes, it is not possible to simply change the dose because of the limited number of oral dosage strengths, and the dosage interval must also be changed. Available digoxin tablet strengths are 125 μg and 250 μg while 100 and 200 μg digoxin capsules are available. In some situations, it may be necessary to compute the digoxin pharmacokinetic parameters for the patient and utilize these to calculate the best drug dose (*Pharmacokinetic parameter method*).

Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. An additional benefit of this dosing method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because digoxin follows linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose in μg, Css is the steady-state concentration in ng/mL, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required. Also, because of a limited number of solid oral dosage strengths, it may not be possible to attain desired serum concentrations by only changing the dose. In these cases, dosage intervals are extended for patients receiving tablets so that doses can be given as multiples of 125 μg and for patients receiving capsules so that doses can be given in multiples of 100 μg. The estimated time to achieve steady-state concentrations on a stable digoxin dosage regimen varies according to renal function and are listed in Tables 6-4A–C. An alternative to this way of estimating time to steady state is to compute the expected digoxin half-life ($t_{1/2}$ in days) for a patient using digoxin clearance (Cl in L/d) and volume of distribution (V in liters) and allow 3–5 half lives to pass before obtaining digoxin serum concentrations: $t_{1/2} = (0.693 \cdot V)/Cl$.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with moderate heart failure. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 6 months. A digoxin dose of 250 μg/d using oral tablets was prescribed and expected to achieve

steady-state concentrations equal to 0.8 ng/mL. After a week of treatment, a steady-state digoxin concentration was measured and equalled 0.6 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 0.9 ng/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 0.9\ mg/dL)$$

$$CrCl_{est} = 97\ mL/min$$

The patient has good renal function and would be expected to have achieved steady state after 7 days of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (0.9\ ng/mL / 0.6\ ng/mL)\ 250\ \mu g/d = 375\ \mu g/d$$

The new suggested dose would be 375 μg/d given as digoxin tablets to be started at the next scheduled dosing time.

Example 2 OI is a 65-year-old, 170-kg (5 ft 5 in) female with NYHA class III heart failure. Her current serum creatinine is 4.7 mg/dL and is stable. A digoxin dose of 125 μg/d given as tablets was prescribed and expected to achieve steady-state concentrations equal to 1 ng/mL. After the 3 weeks of therapy, a steady-state digoxin concentration was measured and equalled 2.5 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 1.2 ng/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 65\ y)\{(0.287 \cdot 170\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 4.7\ mg/dL)} = 22\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in)/(100 cm/m) = 1.65 m.

This patient has poor renal function, but would be expected to be at steady state with regard to digoxin serum concentrations after 3 weeks of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (1.2 \text{ ng/mL} / 2.5 \text{ ng/mL})\ 125\ \mu\text{g/d}$$
$$= 60\ \mu\text{g/d, or } 120\ \mu\text{g every other day } (60\ \mu\text{g/d} \cdot 2 \text{ days} = 120\ \mu\text{g every 2 days})$$

This would be rounded to digoxin tablets 125 µg every other day.

The new suggested dose would be 125 µg every other day given as digoxin tablets to be started at next scheduled dosing time. Since the dosage interval is being changed a day would be skipped before the next dose was given.

Pharmacokinetic Parameter Method

This method calculates the patient-specific drug clearance, and uses it to design improved dosage regimens.[28,29] Digoxin clearance can be measured using a single steady-state digoxin concentration (Css) and the following formula: $Cl = [F(D/\tau)] / Css$, where Cl is digoxin clearance in L/d, F is the bioavailability factor for the dosage form used, τ is the dosage interval in days, and Css is the digoxin steady-state concentration in ng/mL which also equals µg/L. Although this method does allow computation of digoxin clearance, it yields exactly the same digoxin dose as that supplied using linear pharmacokinetics. As a result, most clinicians prefer to directly calculate the new dose using the simpler linear pharmacokinetics method. To illustrate this point, the patient cases used to illustrate the linear pharmacokinetics method will be used as examples for the pharmacokinetic parameter method.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with moderate heart failure. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 6 months. A digoxin dose of 250 µg/d using oral tablets was prescribed and expected to achieve steady-state concentrations equal to 0.8 ng/mL. After a week of treatment, a steady-state digoxin concentration was measured and equalled 0.6 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 0.9 ng/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - \text{age})BW] / (72 \cdot S_{Cr}) = [(140 - 50\text{ y})70\text{ kg}] / (72 \cdot 0.9\text{ mg/dL})$$

$$CrCl_{est} = 97 \text{ mL/min}$$

The patient has good renal function and would be expected to have achieved steady state after 7 days of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for µg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)] / Css = [0.7(250\ \mu\text{g/d})] / 0.6\ \mu\text{g/L} = 292 \text{ L/d}$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$$D/\tau = (Css \cdot Cl)/F = (0.9\ \mu g/L \cdot 292\ L/d)/0.7 = 375\ \mu g/d$$

The new suggested dose would be 375 μg/d given as digoxin tablets to be started at next scheduled dosing time.

Example 2 OI is a 65-year-old, 170-kg (5 ft 5 in) female with NYHA class III heart failure. Her current serum creatinine is 4.7 mg/dL and is stable. A digoxin dose of 125 μg/d given as tablets was prescribed and expected to achieve steady-state concentrations equal to 1 ng/mL. After the 3 weeks of therapy, a steady-state digoxin concentration was measured and equalled 2.5 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 1.2 ng/mL.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) = 45 + 2.3(65 in − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 65\ y)\{(0.287 \cdot 170\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 4.7\ mg/dL)} = 22\ mL/min$$

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) = 1.65 m.

This patient has poor renal function, but would be expected to be at steady state with regard to digoxin serum concentrations after 3 weeks of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for μg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)]/Css = [0.7(125\ \mu g/d)]/2.5\ \mu g/L = 35\ L/d$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$$D/\tau = (Css \cdot Cl)/F = (1.2\ \mu g/L \cdot 35\ L/d)/0.7$$

= 60 μg/d, or 120 μg every other day (60 μg/d · 2 days = 120 μg every 2 days)
This would be rounded to digoxin tablets 125 μg every other day.

The new suggested dose would be 125 μg every other day given as digoxin tablets to be started at next scheduled dosing time. Since the dosage interval is being changed, a day would be skipped before the next dose was given.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[87,88] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, renal function, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters are generated that result in estimated serum concentrations that are statistically closest to the actual serum concentrations. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[89]

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with moderate heart failure. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 6 months. A digoxin dose of 250 μg/d using oral tablets was prescribed and expected to achieve steady-state concentrations equal to 0.8 ng/mL. After a week of treatment, a steady-state

digoxin concentration was measured and equalled 0.6 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 0.9 ng/mL.

1. *Enter patient demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 8.8 L/h, a volume of distribution of 578 L, and a half-life equal to 46 hours.

3. *Compute dose required to achieve desired digoxin serum concentration.*

The one-compartment model equations used by the program to compute doses indicates that a dose of 343 μg/d of digoxin tablets will produce a steady-state concentration of 0.9 ng/mL. This dose would be rounded off to 375 μg/d. Using the simpler linear pharmacokinetics method previously described in the chapter, the identical dose of 375 μg/d was computed.

Example 2 OI is a 65-year-old, 170-kg (5 ft 5 in) female with NYHA class III heart failure. Her current serum creatinine is 4.7 mg/dL and is stable. A digoxin dose of 125 μg/d given as tablets was prescribed and expected to achieve steady-state concentrations equal to 1 ng/mL. After the 3 weeks of therapy, a steady-state digoxin concentration was measured and equalled 2.5 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 1.2 ng/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 1.4 L/h, a volume of distribution of 516 L, and a half-life equal to 249 hours. The clearance value is slightly different from that computed using the steady-state pharmacokinetic parameter method (35 L/d or 1.5 L/h) because the patient probably was not at steady state when the serum concentrations were drawn.

3. *Compute dose required to achieve desired digoxin serum concentration.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a dose of 141 μg every 3 days will produce a steady-state concentration of 1.2 ng/mL. This would be rounded to 125 μg every 3 days. Using the steady-state pharmacokinetic parameter method previously described in this chapter, a similar dose of 125 ng every other day was computed.

Example 3 JH is a 74-year-old, 85-kg (5 ft 8 in) male with atrial fibrillation. His current serum creatinine is 1.9 mg/dL, and it has been stable over the last 7 days since admission. An intravenous digoxin loading dose of 500 μg was prescribed (given as doses of 250 μg, 125 μg, and 125 μg every 4 hours at 0800 H, 1200 H, and 1600 H, respectively). An oral maintenance dose of digoxin tablets 125 μg was given the next

morning at 0800 H. Because the patient still had a rapid ventricular rate, a digoxin concentration was obtained at 1600 H and equalled 0.9 ng/mL. Recommend a stat intravenous digoxin dose to be given at 2300 H which will achieve a digoxin serum concentration of 1.5 μg and an oral maintenance dose which will provide a steady-state concentration of the same level.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 4.8 L/h, a volume of distribution of 390 L, and a half-life equal to 57 hours.

3. *Compute dose required to achieve desired digoxin serum concentration.*

The stat intravenous digoxin dose will be calculated using the volume of distribution supplied by the computer program. The booster dose (BD) which will change serum concentrations by the desired amount is $BD = [V(\Delta C)]/F$, where V is the volume of distribution in liters, ΔC is the necessary change in digoxin serum concentration in μg/L, and F is the bioavailability for the dosage form.

$$BD = [V(\Delta C)]/F = [390\ L(1.5\ \mu g/L - 0.9\ \mu g/L)]/1$$
$$= 234\ \mu g, \text{ round to } 250\ \mu g \text{ intravenously stat}$$

The one-compartment model intravenous infusion equations used by the program to compute doses indicates that a digoxin tablet dose of 273 μg/d will produce a steady-state concentration of 1.5 ng/mL. This dose would be rounded to 250 μg/d of digoxin tablets and would be started at 0800 H the next morning.

Dosing Strategies

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 6-5.

TABLE 6-5 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/ equations	Pharmacokinetic dosing or Jelliffe method	Pharmacokinetic parameter or linear pharmacokinetics method
Nomograms/concepts	Nomograms	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

SPECIAL DOSING CONSIDERATIONS

Use of Digoxin Immune Fab in Digoxin Overdoses

Digoxin immune Fab (Digibind) are digoxin antibody molecule segments that bind and neutralize digoxin which can be used in digoxin overdose situations.[90,91] The antibody fragments are derived from antidigoxin antibodies formed in sheep. Improvements in digoxin adverse effects can be seen within 30 minutes of digoxin immune Fab administration. Digoxin serum concentrations are not useful after digoxin immune Fab has been given to a patient because pharmacologically inactive digoxin bound to the antibody segments will be measured and produce falsely high results. The elimination half life for digoxin immune Fab is 15–20 hours in patients with normal renal function, and it is eliminated by the kidney. The half-life of digoxin immune Fab is not known in patients with impaired renal function, but is assumed to be prolonged. In functionally anephric patients, the Fab fragment-digoxin complex may not be readily cleared from the body, so these patients should be closely monitored in the event digoxin dissociates from the Fab fragment and reintoxication occurs.

Because digoxin immune Fab is a foreign protein, allergic reactions can occur including anaphylactic shock, so patient blood pressure and temperature should be closely monitored. For high-risk patients, such as those known to be allergic or those who have previously received Digibind, intradermal skin testing can be conducted before drug administration.[92] Additionally, the electrocardiogram and serum potassium concentration should be closely followed for patients receiving this agent. Initially, patients may be hyperkalemic due to digoxin-induced displacement of intracellular potassium. However, hypokalemia can occur rapidly as the Fab fragments bind digoxin. As a result, repeated measurements of serum potassium are necessary, especially after the first few hours of digoxin immune Fab. Because the pharmacologic effects of digoxin will be lost, heart failure may worsen or a rapid ventricular rate may develop in patients treated for atrial fibrillation. Readministration of Digibind may be necessary if digoxin adverse effects have not abaited several hours after administration of the antibody fragments or if adverse effects recur. When patients do not respond to Digibind, clinicians should consider the possibility that the patient is not digoxin toxic and seek other etiologies for the patients' clinical symptomatology.

If a digoxin serum concentration or an estimate of the number of tablets ingested are not available, 20 vials of Digibind are usually adequate to treat most life-threatening acute overdoses in children and adults. In less emergent situations, 10 vials may be initially given, patient response monitored, and an additional 10 vials administered, if necessary. To treat chronic digoxin overdoses, 6 vials are usually needed for adults and older children while 1 vial is usually adequate for children under the weight of 20 kg.[92]

If digoxin serum concentrations are available or a reasonable estimate for the number of digoxin tablets acutely ingested is available, the Digibind dose should be computed using one of the two approaches outlined below.[92] The computations assume an a volume of distribution of 5 L/kg. If it is possible to calculate a Digibind dose using both of the following methods, it is recommended that the higher dose be administered to the patient.

CHRONIC OVERDOSE OR ACUTE OVERDOSE 8–12 HOURS AFTER INGESTION

In these cases, a postabsorption, postdistribution digoxin concentration can be used to estimate the necessary dose of Digibind for a patient using the following formula: Digibind dose (in vials) = (digoxin concentration in ng/mL)(body weight in kg) / 100.

Example HY is a 72-year-old, 80-kg (5 ft 7 in) male who has accidently been taking twice his prescribed dose of digoxin tablets. The admitting digoxin serum concentration is 4.1 ng/mL. Compute an appropriate dose of Digibind for this patient.

Digibind dose (in vials) = (digoxin concentration in ng/mL)(body weight in kg)/100 = (4.1 ng/mL · 80 kg)/100 = 3.3 vials, rounded up to 4 vials

ACUTE OVERDOSE WHERE NUMBER OF TABLETS IS KNOWN OR CAN BE ESTIMATED

For this situation, digoxin total body stores are estimated using the number of tablets ingested corrected for dosage form bioavailability: TBS = F(# dosage units)(dosage form strength), where TBS is digoxin total body stores in mg, F is the bioavailability for the dosage form (Note: the suggested bioavailability constant for digoxin in the Digibind package insert is 0.8 for tablets and 1 for capsules which allows for variability in the fraction of the dose that was absorbed), # dosage units is the number of tablets or capsules, and dosage form strength is in mg (Note: 250 μg = 0.25 mg). Each vial of Digibind will inactivate approximately 0.5 mg of digoxin, so the dose of Digibind (in vials) can be calculated using the following equation: Digibind dose = TBS / (0.5 mg/vial), where TBS is digoxin total body stores in mg.

Example DL is a 22-year-old, 85-kg (5 ft 9 in) male who took approximately 50 digoxin tablets of 0.25-mg strength about 4 hours ago. Compute an appropriate dose of Digibind for this patient.

TBS = F(# dosage units)(dosage form strength) = 0.8 (50 tablets · 0.25 mg/tablet) = 10 mg

Digibind dose = TBS / (0.5 mg/vial) = 10 mg / (0.5 mg/vial) = 20 vials

Conversion of Patient Doses Between Dosage Forms

When patients are switched between digoxin dosage forms, differences in bioavailability should be accounted for within the limits of available oral dosage forms using the following equation: $D_{IV} = D_{PO} \cdot F$, where D_{IV} is the equivalent digoxin intravenous dose in μg, D_{PO} is the equivalent digoxin oral dose, and F is the bioavailability fraction appropriate for the oral dosage form (F = 0.7 for tablets, 0.8 for elixir, 0.9 for capsules). Where possible, digoxin tablet doses should be rounded to the nearest 125 μg to avoid the necessity of breaking tablets in half. Similarly, digoxin capsule doses should be rounded to the nearest 100 μg as that is the smallest dosage size available. In either case, it is best to avoid mixing tablet or capsule dosage strengths so that patients do not become confused with multiple prescription vials and take the wrong dose of medication. For example, if it were necessary to prescribe 375 μg/d of digoxin tablets, it would be preferable to have the patient take three 125 μg tablets daily rather than one and a half 250 μg tablets daily or a 125 μg and 250 μg tablet each day.

Example 1 YT is a 67-year-old, 60-kg (5 ft 5 in) male with atrial fibrillation receiving 200 μg of intravenous digoxin daily which produces a steady-state digoxin concentration of 1.3 ng/mL. Compute an oral tablet dose that will maintain steady-state digoxin concentrations at approximately the same level.

1. *Convert current digoxin dose to the equivalent amount for the new dosage form/route.*

$$D_{PO} = D_{IV}/F = 200\ \mu g/0.7 = 286\ \mu g \text{ digoxin tablets, round to } 250\ \mu g$$

2. *Estimate change in digoxin steady-state concentration due to rounding of dose.*

The oral tablet dose of 286 μg would have produced a steady-state concentration similar to the intravenous dose of 200 μg. However, the dose had to be rounded a dose that could be given as a tablet. The expected digoxin steady-state concentration from the rounded dose would be proportional to the ratio of the rounded dose and the actual computed dose:

$$Css_{new} = Css_{old}(D_{rounded}/D_{computed}) = 1.3\ ng/mL(250\ \mu g/286\ \mu g) = 1.1\ ng/mL$$

where Css_{new} is the new expected digoxin steady-state concentration due to tablet administration in ng/mL, Css_{old} is the measured digoxin steady-state concentration due to intravenous administration in ng/mL, $D_{rounded}$ is the oral dose rounded to account for dosage form strengths in μg, and $D_{computed}$ is the exact oral dose computed during the intraveous to oral conversion calculation in μg. However, the steady-state digoxin concentration after the dosage form change may not be exactly the value calculated due to a variety of causes. Because of interindividual variations in digoxin bioavailability, the patient's actual bioavailability constant for oral tablets may be different from the average population bioavailability constant used to convert the dose. Also, there are day-to-day intrasubject variations in the rate and extent of digoxin absorption that will affect the actual steady-state digoxin concentration obtained while taking the drug orally. Finally, other oral drug therapy that did not influence digoxin pharmacokinetics when given intravenously may alter the expected digoxin concentration.

Example 2 KL is a 82-year-old, 45-kg female (4 ft 10 in) with heart failure receiving 125 μg of oral digoxin daily as tablets which produces a steady-state digoxin concentration of 1 ng/mL. Compute an intravenous dose that will maintain steady-state digoxin concentrations at approximately the same level.

1. *Convert current digoxin dose to the equivalent amount for the new dosage form/route.*

$$D_{IV} = D_{PO} \cdot F = 125\ \mu g \cdot 0.7 = 87.5\ \mu g \text{ digoxin tablets, round to } 90\ \mu g$$

2. *Estimate change in digoxin steady-state concentration due to rounding of dose.*

The intravenous dose of 87.5 μg would have produced a steady-state concentration similar to the oral tablet dose of 125 μg. However, the dose was rounded to an amount that could be reasonably measured in a syringe. The expected digoxin steady-state concentration from the rounded dose would be proportional to the ratio of the rounded dose and the actual computed dose:

$$Css_{new} = Css_{old}(D_{rounded}/D_{computed}) = 1\ ng/mL(90\ \mu g/87.5\ \mu g) = 1\ ng/mL$$

where Css_{new} is the new expected digoxin steady-state concentration due to intravenous administration in ng/mL, Css_{old} is the measured digoxin steady-state concentration due to oral tablet administration in ng/mL, $D_{rounded}$ is the intravenous dose rounded to allow accurate dosage measurement in μg, and $D_{computed}$ is the exact intravenous dose computed during the intraveous to oral conversion calculation in μg. Since the rounded intravenous digoxin dose is so close to the exact dose needed, steady-state digoxin concentrations are not

expected to change appreciably. However, the steady-state digoxin concentration after the dosage form change may not be exactly the value calculated due to a variety of causes. Because of interindividual variations in digoxin bioavailability, the patient's actual bioavailability constant for oral tablets may be different from the average population bioavailability constant used to convert the dose. Also, there are day-to-day intrasubject variations in the rate and extent of digoxin absorption that will affect the steady-state digoxin concentration obtained while taking the drug orally that will not be present when the drug is given intraveously. Finally, other oral drug therapy that influenced digoxin pharmacokinetics when given orally, but not intravenously, may alter the expected digoxin concentration.

Use of Digoxin Booster Doses to Immediately Increase Serum Concentrations

If a patient has a subtherapeutic digoxin serum concentration in an acute situation, it may be desirable to increase the digoxin concentration as quickly as possible. A rational way to increase the serum concentrations rapidly is to administer a booster dose of digoxin, a process also known as "reloading" the patient with digoxin, computed using pharmacokinetic techniques. A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current digoxin concentration present in the patient: $BD = [(C_{desired} - C_{actual})V]/F$, where $C_{desired}$ is the desired digoxin concentration, C_{actual} is the actual current digoxin concentration for the patient, F is the bioavailability fraction of the digoxin dosage form, and V is the volume of distribution for digoxin. If the volume of distribution for digoxin is known for the patient, it can be used in the calculation. However, this value is not usually known and is assumed to equal the population average for the patient.

Concurrent with the administration of the booster dose, the maintenance dose of digoxin is usually increased. Clinicians need to recognize that the administration of a booster dose does not alter the time required to achieve steady-state conditions when a new digoxin dosage rate is prescribed. It still requires a sufficient time period to attain steady state when the dosage rate is changed. However, usually the difference between the postbooster dose digoxin concentration and the ultimate steady-state concentration has been reduced by giving the extra dose of drug.

Example 1 BN is a 52-year-old, 85-kg (6 ft 2 in) male with atrial fibrillation who is receiving therapy with intravenous digoxin. He has normal liver and renal function. After receiving an initial loading dose of digoxin (1000 μg) and a maintenance dose of 250 μg/d of digoxin for 5 days, his digoxin concentration is measured at 0.6 ng/mL immediately after pulse rate increased to 200 beats/min. Compute a booster dose of digoxin to achieve a digoxin concentration equal to 1.5 ng/mL.

1. *Estimate volume of distribution according to disease states and conditions present in the patient.*

In the case of digoxin, the population average volume of distribution equals 7 L/kg and this will be used to estimate the parameter for the patient. The patient is nonobese, so his actual body weight will be used in the computation: $V = 7\ L/kg \cdot 85\ kg = 595\ L$.

2. *Compute booster dose.*

The booster dose is computed using the following equation: $BD = [(C_{desired} - C_{actual})V]/F = [(1.5\ \mu g/L - 0.6\ \mu g/L)595\ L]/1 = 536\ \mu g$, rounded to 500 μg of digoxin.

(Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). This booster dose could be split into two equal doses and given 4–6 hours apart with appropriate monitoring to avoid adverse side effects. If the maintenance dose was also increased, it will take additional time for new steady-state conditions to be achieved. Digoxin serum concentrations should be measured at this time.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that other drug therapy is appropriate for current disease state signs and symptoms. Also, it should be confirmed that the patient is receiving other appropriate concurrent therapy, when necessary, to treat the cardiovascular condition.

1. UV is a 75-year-old, 62-kg (5 ft 9 in) male with atrial fibrillation. His current serum creatinine is 1.3 mg/dL, and it has been stable since admission. Compute an intravenous loading and maintenance digoxin dose for this patient to provide a steady-state concentration of 1.5 ng/mL or digoxin total body store equal to 15 μg/kg.

2. Patient UV (please see problem 1) was prescribed digoxin 200 μg/d intravenously, and this dose has been given for 2 weeks. A steady-state digoxin concentration was 2.4 ng/mL. Compute a revised digoxin dose for this patient to provide a steady-state concentration of 1.5 ng/mL.

3. Patient UV (please see problem 1 and 2) had a dosage change to digoxin 125 μg/d intravenously which produced a steady-state concentration equal to 1.4 ng/mL. Compute an oral tablet digoxin dose for this patient that will provide about the same steady-state drug concentration as that found during intravenous therapy.

4. SD is a 35-year-old, 75-kg (5 ft 7 in) female with NYHA class IV heart failure secondary to viral cardiomyopathy. Her current serum creatinine is 3.7 mg/dL, and it has been stable since admission. Compute oral digoxin loading and maintenance doses using tablets for this patient to provide a steady-state concentration of 1 ng/mL.

5. Patient SD (please see problem 4) was prescribed digoxin 187.5 μg/d orally as tablets. A steady-state digoxin concentration was obtained and equalled 0.7 ng/mL. Compute a revised digoxin dose for this patient using oral tablets to provide a steady-state concentration of 1 ng/mL.

6. Patient SD (please see problem 4 and 5) had a dosage change to digoxin 250 μg/d orally as tablets which produced a steady-state concentration equal to 1.2 ng/mL. Compute an intravenous digoxin dose for this patient that will provide about the same steady-state drug concentration as that found during oral tablet therapy.

7. BN is a 55-year-old, 140-kg (5 ft 8 in) male with atrial fibrillation. His current serum creatinine is 0.9 mg/dL, and it has been stable since admission. Compute an intravenous loading dose and oral tablet maintenance dose of digoxin for this patient to provide a steady-state concentration of 1.2 ng/mL.

8. Patient BN (please see problem 7) was prescribed digoxin tablets 500 μg/d. A steady-state digoxin concentration was obtained and was 2.4 ng/mL. Compute a revised digoxin tablet dose for this patient to provide a steady-state concentration of 1.5 ng/mL.

9. VG is a 75-year-old, 180-kg (5 ft 2 in) female with NYHA class III heart failure. Her current serum creatinine is 6 mg/dL and is stable. Compute digoxin oral capsule loading and maintenance doses for this patient to provide a steady-state concentration of 1 ng/mL.

10. Patient VG (please see problem 9) was prescribed digoxin capsules 100 μg every other day. A steady-state digoxin concentration was obtained and was 0.5 ng/mL. Compute a revised digoxin capsule dose for this patient to provide a steady-state concentration of 1 ng/mL.

11. QW is a 34-year-old, 50-kg (5 ft 4 in) female with atrial fibrillation secondary to hyperthyroidism. Her current serum creatinine is 0.8 mg/dL and stable. Compute a digoxin intravenous loading dose and oral capsule maintenance dose for this patient to provide a steady-state concentration of 1.2 ng/mL.

12. RT is a 68-year-old, 88-kg (5 ft 11 in) male with NYHA class II heart failure. His current serum creatinine is 2.3 mg/dL and is stable. Digoxin therapy was initiated, and after the third oral dose of digoxin tablets 250 μg/d, a digoxin serum concentration was obtained according to the following schedule:

DAY/TIME	DIGOXIN DOSE/CONCENTRATION
Day 1/0800 H	250 μg
Day 2/0800 H	250 μg
Day 3/0800 H	250 μg
Day 4/0730 H	C = 1 ng/mL

Calculate a digoxin tablet dose that will provide a steady-state digoxin concentration equal to 0.8 ng/mL.

13. LK is a 72-year-old, 68-kg (5 ft 1 in) female with NYHA class III heart failure. Her current serum creatinine is 2.9 mg/dL and is stable. Digoxin therapy was initiated, and after an intravenous loading dose of 500 μg plus two intravenous doses of digoxin 125 μg/d, a digoxin serum concentration was obtained according to the following schedule:

TIME	DIGOXIN DOSE/CONCENTRATION
Day 1/0800 H	250 μg
Day 1/1200 H	125 μg
Day 1/1600 H	125 μg
Day 2/0800 H	125 μg
Day 3/0800 H	125 μg
Day 4/0730 H	C = 2 ng/mL

Calculate a digoxin tablet dose that will provide a steady-state digoxin concentration equal to 1 ng/mL.

14. BH is a 61-year-old, 91-kg (6 ft 1 in) male with atrial fibrillation. His current serum creatinine is 1.9 mg/dL and is stable. Digoxin therapy was initiated, and after an intravenous loading dose of 1000 µg plus three oral doses of digoxin tablets 125 µg/d, a digoxin serum concentration was obtained according to the following schedule:

TIME	DIGOXIN DOSE/CONCENTRATION
Day 1/0800 H	500 µg IV
Day 1/1200 H	250 µg IV
Day 1/1600 H	250 µg IV
Day 2/0800 H	125 µg tablet
Day 3/0800 H	125 µg tablet
Day 4/0800 H	125 µg tablet
Day 5/0730 H	C = 0.9 ng/mL

Calculate a digoxin tablet dose that will provide a steady-state digoxin concentration equal to 1.5 ng/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial digoxin doses for patient UV would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 40 mL/min since the patient does not have moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(43\ mL/min) + 40\ mL/min = 96\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL. A serum concentration equal to 1.5 ng/mL was chosen for this patient, and intravenous digoxin will be used (F = 1). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (1.5\ \mu g/L \cdot 96\ mL/min \cdot 1440\ min/d)/(1 \cdot 1000\ mL/L)$$
$$= 208\ \mu g/d, \text{ round to } 200\ \mu g/d$$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has moderate renal function and is nonobese. Therefore, a volume of distribution equal to 7 L/kg and actual body weight can be used to compute the digoxin loading dose. An intravenous loading dose (F = 1) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used and concentrations allowed to accumulate over 3–5 half-lives.

$$V = 7\ L/kg \cdot 62\ kg = 434\ L$$

$$LD = (Css \cdot V)/F = (1.5\ \mu g/L \cdot 434\ L)/1 = 651\ \mu g \text{ rounded to } 600\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 300 μg would be given initially, followed by two additional intravenous doses of 150 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Jelliffe Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg]/(72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has moderate renal function and is nonobese. Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 15 μg/kg was chosen for this patient.

$$TBS = 15\ \mu g/kg \cdot 62\ kg = 930\ \mu g$$

$$D = \{TBS \cdot [14\% + 0.20(CrCl)]\}/(F \cdot 100) = \{930\ \mu g \cdot [14\% + 0.20(43\ mL/min)]\}/$$
$$(1 \cdot 100) = 210\ \mu g/d, \text{ round to } 200\ \mu g/d$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$LD = TBS / F = 930\ \mu g / 1 = 930\ \mu g, \text{ round to } 1000\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 500 μg would be given initially, followed by two additional intravenous doses of 250 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats/min or other undesirable digoxin adverse effects were noted.

2. *Solution to problem 2* The revised digoxin dose for patient UV would be calculated as follows:

Linear Pharmacokinetics Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

The patient has moderate renal function and would be expected to have achieved steady state after 14 days of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (1.5\ ng/mL / 2.4\ ng/mL)\ 200\ \mu g/d = 125\ \mu g/d$$

The new dose would be 125 μg/d given as intravenous digoxin to be started at next scheduled dosing time.

Pharmacokinetic Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

The patient has good renal function and would be expected to have achieved steady state after 14 days of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for μg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)] / Css = [1(200\ \mu g/d)] / 2.4\ \mu g/L = 83\ L/d$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$$D/\tau = (Css \cdot Cl) / F = (1.5\ \mu g/L \cdot 83\ L/d) / 1 = 125\ \mu g/d$$

The new suggested dose would be 125 μg/d given as digoxin tablets to be started at next scheduled dosing time.

3. *Solution to problem 3* An equivalent oral dose for patient UV would be computed as follows:

1. *Convert current digoxin dose to the equivalent amount for the new dosage form/route.*

$$D_{PO} = D_{IV}/F = 125\ \mu g/0.7$$

$$= 179\ \mu g \text{ digoxin tablets, round to } 187.5\ \mu g\ (1^1/_2 \text{ 125-}\mu g \text{ tablets})$$

2. *Estimate change in digoxin steady-state concentration due to rounding of dose.*

The oral tablet dose of 179 μg would have produced a steady-state concentration similar to the intravenous dose of 125 μg. However, the dose had to be rounded a dose that could be given as tablets. The expected digoxin steady-state concentration from the rounded dose would be proportional to the ratio of the rounded dose and the actual computed dose:

$$Css_{new} = Css_{old}(D_{rounded} / D_{computed}) = 1.4\ ng/mL(187.5\ \mu g / 179\ \mu g) = 1.5\ ng/mL$$

4. *Solution to problem 4* The initial digoxin doses for patient SD would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85$$

$$= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 20 mL/min since the patient has moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(25\ mL/min) + 20\ mL/min = 53\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with heart failure the desired digoxin concentration would be 0.5–1 ng/mL. A serum concentration equal to 1 ng/mL was chosen for this patient, and oral digoxin will be used (F = 0.7). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (1\ \mu g/L \cdot 53\ mL/min \cdot 1440\ min/d)/(0.7 \cdot 1000\ mL/L)$$
$$= 108\ \mu g/d, \text{ round to } 125\ \mu g/d$$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has poor renal function. Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction can be used to compute the digoxin loading dose. An oral loading dose (F = 0.7) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used to allow concentrations to accumulate over 3–5 half-lives.

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt/70)$$
$$= \left(226 + \frac{298 \cdot 25\ mL/min}{29.1 + 25\ mL/min}\right)(75\ kg/70) = 390\ L$$

$$LD = (Css \cdot V)/F = (1\ \mu g/L \cdot 390\ L)/0.7 = 557\ \mu g \text{ rounded to } 500\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial oral dose of 250 μg would be given initially, followed by two additional intravenous doses of 125 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesireable digoxin adverse effects were noted.

Jelliffe Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot S_{Cr})\}0.85$$
$$= \{[(140 - 35\ y)75\ kg]/(72 \cdot 3.7\ mg/dL)\}0.85$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is nonobese. Digoxin total body stores of 6–10 μg/kg are effective in the treatment of heart failure in patients with poor renal function. A digoxin dose of 8 μg/kg was chosen for this patient.

$$TBS = 8\ \mu g/kg \cdot 75\ kg = 600\ \mu g$$

$$\begin{aligned} D &= \{TBS \cdot [14\% + 0.20(CrCl)]\}/(F \cdot 100) \\ &= \{600\ \mu g \cdot [14\% + 0.20(25\ mL/min)]\}/(0.7 \cdot 100) \\ &= 163\ \mu g/d, \text{ round to } 187.5\ \mu g/d \end{aligned}$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$LD = TBS / F = 600\ \mu g / 0.7 = 857\ \mu g, \text{ round to } 750\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial oral dose of 375 µg would be given initially, followed by two additional intravenous doses of 187.5 µg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats/min or other undesirable digoxin adverse effects were noted.

5. *Solution to problem 5* The revised digoxin dose for patient SD would be calculated as follows:

Linear Pharmacokinetics Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW] / (72 \cdot S_{Cr})\}0.85 \\ &= \{[(140 - 35\ y)75\ kg] / (72 \cdot 3.7\ mg/dL)\}0.85 \\ CrCl_{est} &= 25\ mL/min \end{aligned}$$

The patient has poor renal function and would be expected to have achieved steady state after 14 days of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$\begin{aligned} D_{new} &= (C_{ss,new} / C_{ss,old}) D_{old} = (1\ ng/mL / 0.7\ ng/mL)\ 187.5\ \mu g/d \\ &= 268\ \mu g/d, \text{ round to } 250\ \mu g/d \end{aligned}$$

The new dose would be 250 µg/d given as oral digoxin tablets to be started at next scheduled dosing time.

Pharmacokinetic Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot S_{Cr})\}0.85$$
$$= \{[(140 - 35\ y)75\ kg]/(72 \cdot 3.7\ mg/dL)\}0.85$$
$$CrCl_{est} = 25\ mL/min$$

The patient has good renal function and would be expected to have achieved steady state after 14 days of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for μg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)] / Css = [0.7(187.5\ \mu g/d)] / 0.7\ \mu g/L = 188\ L/d$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$D/\tau = (Css \cdot Cl) / F = (1\ \mu g/L \cdot 188\ L/d) / 0.7 = 268\ \mu g/d$, round to 250 μg/d

The new suggested dose would be 250 μg/d given as digoxin tablets to be started at next scheduled dosing time.

6. *Solution to problem 6* An equivalent oral dose for patient SD would be computed as follows:

1. *Convert current digoxin dose to the equivalent amount for the new dosage form/route.*

$$D_{IV} = D_{PO} \cdot F = 250\ \mu g/d \cdot 0.7 = 175\ \mu g/d \text{ intravenous digoxin}$$

2. *Estimate change in digoxin steady-state concentration due to rounding of dose.*

This step is not necessary since the actual equivalent intravenous dose could be given without rounding.

7. *Solution to problem 7* The initial digoxin doses for patient BN would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3(Ht – 60) = 50 + 2.3(68 in – 60) = 68.4 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{(51 \cdot 0.9\ mg/dL)} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in)/(100 cm/m) = 1.73 m.

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 40 mL/min since the patient does not have moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(136\ mL/min) + 40\ mL/min = 217\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL. A serum concentration equal to 1.2 ng/mL was chosen for this patient, and oral digoxin tablets will be used (F = 0.7). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (1.2\ \mu g/L \cdot 217\ mL/min \cdot 1440\ min/d)/(0.7 \cdot 1000\ mL/L)$$
$$= 535\ \mu g/d, \text{ round to } 500\ \mu g/d$$

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has good renal function and is obese. Therefore, a volume of distribution equal to 7 L/kg and ideal body weight can be used to compute the digoxin loading dose. An intravenous loading dose (F = 1) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used and concentrations allowed to accumulate over 3–5 half-lives.

$$V = 7\ L/kg \cdot 68.4\ kg = 479\ L$$

$$LD = (Css \cdot V)/F = (1.2\ \mu g/L \cdot 479\ L)/1 = 575\ \mu g \text{ rounded to } 600\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 300 μg would be given initially, followed by two additional intravenous doses of 150 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Jelliffe Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3(Ht – 60) = 50 + 2.3(68 in – 60) = 68.4 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$\mathrm{CrCl}_{\mathrm{est(males)}} = \frac{(137 - 55\ \mathrm{y})\{(0.285 \cdot 140\ \mathrm{kg}) + [12.1 \cdot (1.73\ \mathrm{m})^2]\}}{51 \cdot 0.9\ \mathrm{mg/dL}} = 136\ \mathrm{mL/min}$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in)/(100 cm/m) = 1.73 m.

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has moderate renal function and is obese. Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 14 μg/kg was chosen for this patient, and ideal body weight will be used to compute doses. Digoxin tablets will be used as the dosage form for maintenance doses.

$$\mathrm{TBS} = 14\ \mu\mathrm{g/kg} \cdot 68.4\ \mathrm{kg} = 958\ \mu\mathrm{g}$$

$$\begin{aligned} \mathrm{D} &= \{\mathrm{TBS} \cdot [14\% + 0.20(\mathrm{CrCl})]\}/(\mathrm{F} \cdot 100) \\ &= \{958\ \mu\mathrm{g} \cdot [14\% + 0.20(136\ \mathrm{mL/min})]\}/(0.7 \cdot 100) \\ &= 563\ \mu\mathrm{g/d}, \text{ round to } 500\ \mu\mathrm{g/d} \end{aligned}$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$\mathrm{LD} = \mathrm{TBS}/\mathrm{F} = 958\ \mu\mathrm{g}/1 = 958\ \mu\mathrm{g}, \text{ round to } 1000\ \mu\mathrm{g}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 500 μg would be given initially, followed by two additional intravenous doses of 250 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats/min or other undesirable digoxin adverse effects were noted.

8. *Solution to problem 8* The revised digoxin dose for patient BN would be calculated as follows:

Linear Pharmacokinetics Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$\mathrm{IBW}_{\mathrm{males}}$ (in kg) = 50 + 2.3(Ht – 60) = 50 + 2.3(68 in – 60) = 68.4 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$\mathrm{CrCl}_{\mathrm{est(males)}} = \frac{(137 - \mathrm{age})[(0.285 \cdot \mathrm{Wt}) + (12.1 \cdot \mathrm{Ht}^2)]}{(51 \cdot \mathrm{S}_{\mathrm{Cr}})}$$

$$\mathrm{CrCl}_{\mathrm{est(males)}} = \frac{(137 - 55\ \mathrm{y})\{(0.285 \cdot 140\ \mathrm{kg}) + [12.1 \cdot (1.73\ \mathrm{m})^2]\}}{51 \cdot 0.9\ \mathrm{mg/dL}} = 136\ \mathrm{mL/min}$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in)/(100 cm/m) = 1.73 m.

The patient has moderate renal function and would be expected to have achieved steady state after 7 days of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old} = (1.5 \text{ ng/mL} / 2.4 \text{ ng/mL})\ 500\ \mu\text{g/d}$$
$$= 313\ \mu\text{g/d, round to } 375\ \mu\text{g/d}$$

The new dose would be 375 μg/d given as digoxin tablets to be started at next scheduled dosing time. If desired, a one daily dose could be withheld to allow the digoxin concentration to decline, and the new dose started the following day.

Pharmacokinetic Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [IBW_{males} (in kg) = 50 + 2.3(Ht – 60) = 50 + 2.3(68 in – 60) = 68.4 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(males)} = \frac{(137 - 55\ y)\{(0.285 \cdot 140\ kg) + [12.1 \cdot (1.73\ m)^2]\}}{51 \cdot 0.9\ mg/dL} = 136\ mL/min$$

Note: Height is converted from inches to meters: Ht = (68 in · 2.54 cm/in)/(100 cm/m) = 1.73 m.

The patient has good renal function and would be expected to have achieved steady state after 7 days of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for μg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)] / Css = [0.7(500\ \mu g/d)] / 2.4\ \mu g/L = 146\ L/d$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$$D/\tau = (Css \cdot Cl) / F = (1.5\ \mu g/L \cdot 146\ L/d) / 0.7 = 313\ \mu g/d, \text{ round to } 375\ \mu g/d$$

The new suggested dose would be 375 μg/d given as digoxin tablets to be started at next scheduled dosing time. If desired, a one daily dose could be withheld to allow the digoxin concentration to decline, and the new dose started the following day.

9. *Solution to problem 9* The initial digoxin doses for patient VG would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht – 60) = 45 + 2.3(62 in – 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 75\ y)\{(0.287 \cdot 180\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 6\ mg/dL)} = 15\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

The patient has poor renal function and would be expected to have achieved steady state after ~20 days of treatment.

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 20 mL/min since the patient has moderate-to-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(15\ mL/min) + 20\ mL/min = 39\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with heart failure the desired digoxin concentration would be 0.5–1 ng/mL. A serum concentration equal to 1 ng/mL was chosen for this patient, and oral digoxin capsules will be used (F = 0.9). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F$$
$$= (1\ \mu g/L \cdot 39\ mL/min \cdot 1440\ min/d)/(0.9 \cdot 1000\ mL/L) = 63\ \mu g/d$$

The smallest digoxin capsule size is 100 μg, so the dosage interval will have to be extended to approximate the required daily dosage rate. A dosage rate of 63 μg/d is equivalent to 126 μg given every other day (126 μg = 63 μg/d · 2 d). Since the

medication is to be given as capsules, the dose would be rounded to 100 μg every other day.

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has poor renal function and is obese. Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction can be used to compute the digoxin loading dose, and ideal body weight will be used as the weight factor. An oral loading dose using capsules (F = 0.9) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used to allow concentrations to accumulate over 3–5 half-lives.

$$V = \left(226 + \frac{298 \cdot \text{CrCl}}{29.1 + \text{CrCl}}\right)(\text{Wt}/70) = \left(226 + \frac{298 \cdot 15\ \text{mL/min}}{29.1 + 15\ \text{mL/min}}\right)(50\ \text{kg}/70) = 234\ \text{L}$$

$$\text{LD} = (\text{Css} \cdot \text{V})/\text{F}$$

$$= (1\ \mu\text{g/L} \cdot 234\ \text{L})/0.9 = 260\ \mu\text{g rounded to } 300\ \mu\text{g}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial oral dose of 200 μg would be given, followed by an additional oral dose of 100 μg given 4–6 hours later so that available capsule strengths could be used. In a nonemergent situation, three 100 μg doses separated by 4–6 hours could also be considered. The additional portions of the loading dose could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Jelliffe Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$\text{IBW}_{\text{females}}$ (in kg) = 45 + 2.3(Ht – 60) = 45 + 2.3(62 in – 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - \text{age})[(0.287 \cdot \text{Wt}) + (9.74 \cdot \text{Ht}^2)]}{(60 \cdot \text{S}_{\text{Cr}})}$$

$$\text{CrCl}_{\text{est(females)}} = \frac{(146 - 75\ \text{y})\{(0.287 \cdot 180\ \text{kg}) + [9.74 \cdot (1.57\ \text{m})^2]\}}{(60 \cdot 6\ \text{mg/dL})} = 15\ \text{mL/min}$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in)/(100 cm/m) = 1.57 m.

The patient has poor renal function and would be expected to have achieved steady state after ~20 days of treatment.

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is obese. Digoxin total body stores of 6–10 μg/kg are effective in the treatment of heart failure in patients with poor renal

function. A digoxin dose of 8 μg/kg was chosen for this patient, and ideal body weight will be used to compute the dose.

$$TBS = 8\ \mu g/kg \cdot 50\ kg = 400\ \mu g$$

$$D = \{TBS \cdot [14\% + 0.20(CrCl)]\} / (F \cdot 100) = \{400\ \mu g \cdot [14\% + 0.20(15\ mL/min)]\} / (0.9 \cdot 100) = 75\ \mu g/d, \text{ rounded to } 100\ \mu g/d$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$LD = TBS / F = 400\ \mu g / 0.9 = 444\ \mu g, \text{ round to } 400\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial oral dose of 200 μg would be given initially, followed by two additional oral doses of 100 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

10. *Solution to problem 10* The revised digoxin dose for patient VG would be calculated as follows:

Linear Pharmacokinetics Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht – 60) = 45 + 2.3(62 in – 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 75\ y)\{(0.287 \cdot 180\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 6\ mg/dL)} = 15\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in)/(100 cm/m) = 1.57 m.

The patient has poor renal function and would be expected to have achieved steady state after ~21 days of treatment.

2. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old}$$

$$= (1\ ng/mL / 0.5\ ng/mL)\ 100\ \mu g/2d = 200\ \mu g/2d \text{ or } 100\ \mu g/d$$

The new dose would be 100 μg/d given as oral digoxin capsules to be started at next scheduled dosing time.

Pharmacokinetic Parameter Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is obese [$IBW_{females}$ (in kg) = 45 + 2.3(Ht – 60) = 45 + 2.3(62 in – 60) = 50 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 75\ y)\{(0.287 \cdot 180\ kg) + [9.74 \cdot (1.57\ m)^2]\}}{(60 \cdot 6\ mg/dL)} = 15\ mL/min$$

Note: Height is converted from inches to meters: Ht = (62 in · 2.54 cm/in)/(100 cm/m) = 1.57 m.

The patient has good renal function and would be expected to have achieved steady state after ~21 days of treatment.

2. *Compute drug clearance.*

Note that digoxin concentrations in ng/mL are the same as those for μg/L. This unit substitution will be directly made to avoid conversion factors in the computation.

$$Cl = [F(D/\tau)]/Css = [0.9(100\ \mu g/2d)]/0.5\ \mu g/L = 90\ L/d$$

3. *Compute new dose to achieve desired serum concentration.*

The average steady-state equation is used to compute the new digoxin dose.

$$D/\tau = (Css \cdot Cl)/F = (1\ \mu g/L \cdot 90\ L/d)/0.9 = 100\ \mu g/d$$

The new suggested dose would be 100 μg/d given as digoxin capsules to be started at next scheduled dosing time.

11. *Solution to problem 11* The initial digoxin doses for patient QW would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = \{[(140 - age)BW]/(72 \cdot S_{Cr})\}0.85$$

$$= \{[(140 - 34\ y)50\ kg]/(72 \cdot 0.8\ mg/dL)\}0.85$$

$$CrCl_{est} = 78\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient (Cl_{NR} = 40 mL/min since the patient does not have moderate-severe heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(78\ mL/min) + 40\ mL/min = 142\ mL/min$$

However, this patient is hyperthyroid which is a disease state known to increase digoxin metabolism and shorten half-life ($t_{1/2}$ = 1 d). Assuming a normal volume of distribution (7 L/kg) and this half-life allows the computation of the expected digoxin clearance rate for the patient:

$$V = 7\ L/kg \cdot 50\ kg = 350\ L$$

$$k_e = 0.693/t_{1/2} = 0.693/1\ d = 0.693\ d^{-1}, \text{ where } k_e \text{ is the terminal elimination rate constant}$$

$$Cl = k_e V = 0.693\ d^{-1} \cdot 350\ L = 243\ L/d$$

This clearance rate is probably more reflective of her digoxin elimination status and will be used to compute her digoxin dose.

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL. A serum concentration equal to 1.2 ng/mL was chosen for this patient, and oral digoxin capsules will be used (F = 0.9). Note that for concentration units ng/mL = μg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$$D/\tau = (Css \cdot Cl)/F = (1.2\ \mu g/L \cdot 243\ L/d)/(0.9)$$
$$= 324\ \mu g/d, \text{ round to } 300\ \mu g/d.$$

This is a large dose of digoxin, but hyperthyroid patients have increased digoxin clearance rates and required larger doses. If this dose were administered to the patient, she would need to be monitored several times daily for digoxin adverse effects and digoxin concentrations should be used to help guide therapy.

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

$$V = 350\ L \text{ from previous calculation}$$

$$LD = (Css \cdot V)/F = (1.2\ \mu g/L \cdot 350\ L)/1 = 420\ \mu g \text{ rounded to } 400\ \mu g$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 200 μg would be given initially, followed by two additional intravenous doses of 100 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats/min or other undesireable digoxin adverse effects were noted.

Jelliffe Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} \mathrm{CrCl_{est}} &= \{[(140 - \mathrm{age})\mathrm{BW}] / (72 \cdot \mathrm{S_{Cr}})\}0.85 \\ &= \{[(140 - 34\ \mathrm{y})50\ \mathrm{kg}] / (72 \cdot 0.8\ \mathrm{mg/dL})\}0.85 \\ \mathrm{CrCl_{est}} &= 78\ \mathrm{mL/min} \end{aligned}$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has good renal function and is nonobese. Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 14 μg/kg was chosen for this patient. Digoxin capsules will be used as the dosage form for maintenance doses. Note that this dosing method does not include a way to adjust dosage requirements for disease states that cause higher than average clearance rates.

$$\mathrm{TBS} = 14\ \mu\mathrm{g/kg} \cdot 50\ \mathrm{kg} = 700\ \mu\mathrm{g}$$

$$\begin{aligned} \mathrm{D} &= \{\mathrm{TBS} \cdot [14\% + 0.20(\mathrm{CrCl})]\} / (\mathrm{F} \cdot 100) \\ &= \{700\ \mu\mathrm{g} \cdot [14\% + 0.20(78\ \mathrm{mL/min})]\} / (0.9 \cdot 100) \\ &= 231\ \mu\mathrm{g/d}, \text{ round to } 200\ \mu\mathrm{g/d} \end{aligned}$$

3. *Use loading dose equation to compute digoxin loading dose (if needed).*

Digoxin total body store is used to calculate the loading dose after correcting for bioavailability:

$$\mathrm{LD} = \mathrm{TBS} / \mathrm{F} = 700\ \mu\mathrm{g} / 1 = 700\ \mu\mathrm{g}, \text{ round to } 750\ \mu\mathrm{g}$$

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 375 μg would be given initially, followed by two additional intravenous doses of 187.5 μg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesireable digoxin adverse effects were noted.

12. *Solution to problem 12* The digoxin doses for patient RT would be calculated as follows:

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 3 L/h, a volume of distribution of 403 L, and a half-life equal to 92 h.

3. *Compute dose required to achieve desired digoxin serum concentrations.*

The one-compartment model equations used by the program to compute doses indicates that a dose of 185 μg every 2 days of digoxin tablets will produce a predose

steady-state concentration of 0.8 ng/mL. This dose would be rounded off to 187.5 μg (one and a half 125 μg tablets) every other day.

13. *Solution to problem 13* The digoxin doses for patient LK would be calculated as follows:

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 1.5 L/h, a volume of distribution of 276 L, and a half-life equal to 124 hours.

3. *Compute dose required to achieve desired digoxin serum concentrations.*

The one-compartment model equations used by the program to compute doses indicates that a dose of 193 μg every 3 days of digoxin tablets will produce a predose steady-state concentration of 1 ng/mL. This dose would be rounded off to 187.5 μg (one and a half 125 μg tablets) every third day.

14. *Solution to problem 14* The digoxin doses for patient BH would be calculated as follows:

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a clearance equal to 6.5 L/h, a volume of distribution of 509 L, and a half-life equal to 54 hours.

3. *Compute dose required to achieve desired digoxin serum concentrations.*

The one-compartment model equations used by the program to compute doses indicate that a dose of 383 μg/d of digoxin tablets will produce a predose steady-state concentration of 1.5 ng/mL. This dose would be rounded off to 375 μg/d.

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7

LIDOCAINE

INTRODUCTION

Lidocaine is a local anesthetic agent that also has antiarrhythmic effects. It is classified as a type IB antiarrhythmic agent and is a treatment for ventricular tachycardia or ventricular fibrillation.[1,2] For episodes of sustained ventricular tachycardia with signs or symptoms of hemodynamic instability (angina, pulmonary edema, hypotension, hemodynamic collapse), electrical cardioversion is the treatment of choice. However, for patients who are more hemodynamically stable, sustained monomorphic ventricular tachycardia due to myocardial ischemia or infarction may be successfully treated using lidocaine therapy. Lidocaine therapy can also be considered for the treatment of polymorphic ventricular tachycardia due to myocardial ischemia or infarction.[3]

The primary treatment for ventricular fibrillation is also direct-current cardioversion. Lidocaine is an alternative antiarrhythmic drug treatment to amiodarone for patients that are not converted using electrical shock and intravenous epinephrine or vasopressin.[4]

Lidocaine inhibits transmembrane sodium influx into the His-Purkinje fiber conduction system thereby decreasing conduction velocity.[2] It also decreases the duration of the action potential and as a result decreases the duration of the absolute refractory period in Purkinje fibers and bundle of His. Automaticity is decreased during lidocaine therapy. The net effect of these cellular changes is that lidocaine eradicates ventricular reentrant arrhythmias by abolishing unidirectional blocks via increased conduction through diseased fibers.

THERAPEUTIC AND TOXIC CONCENTRATIONS

When given intravenously, the serum lidocaine concentration/time curve follows a two-compartment model.[5,6] This is especially apparent when initial loading doses of lidocaine are given as rapid intravenous injections over 1–5 minutes (maximum rate: 25–50 mg/min) and a distribution phase of 30–40 minutes is observed after drug administration (Figure 7-1).

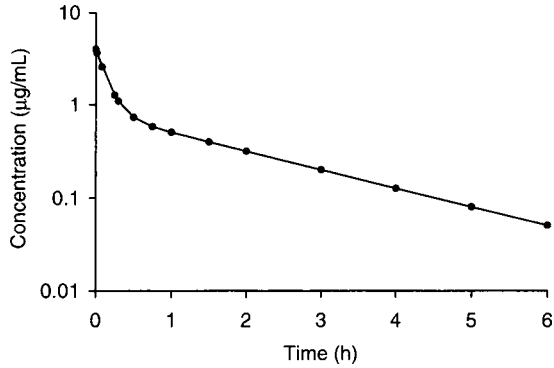

FIGURE 7-1 Lidocaine serum concentrations initially drop rapidly after an intravenous bolus as drug distributes from blood into the tissues during the distribution phase. During the distribution phase, drug leaves the blood due to tissue distribution and elimination. After 0.5–1 hour, an equilibrium is established between the blood and tissues, and serum concentrations drop more slowly since elimination is the primary process removing drug from the blood. This type of serum concentration/time profile is described by a two-compartment model. The conduction system of the heart responds to the high concentrations of lidocaine present during the distribution phase, so lidocaine has a quick onset of action.

Unlike digoxin, the myocardium responds to the higher concentrations achieved during the distribution phase because lidocaine moves rapidly from the blood into the heart, and the onset of action for lidocaine after a loading dose is within a few minutes after completion of the intravenous injection.[1,2] Because of these factors, the heart is considered to be located in the central compartment of the two-compartment model for lidocaine.

The generally accepted therapeutic range for lidocaine is 1.5–5 µg/mL. In the upper end of the therapeutic range (>3 µg/mL), some patients will experience minor side effects including drowsiness, dizziness, paresthesias, or euphoria. Lidocaine serum concentrations above the therapeutic range can cause muscle twitching, confusion, agitation, dysarthria, psychosis, seizures, or coma. Cardiovascular adverse effects such as atrioventricular block, hypotension, and circulatory collapse have been reported at lidocaine concentrations above 6 µg/mL, but are not strongly correlated with specific serum levels. Lidocaine-induced seizures are not as difficult to treat as theophylline-induced seizures and usually respond to traditional antiseizure medication therapy. Lidocaine metabolites (MEGX and GX, please see Basic Clinical Pharmacokinetic Parameter section) probably contribute to the central nervous system side effects attributed to lidocaine therapy.[7–9] Clinicians should understand that all patients with "toxic" lidocaine serum concentrations in the listed ranges will not exhibit signs or symptoms of lidocaine toxicity. Rather, lidocaine concentrations in the given ranges increase the likelihood that an adverse effect will occur.

For dose adjustment purposes, lidocaine serum concentrations are best measured at steady state after the patient has received a consistent dosage regimen for 3–5 drug half-lives. Lidocaine half-life varies from 1–1.5 hours in normal adults to 5 hours or more in adult patients with liver failure. If lidocaine is given as a continuous intravenous infusion, it can take a considerable amount of time (3–5 half-lives or 7.5–25 hours) for patients to

achieve effective concentrations so an intravenous loading dose is commonly administered to patients (Figure 7-2). The ideal situation is to administer an intravenous loading dose that will achieve the desired concentration immediately, then start an intravenous continuous infusion that will maintain that concentration (Figure 7-2). In order to derive this perfect situation, the lidocaine volume of distribution for the central compartment (Vc in L) would have to be known to compute the loading dose (LD in mg): LD = Css · Vc, where Css is the desired lidocaine concentration in mg/L. The volume of distribution for the central compartment of the two-compartment model is used to compute the loading dose because lidocaine distributes rapidly to the myocardium and the heart is considered to reside in the central compartment of the model. However, this pharmacokinetic parameter is rarely, if ever, known for a patient, so a loading dose based on a population average central volume of distribution is used to calculate the amount of lidocaine needed. Since the patient's own, unique central volume of distribution will most likely be greater (resulting in too low of a loading dose) or less (resulting in too large of a loading dose) than the population average volume of distribution used to compute the loading dose, the desired steady-state lidocaine concentration will not be achieved. Because of this, it will still take 3–5 half-lives for the patient to reach steady-state conditions while receiving a constant intravenous infusion rate (Figure 7-3).

After a lidocaine loading dose is given, serum concentrations from this dose rapidly decline due to distribution from blood to tissues, and serum concentrations due to the infusion are not able to increase rapidly enough to avoid a temporary decline or dip in lidocaine concentrations (Figure 7-2). The decline may be severe enough that ventricular arrhythmias which were initially suppressed by lidocaine may recur due to subtherapeutic antiarrhythmic concentrations. Because of this dip in concentrations due to distribution of drug after the intravenous loading dose, an additional dose (50% of original loading dose) can be given 20–30 minutes after the original loading dose or several additional doses

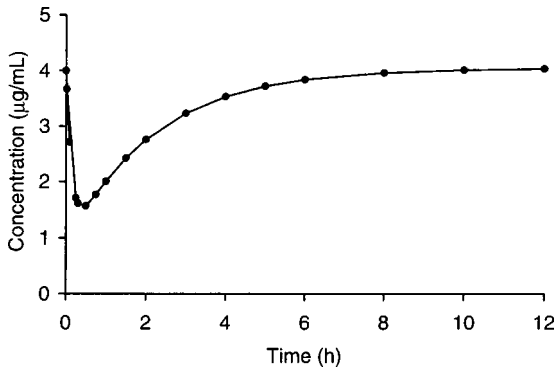

FIGURE 7-2 To maintain therapeutic lidocaine concentrations, an intravenous bolus (over 1–5 minutes) of lidocaine is followed by a continuous intravenous infusion of the drug. Even though the infusion is started right after the loading dose is given, serum concentrations due to the infusion cannot increase rapidly enough to counter the large decrease in concentrations during the distribution phase from the bolus dose. The dip in serum lidocaine concentrations below therapeutic amounts can allow previously treated arrhythmias to recur.

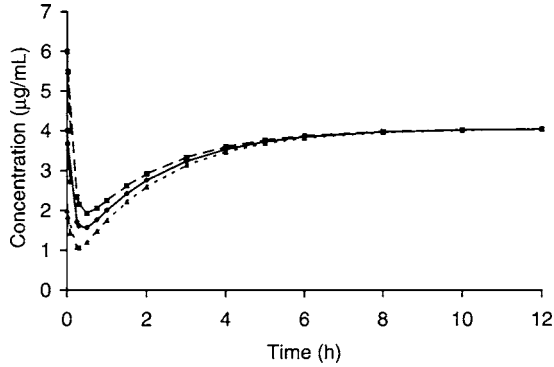

FIGURE 7-3 Because the central volume of distribution is not known at the time an intravenous loading dose of lidocaine is administered, average population parameters must be assumed and almost always result in initial lidocaine serum concentrations that are higher *(dashed line with squares)* or lower *(dotted line with triangles)* than those that were expected *(solid line with circles).* So, the main clinical goal of administering loading doses of lidocaine is to achieve therapeutic concentrations as soon as possible, not to attain steady-state concentrations immediately after the loading dose is given.

(33–50% of original loading dose) can be given every 5–10 minutes to a total maximum of 3 mg/kg (Figure 7-4).[6] Thus, lidocaine intravenous loading doses do not usually achieve steady-state serum concentrations immediately, but, hopefully, they do result in therapeutic concentrations and response sooner than simply starting an intravenous infusion alone.

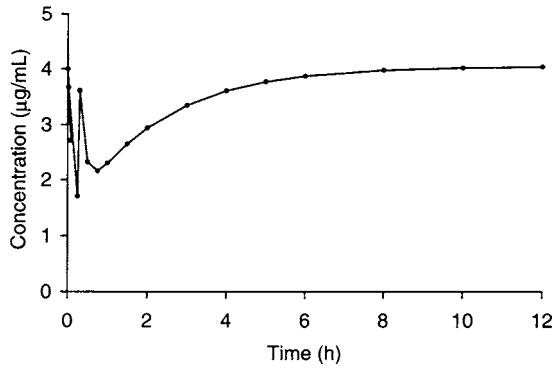

FIGURE 7-4 Since the dip in serum lidocaine concentrations below therapeutic amounts can allow previously treated arrhythmias to recur, a supplemental loading or "booster" dose is typically given 20–30 minutes after the initial loading dose. This prevents lidocaine serum concentrations from declining too far during the distribution phase of the intravenous bolus dose and before serum concentrations from the intravenous infusion have had an opportunity to attain therapeutic concentrations.

CLINICAL MONITORING PARAMETERS

The electrocardiogram (ECG or EKG) should be monitored to determine the response to lidocaine in patients with ventricular tachycardia or fibrillation. The goal of therapy is suppression of ventricular arrhythmias and avoidance of adverse drug reactions. Lidocaine therapy is often discontinued after 6–24 hours of treatment so the need for long-term antiarrhythmic drug use can be reassessed, although longer infusions may be used in patients with persistent tachyarrhythmias. For long-term therapy, electrophysiologic studies using programmed stimulation to replicate the ventricular arrhythmia or 24-hour ECG monitoring using a Holter monitor can be performed in patients while receiving a variety of antiarrhythmic agents to determine effective antiarrhythmic drug therapy. Because lidocaine is only administered parenterally, it is rarely used for more than a few days unless oral antiarrhythmic agents are ineffective.

Because lidocaine is usually given for a short duration (<24 hours), it is often not necessary to obtain serum lidocaine concentrations in patients receiving appropriate doses who currently have no ventricular arrhythmia or adverse drug effects. However, lidocaine serum concentrations should be obtained in patients who have a recurrence of ventricular tachyarrhythmias, are experiencing possible lidocaine side effects, or are receiving lidocaine doses not consistent with disease states and conditions known to alter lidocaine pharmacokinetics (please see Effects of Disease States and Conditions on Lidocaine Pharmacokinetics and Dosing section). Serum concentration monitoring can aid in the decision to increase or decrease the lidocaine dose. For instance, if the ventricular arrhythmia reappears and the lidocaine serum concentration is <5 μg/mL, increasing the lidocaine dose is a therapeutic option. However, if the lidocaine serum concentration is over 5 μg/mL, it is unlikely a dosage increase will be effective in suppressing the arrhythmia and there is an increased likelihood that drug side effects may occur. Similarly, if a possible lidocaine adverse drug reaction is noted in a patient and the lidocaine serum concentration is <3–5 μg/mL, it is possible that the observed problem may not be due to lidocaine treatment and other sources can be investigated. Patients receiving lidocaine infusions for longer than 24 hours are prone to unexpected accumulation of lidocaine concentrations in the serum and should be closely monitored for lidocaine side effects.[10–13] While receiving lidocaine, patients should be monitored for the following adverse drug effects: drowsiness, dizziness, paresthesias, euphoria, muscle twitching, confusion, agitation, dysarthria, psychosis, seizures, coma, atrioventricular block, or hypotension.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Lidocaine is almost completely eliminated by hepatic metabolism (>95%).[5,14] Hepatic metabolism is mainly via the CYP3A enzyme system. Monoethylglycinexylidide (MEGX) is the primary metabolite resulting from lidocaine metabolism.[7–9] While a portion of MEGX is eliminated renally, most of the metabolite is further converted hepatically to glycinexylidide (GX) and other, inactive metabolites. GX is primarily eliminated by the kidney. MEGX and GX have some antiarrhythmic activity (MEGX ~80% and GX ~10%, relative to lidocaine), but have also been implicated as the cause of some adverse effects attributed to lidocaine therapy.[7–9] Because both metabolites are eliminated

by the kidney, patients with renal failure should be monitored for adverse effects due to metabolite accumulation even though lidocaine serum concentrations are within the therapeutic range. The hepatic extraction ratio of lidocaine is about 70%, so lidocaine is typically classified as a high extraction ratio drug. Because of this, it is expected that liver blood flow will be the predominate factor influencing the clearance of lidocaine (Cl ≈ LBF, where Cl is lidocaine clearance and LBF is liver blood flow, both in L/min), and many disease states and conditions that alter lidocaine clearance do so via changes in liver blood flow. However, because a hepatic extraction ratio >70% is the definition of a high extraction ratio agent and the extraction ratio for lidocaine is on the margin of this range, it is very possible that changes in lidocaine intrinsic clearance or plasma protein binding will change lidocaine clearance.

Lidocaine is usually given intravenously but may also be given intramuscularly.[15] After intramuscular injection, absorption is rapid and complete with maximum concentrations occurring about 1 hour after administration and 100% bioavailability as long as the patient's peripheral circulation is not compromised due to hypotension or shock. Intramuscular administration of medications can increase creatine kinase (CK) concentrations due to minor skeletal muscle trauma inflicted by the injection, and this enzyme is monitored in patients who may have had a myocardial infarction. Thus, the creatine kinase isozyme that is relatively specific to the heart (CK-MB) needs to be measured in myocardial infarction patients who have received intramuscular injections. Oral absorption of lidocaine is nearly 100%.[5] However, lidocaine is extensively metabolized by the CYP3A enzymes contained in the intestinal wall and liver resulting in a large first-pass effect and low, variable oral bioavailability (F ≈ 30%). Because roughly 70% of an oral dose is converted to metabolites, MEGX and GX concentrations are high after oral administration of lidocaine resulting in a high incidence of adverse effects.

Plasma protein binding in normal individuals is about 70%.[16–18] Of this value, approximately 30% is due to drug binding to albumin while 70% is due to lidocaine bound to α_1-acid glycoprotein (AGP).[10,12,13] AGP is classified as an acute phase reactant protein that is present in lower amounts in all individuals but is secreted in large amounts in response to certain stresses and disease states such as trauma, heart failure, and myocardial infarction. In patients with these disease states, lidocaine binding to AGP can be even larger resulting in an unbound fraction as low as 10–15%. AGP concentrations continuously increase during the first 12–72 hours after a myocardial infarction, and, as a result, the lidocaine unbound fraction decreases on average from about 30% to 20% during this time period. The continuous increase in protein binding due to AGP secretion causes a continuous decrease in lidocaine clearance in patients with myocardial infarction, and lidocaine concentrations can accumulate to unexpectedly high levels in patients receiving the drug for longer than 24 hours. Patients without myocardial infarction also experience accumulation of lidocaine concentrations during long-term (>24 hours) infusions due to competition for hepatic metabolism between parent drug and metabolites.[11,19] Thus, monitoring for adverse reactions in patients receiving long-term lidocaine infusions is important, and lidocaine serum concentrations can be useful adjuncts to avoid lidocaine toxicity.

The recommended dose of lidocaine is based on the concurrent disease states and conditions present in the patient that can influence lidocaine concentrations. Lidocaine pharmacokinetic parameters used to compute doses are given in the following section for specific patient profiles.

EFFECTS OF DISEASE STATES AND CONDITIONS ON LIDOCAINE PHARMACOKINETICS AND DOSING

Normal adults without the disease states and conditions given later in this section with normal liver function have an average lidocaine half-life of 1.5 hours (range: 1–2 hours), a central volume of distribution of 0.5 L/kg (Vc = 0.4–0.6 L/kg) and the volume of distribution for the entire body of 1.5 L/kg (V_{area} = 1–2 L/kg; Table 7-1).[5,11,20] Disease states and conditions that change lidocaine pharmacokinetics and dosage requirements may alter clearance, the central volume of distribution, and the volume of distribution for the entire body. The volume of distribution for the central compartment of the two-compartment model is used to compute the loading dose because lidocaine distributes rapidly to the myocardium and the heart is considered to reside in the central compartment of the model. The elimination rate constant ($k = 0.693/t_{1/2}$, where $t_{1/2}$ is the half-life) and clearance ($Cl = kV_{area}$) can be computed from the aforementioned pharmacokinetic parameters.

Patients with liver cirrhosis or acute hepatitis have reduced lidocaine clearance which results in a prolonged average lidocaine half-life of 5 hours.[14,21–24] The mechanism for depressed clearance in liver disease patients is destruction of liver parenchyma where hepatic drug metabolizing enzymes are present and reduction of liver blood flow. The central volume of distribution and volume of distribution for the entire body are larger in patients with liver disease because albumin and AGP concentrations are lower in these patients and result in reduced lidocaine plasma protein binding (average Vc = 0.6 L/kg, average V_{area} = 2.6 L/kg). However, the effect that liver disease has on lidocaine pharmacokinetics is highly variable and difficult to accurately predict, especially in patients with acute hepatitis. It is possible for a patient with liver disease to have relatively normal or grossly abnormal lidocaine clearance, volumes of distribution, and half-life. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 7-2).[25] Child-Pugh scores are completely discussed in Chapter 3 (Drug Dosing in Special Populations: Renal and Hepatic Disease, Dialysis, Heart Failure, Obesity, and Drug Interactions), but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 7-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease in the initial daily drug dose for lidocaine ($t_{1/2}$ = 5 hours). As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Lidocaine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Heart failure causes reduced lidocaine clearance because of decreased hepatic blood flow secondary to compromised cardiac output (Table 7-3).[7,14,23,26,27,38] Patients with cardiogenic shock experience extreme declines in lidocaine clearance due to severe decreases in cardiac output and liver blood flow. Central volume of distribution (Vc = 0.3 L/kg) and

TABLE 7-1 Disease States and Conditions that Alter Lidocaine Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	CENTRAL VOLUME OF DISTRIBUTION (Vc)	VOLUME OF DISTRIBUTION FOR ENTIRE BODY (V_{area})	COMMENT
Adult, normal liver function	1.5 hours (range: 1–2 hours)	0.5 L/kg (range: 0.4–0.6 L/kg)	1.5 L/kg (range: 1–2 L/kg)	Lidocaine has a high hepatic extraction ratio of ~70%, so liver blood flow is primary determinate of clearance rate. Accumulation of serum lidocaine concentrations can occur with long-term (>24 h) infusions.
Adult, hepatic disease (liver cirrhosis or acute hepatitis)	5 hours	0.6 L/kg	2.6 L/kg	Lidocaine is metabolized >95% by hepatic microsomal enzymes (primarily CYP3A), so loss of functional liver tissue, as well as reduced liver blood flow, decreases lidocaine clearance. Pharmacokinetic parameters highly variable in liver disease patients. Volumes of distribution are larger due to decreased α_1-acid glycoprotein and albumin drug binding in the plasma.
Adult, heart failure	2 hours	0.3 L/kg	1 L/kg	Decreased liver blood flow secondary to reduced cardiac output reduces lidocaine clearance. Volumes of distribution are smaller due to

(*Continued*)

TABLE 7-1 Disease States and Conditions that Alter Lidocaine Pharmacokinetics *(Continued)*

DISEASE STATE/ CONDITION	HALF-LIFE	CENTRAL VOLUME OF DISTRIBUTION (Vc)	VOLUME OF DISTRIBUTION FOR ENTIRE BODY (V_{area})	COMMENT
Adult, heart failure *(continued)*				increased α_1-acid glycoprotein drug binding in the plasma. Heart failure results in large and variable reductions in lidocaine clearance. Cardiac status must be monitored closely in heart failure patients, since lidocaine clearance changes with acute changes in cardiac output.
Adult, postmyocardial infarction (<12 h)	4 hours	0.5 L/kg	1.5 L/kg	Myocardial infarction reduces cardiac output, resulting in variable reductions in lidocaine clearance. These patients are especially prone to accumulation of serum lidocaine concentrations during long-term (>24 h) infusions due to secretion of α_1-acid glycoprotein.
Adult, obese (>30% over ideal body weight)	According to other disease states/ conditions that affect lidocaine pharmacokinetics.	According to other disease states/ conditions that affect lidocaine pharmacokinetics.	According to other disease states/ conditions that affect lidocaine pharmacokinetics.	Lidocaine doses should be based on ideal body weight for patients who weight more that 30% above IBW.

TABLE 7-2 Child-Pugh Scores for Patients with Liver Disease[25]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

volume of distribution for the entire body (V_{area} = 1 L/kg) are decreased because heart failure patients have elevated AAG serum concentrations which leads to increased lidocaine plasma protein binding and decreased lidocaine unbound fraction. Patients with heart failure have an average lidocaine half-life equal to 2 hours (range: 1–24 hours). Half-life ($t_{1/2}$) does not change as much as expected from the change in clearance (Cl) because the volume of distribution simultaneously decreases [$t_{1/2} = (0.693 \cdot \downarrow V_{area}) / \downarrow Cl$]. Obviously, the effect that heart failure has on lidocaine pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with heart failure to have relatively normal or grossly abnormal lidocaine clearance and half-life. For heart failure patients, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Lidocaine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with heart failure.

TABLE 7-3 New York Heart Association (NYHA) Functional Classification for Heart Failure[38]

NYHA HEART FAILURE CLASS	DESCRIPTION
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitations of physical activity. Although patients are comfortable at rest, less than ordinary activity lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Patients with myocardial infarction may develop serious ventricular arrhythmias that require therapy with lidocaine. After a myocardial infarction, serum AAG concentrations increase up to 50% over a 12- to 72-hour time period.[10,12,13] As AAG serum concentrations increase, plasma protein binding of lidocaine decreases and the unbound fraction of lidocaine decreases from about 30% to about 20%. Although lidocaine is considered a high hepatic extraction ratio drug with liver blood flow having the major influence on lidocaine clearance, a decline in the unbound fraction of lidocaine in the plasma decreases lidocaine clearance. The reduction in lidocaine clearance is continuous as long as AAG concentrations continue to rise. A result of this phenomenon is lidocaine serum concentrations do not reach steady state during long-term (>24 hours) intravenous infusions of lidocaine in myocardial infarction patients and results of pharmacokinetic studies in this patient population differ according to when the investigation took place in relation to the myocardial damage. When studied within 12 hours of myocardial infarction, patients had decreased lidocaine clearance due to decreased cardiac output and liver blood flow, relatively normal volumes of distribution (Vc = 0.5 L/kg, V_{area} = 1.5 L/kg), and a prolonged half-life of 4 hours.[27–29] When similar myocardial infarction patients are studied after longer lidocaine infusions, the central volume of distribution and volume of distribution representing the entire body are smaller because AAG serum concentrations have had an opportunity to increase and change lidocaine plasma protein binding.[10,12,13]

Although the volume of distribution representing the entire body (V_{area}) correlates most closely with total body weight, obese patients (>30% above ideal body weight or IBW) should have central volume of distribution and clearance estimates based on ideal body weight.[20] Lidocaine pharmacokinetic parameter estimates should be based on the concurrent disease states and conditions present in the patient. If weight-based dosage recommendations are to be used, ideal body weight should be used to compute maintenance infusions (mg/kg/min) and loading doses (mg/kg) for obese individuals.

Patient age has an effect on lidocaine volumes of distribution and half-life.[26] For elderly patients over the age of 65, studies indicate that lidocaine clearance is unchanged, the volumes of distribution are slightly larger, and half-life is longer (average half-life = 2.3 hours, range: 1.7–4.5 hours) compared to younger subjects. A confounding factor found in lidocaine pharmacokinetic studies conducted in older adults is the possible accidental inclusion of subjects that have subclinical or mild cases of the disease states associated with reduced lidocaine clearance (heart failure, liver disease, etc.). Additionally, most patients with serious ventricular arrhythmias studied in all of the previously mentioned studies are older and those results include any influence of age. Thus, in most cases elderly patients are treated with lidocaine according to the other disease states or conditions present that influence lidocaine pharmacokinetics.

Lidocaine serum concentrations accumulate in patients receiving long-term (>24 hours) infusions even if the patient did not have a myocardial infarction.[11,19] Accumulation of lidocaine in these patients is due to competition for hepatic metabolism between parent drug and metabolites. Because MEGX and GX metabolites are eliminated to some extent by the kidney, patients with renal failure should be monitored for lidocaine adverse effects due to metabolite accumulation even though lidocaine serum concentrations are within the therapeutic range. Lidocaine is not appreciably removed by hemodialysis. Because lidocaine has a sieving coefficient of 0.14, continuous hemofiltration does not remove a significant amount of drug.[30,31]

DRUG INTERACTIONS

Lidocaine has serious drug interactions with β-adrenergic receptor blockers and cimetidine that decrease lidocaine clearance 30% or more.[32] Propranolol, metoprolol, and nadolol have been reported to reduce lidocaine clearance due to the decrease in cardiac output caused by β-blocker agents. Decreased cardiac output results in reduced liver blood flow which explains the decline in lidocaine clearance caused by these drugs. Cimetidine also decreases lidocaine clearance, but the mechanism of the interaction is different. Because cimetidine does not change liver blood flow, it is believed that cimetidine decreases lidocaine clearance by inhibiting hepatic microsomal enzymes.[33,34]

Lidocaine clearance may be accelerated by concomitant use of phenobarbital or phenytoin.[32] Both of these agents are known to be hepatic drug metabolizing enzyme inducers, and this is the probable mechanism of their drug interaction with lidocaine. It is important to remember that phenytoin has antiarrhythmic effects and is also classified as a type IB antiarrhythmic agent. Because of this, phenytoin and lidocaine may have additive pharmacologic effects that could result in a pharmacodynamic drug interaction.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate lidocaine therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of lidocaine. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of lidocaine is to compute the best dose possible for the patient given their set of disease states and conditions that influence lidocaine pharmacokinetics and the arrhythmia being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Lidocaine is predominately metabolized by liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change lidocaine half-life, and the half-life previously measured in these studies is used as an estimate of the current patient's half-life (Table 7-1). For example, if a patient has suffered an uncomplicated myocardial infarction, lidocaine half-life would be assumed to equal 4 hours. Alternatively, for a patient with moderate heart failure (NYHA CHF class III), lidocaine half-life

would be assumed to equal 2 hours, while a patient with severe liver disease (Child-Pugh score = 12) would be assigned an estimated half-life of 5 hours. To produce the most conservative lidocaine doses in patients with multiple concurrent disease states or conditions that affect lidocaine pharmacokinetics, the disease state or condition with the longest half-life should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible. Once the correct half-life is identified for the patient, it can be converted into the lidocaine elimination rate constant (k) using the following equation: $k = 0.693/t_{1/2}$.

VOLUME OF DISTRIBUTION ESTIMATE

As with the half-life estimate, lidocaine volume of distribution values are chosen according to the disease states and conditions that are present (Table 7-1). The central volume of distribution (Vc) is used to compute loading doses because lidocaine has a rapid onset of action after administration, and the heart acts as if it is in the central compartment of the two-compartment model used to describe lidocaine pharmacokinetics. The central volume of distribution is assumed to equal 0.6 L/kg for liver disease patients, 0.3 L/kg for heart failure and cardiogenic shock patients, and 0.5 L/kg for all other patients. The volume of distribution for the entire body after distribution is complete (V_{area}) is used to help compute lidocaine clearance, and is assumed to equal 2.6 L/kg for liver disease patients, 1 L/kg for heart failure and cardiogenic shock patients, and 1.5 L/kg for all other patients. For obese patients (>30% above ideal body weight), ideal body weight is used to compute lidocaine volume of distribution. Thus, for a nonobese 80-kg patient without heart failure or liver disease, the estimated lidocaine central volume of distribution would be 40 L: Vc = 0.5 L/kg · 80 kg = 40 L. For a 150-kg obese patient with an ideal body weight of 60 kg and normal cardiac and liver function, the estimated lidocaine volume of distribution is 30 L: V = 0.5 L/kg · 60 kg = 30 L.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by continuous intravenous infusion, lidocaine follows a two-compartment pharmacokinetic model (Figures 7-1 through 7-3). A simple pharmacokinetic equation that computes the lidocaine steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows dosage calculation for a continuous infusion: $Css = k_0 / Cl$ or $k_0 = Css \cdot Cl$, where k_0 is the dose of lidocaine in mg and Cl is lidocaine clearance in L/h. Clearance is computed using estimates of lidocaine elimination rate constant (k) and volume of distribution for the entire body after distribution is complete (V_{area}): $Cl = kV_{area}$. For example, if a patient has an estimated elimination rate constant equal to 0.173 h^{-1} and an estimated volume of distribution equal to 105 L, the estimated clearance would equal 18.2 L/h: $Cl = 0.173h^{-1} \cdot 105\ L = 18.2$ L/h.

The equation used to calculate an intravenous loading dose (LD in mg) is based on a two-compartment model: LD = (Css · Vc), where Css is the desired lidocaine steady-state concentration in μg/mL which is equivalent to mg/L, and Vc is the lidocaine central volume of distribution. Intravenous lidocaine loading doses should be given as an intravenous bolus no faster than 25–50 mg/min.

STEADY-STATE CONCENTRATION SELECTION

The general accepted therapeutic range for lidocaine is 1.5–5 μg/mL. However, lidocaine therapy much be individualized for each patient in order to achieve optimal responses and minimal side effects.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver and cardiac function. Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 1.5 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 1.5\ h = 0.462\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: $Vc = 0.5\ L/kg \cdot 75\ kg = 38\ L$, $V_{area} = 1.5\ L/kg \cdot 75\ kg = 113\ L$. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: $Cl = kV_{area} = 0.462\ h^{-1} \cdot 113\ L = 52.2\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: $LD = Css \cdot Vc = 3\ mg/L \cdot 38\ L = 114\ mg$, rounded to 100 mg intravenously over 2–4 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (3\ mg/L \cdot 52.2\ L/h) / (60\ min/h) = 2.6\ mg/min$, rounded to 2.5 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = $5 \cdot 1.5\ h = 7.5\ h$). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11). Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 4 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: Vc = 0.6 L/kg · 85 kg = 51 L, V_{area} = 2.6 L/kg · 85 kg = 221 L. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: Cl = kV_{area} = 0.139 h^{-1} · 221 L = 31 L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: LD = Css · Vc = 4 mg/L · 51 L = 204 mg, rounded to 200 mg intravenously over 4–8 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: k_0 = Css · Cl = (4 mg/L · 31 L/h) / (60 min/h) = 2.1 mg/min, rounded to 2 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 3 MN is a 64–year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has moderate heart failure (NYHA CHF class III). Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 2 hours. The elimination rate constant is computed using the following formula: k = 0.693 / $t_{1/2}$ = 0.693 / 2 h = 0.347 h^{-1}.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: Vc = 0.3 L/kg · 78 kg = 23 L, V_{area} = 1 L/kg · 78 kg = 78 L. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: Cl = kV_{area} = 0.347 h^{-1} · 78 L = 27 L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: LD = Css · Vc = 3 mg/L · 23 L = 69 mg, rounded to 75 mg intravenously over

2–3 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (3\ mg/L \cdot 27\ L/h) / (60\ min/h) = 1.4\ mg/min$, rounded to 1.5 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in lidocaine pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard lidocaine doses for various situations is warranted.[35] The original computation of these doses were based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. In general, the lidocaine steady-state serum concentration expected from the lower end of the dosage range was 1.5–3 μg/mL and 3–5 μg/mL for the upper end of the dosage range. Suggested intravenous lidocaine continuous infusion maintenance doses are 1–2 mg/min for patients with liver disease or heart failure and 3–4 mg/min for all other patients. When more than one disease state or condition is present in a patient, choosing the lowest infusion rate will result in the safest, most conservative dosage recommendation. With regard to loading doses, lidocaine is given intravenously at the dose of 1–1.5 mg/kg (not to exceed 25–50 mg/min) for all patients except those with heart failure. The suggested lidocaine intravenous loading dose for heart failure patients is 0.5–0.75 mg/kg (not to exceed 25–50 mg/min), although some clinicians advocate the administration of full loading doses of lidocaine in heart failure patients. Ideal body weight is used to compute loading doses for obese patients (>30% over ideal body weight).

Pediatric doses are similar to that given to adults when adjusted for differences in body weight. Intravenous loading doses are 1 mg/kg with up to two additional doses, if needed (total dose not to exceed 3–5 mg/kg for first hour). Continuous intravenous infusions doses are 20–50 μg/kg/min. For patients with shock, heart failure, or liver disease patients, initial doses should not exceed 20 μg/kg/min.[36]

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver and cardiac function.

Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 1–1.5 mg/kg and maintenance infusion of 3–4 mg/min is suggested for a patient without heart failure or liver disease.

2. *Compute dosage regimen.*

Because the desired concentration is in the lower end of the therapeutic range, a dose in the lower end of the suggested ranges will be used. A lidocaine loading dose of 1 mg/kg will be administered: LD = 1 mg/kg · 75 kg = 75 mg over 1.5–3 minutes. A lidocaine maintenance infusion equal to 3 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = 5 · 1.5 h = 7.5 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11). Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 4 μg/mL.

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 1–1.5 mg/kg and maintenance infusion of 1–2 mg/min is suggested for a patient with liver disease.

2. *Compute dosage regimen.*

Because the desired concentration is in the upper end of the therapeutic range, a dose in the upper end of the suggested ranges will be used. A lidocaine loading dose of 1.5 mg/kg will be administered: LD = 1.5 mg/kg · 85 kg = 128 mg, rounded to 150 mg over 3–6 minutes. A lidocaine maintenance infusion equal to 2 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has moderate heart failure (NYHA

CHF class III). Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 0.5–0.75 mg/kg and maintenance infusion of 1–2 mg/min is suggested for a patient with heart failure.

2. *Compute dosage regimen.*

Because the desired concentration is in the lower end of the therapeutic range, a dose in the lower end of the suggested ranges will be used. A lidocaine loading dose of 0.5 mg/kg will be administered: LD = 0.5 mg/kg · 78 kg = 39 mg, rounded to 50 mg over 1–2 minutes. A lidocaine maintenance infusion equal to 1 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

USE OF LIDOCAINE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce lidocaine serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the narrow therapeutic index of lidocaine, and the desire to avoid of lidocaine adverse side effects, measurement of lidocaine serum concentrations can be a useful adjunct for patients to ensure that therapeutic, nontoxic levels are present. In addition to lidocaine serum concentrations, important patient parameters (electrocardiogram, clinical signs and symptoms of the ventricular arrhythmia, potential lidocaine side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When lidocaine serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change lidocaine doses assuming the drug follows *linear pharmacokinetics*. Although it has been clearly demonstrated in research studies that lidocaine serum concentrations accumulate in patients during long-term (>24 hours) infusions, in the clinical setting most patients' steady-state serum concentrations change proportionally to lidocaine dose for shorter infusion times. Thus, assuming linear pharmacokinetics is adequate for dosage adjustments in most patients.

Sometimes, it is useful to compute lidocaine pharmacokinetic constants for a patient and base dosage adjustments on these. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the lidocaine dose.

In some situations, it may be necessary to compute lidocaine clearance for the patient during a continuous infusion before steady-state conditions occur and utilize this pharmacokinetic parameter to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where serum concentrations are obtained at suboptimal times or the patient was not at steady state when serum concentrations were measured. An additional benefit is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because lidocaine follows linear, dose-proportional pharmacokinetics in most patients during short-term infusions (<24 hours), steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or $D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and accumulation of serum lidocaine concentrations can occur with long-term (>24 hours) infusions. When steady-state serum concentrations are higher than expected during long-term lidocaine infusions, lidocaine accumulation pharmacokinetics is a possible explanation for the observation. Because of this, suggested dosage increases greater than 75% using this method should be scrutinized by the prescribing clinician, and the risk versus benefit for the patient assessed before initiating large dosage increases (>75% over current dose).

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver and cardiac function. The current steady-state lidocaine concentration equals 2.2 μg/mL at a dose of 2 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 8 hours ($5\ t_{1/2} = 5 \cdot 1.5\ h = 7.5\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.2\ \mu g/mL)\ 2\ mg/min$$
$$= 3.6\ mg/min, \text{ rounded to } 3.5\ mg/min$$

The new suggested dose would be 3.5 mg/min of intravenous lidocaine to be started immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = $5 \cdot 1.5\ h = 7.5\ h$). Lidocaine serum concentrations should also be

measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11). The current steady-state lidocaine concentration equals 6.4 μg/mL at a dose of 2 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 3 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after a day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (3\ \mu g/mL / 6.4\ \mu g/mL)\ 2\ mg/min$$
$$= 0.9\ mg/min, \text{ rounded to } 1\ mg/min$$

The new suggested dose would be 1 mg/min of intravenous lidocaine. If the patient was experiencing adverse drug effects, the infusion could be held for one estimated half-life (5 hours) until the new dose was started.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has moderate heart failure (NYHA CHF class III). The current steady-state lidocaine concentration equals 2.2 μg/mL at a dose of 1 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 10–12 hours (5 $t_{1/2}$ = 5 · 2 h = 10 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.2\ \mu g/mL)\ 1\ mg/min$$
$$= 1.8\ mg/min, \text{ rounded to } 2\ mg/min$$

The new suggested dose would be 2 mg/min of intravenous lidocaine to begin immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours,

the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired lidocaine concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state lidocaine concentration (Css in mg/L or μg/mL). During a continuous intravenous infusion, the following equation is used to compute lidocaine clearance (Cl in L/min): $Cl = k_0/Css$, where k_0 is the dose of lidocaine in mg/min. The clearance measured using this technique is the patient's own, unique lidocaine pharmacokinetic constant and can be used in the intravenous continuous infusion equation to compute the required dose (k_0 in mg/min) to achieve any desired steady-state serum concentration (Css in mg/L or μg/mL): $k_0 = CssCl$, where Cl is lidocaine clearance in L/min. Because this method also assumes linear pharmacokinetics, lidocaine doses computed using the pharmacokinetic parameter method and the linear pharmacokinetic method should be identical.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver and cardiac function. The current steady-state lidocaine concentration equals 2.2 μg/mL at a dose of 2 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first 8 hours (5 $t_{1/2}$ = 1.5 · 5 h = 7.5 h) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration $Cl = k_0 / Css$ = (2 mg/min) / (2.2 mg/L) = 0.91 L/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: $k_0 = Css \cdot Cl$ = 4 mg/L · 0.91 L/min = 3.6 mg/min, round to 3.5 mg/min.

The new lidocaine infusion rate would be instituted immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = 5 · 1.5 h = 7.5 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11). The current steady-state lidocaine concentration equals 6.4 μg/mL at a dose of 2 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 3 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after a day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration Cl = k_0 / Css = (2 mg/min) / (6.4 mg/L) = 0.31 L/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: k_0 = Css · Cl = 3 mg/L · 0.31 L/min = 0.9 mg/min, round to 1 mg/min.

The new suggested dose would be 1 mg/min of intravenous lidocaine. If the patient was experiencing adverse drug effects, the infusion could be held for one estimated half-life (5 hours) until the new dose was started.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has moderate heart failure (NYHA CHF class III). The current steady-state lidocaine concentration equals 2.2 μg/mL at a dose of 1 mg/min. Compute a lidocaine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 10–12 hours (5 $t_{1/2}$ = 5 · 2 h = 10 h) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration Cl = k_0 / Css = (1 mg/min) / (2.2 mg/L) = 0.45 L/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: k_0 = Css · Cl = 4 mg/L · 0.45 L/min = 1.8 mg/min, round to 2 mg/min.

The new suggested dose would be 2 mg/min of intravenous lidocaine to begin immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[37]

Example 1 OY is a 57-year-old, 79-kg (height 5 ft 8 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 gm/dL) and cardiac function. He received a 100-mg loading dose of lidocaine at 0800 H and a continuous intravenous infusion of lidocaine was started at 0810 H at the rate of 2 mg/min. The lidocaine serum concentration equals 2.1 μg/mL at 1030 H. Compute a lidocaine infusion rate that will provide a steady-state concentration of 4 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 2 mg/min infusion rate is equivalent to 120 mg/h (k_0 = 2 mg/min · 60 min/h = 120 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 100 L, a half-life equal to 1.6 hours, and a clearance equal to 43.6 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 180 mg/h or 3 mg/min [k_0 = (180 mg/h) / (60 mg/h) = 3 mg/min] will produce a steady-state lidocaine concentration of 4.1 μg/mL. This infusion rate would be started immediately.

Example 2 SL is a 71-year-old, 82-kg (height 5 ft 10 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 12, bilirubin = 3.2 mg/dL, albumin = 2.5 gm/dL) and normal cardiac function. He received a 150 mg loading dose of lidocaine at 1300 H and a continuous intravenous infusion of lidocaine was started at 1305 H at the rate of 2 mg/min. The lidocaine serum concentration equals 5.7 μg/mL at 2300 H. Compute a lidocaine infusion rate that will provide a steady-state concentration of 4 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 2 mg/min infusion rate is equivalent to 120 mg/h (k_0 = 2 mg/min · 60 min/h = 120 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 142 L, a half-life equal to 6.5 hours, and a clearance equal to 15 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 60 mg/h or 1 mg/min [k_0 = (60 mg/h) / (60 mg/h) = 1 mg/min] will produce a steady-state lidocaine concentration of 4 μg/mL. This infusion rate could be started immediately, or if the patient was experiencing adverse drug effects, the infusion could be held for $^1/_2$–1 half-life to allow lidocaine serum concentrations to decline and restarted at that time.

Example 3 TR is a 75-year-old, 85-kg (5 ft 8 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has moderate heart failure (NYHA CHF class III). He received a 75-mg loading dose of lidocaine at 0100 H and a continuous intravenous infusion of lidocaine was started at 0115 H at the rate of 1 mg/min. The lidocaine serum concentration equals 1.7 μg/mL at 0400 H. Compute a lidocaine infusion rate that will provide a steady-state concentration of 3 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 1 mg/min infusion rate is equivalent to 60 mg/h (k_0 = 1 mg/min · 60 min/h = 60 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 74 L, a half-life equal to 1.8 hours, and a clearance equal to 29 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 90 mg/h or 1.5 mg/min [k_0 = (90 mg/h) / (60 mg/h) = 1.5 mg/min] will produce a steady-state lidocaine concentration of 3 μg/mL. This infusion rate would be started immediately.

Dosing Strategies

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 7-4.

USE OF LIDOCAINE BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

If a patient has a subtherapeutic lidocaine serum concentration and is experiencing ventricular arrhythmias in an acute situation, it is desirable to increase the lidocaine concentration as quickly as possible. In this setting, it would not be acceptable to simply

TABLE 7-4 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing	Linear pharmacokinetic method
Computerized	Bayesian computer program	Bayesian computer program

increase the maintenance dose and wait 3–5 half-lives for therapeutic serum concentrations to be established in the patient. A rational way to increase the serum concentrations rapidly is to administer a booster dose of lidocaine, a process also known as "reloading" the patient with lidocaine, computed using pharmacokinetic techniques. A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current lidocaine concentration present in the patient: $BD = (C_{desired} - C_{actual})Vc$, where $C_{desired}$ is the desired lidocaine concentration, C_{actual} is the actual current lidocaine concentration for the patient, and Vc is the central volume of distribution for lidocaine. If the central volume of distribution for lidocaine is known for the patient, it can be used in the calculation. However, this value is not usually known and is typically assumed to equal the population average appropriate for the disease states and conditions present in the patient (Table 7-1).

Concurrent with the administration of the booster dose, the maintenance dose of lidocaine is usually increased. Clinicians need to recognize that the administration of a booster dose does not alter the time required to achieve steady-state conditions when a new lidocaine dosage rate is prescribed (Figure 7-3). It still requires 3–5 half-lives to attain steady state when the dosage rate is changed. However, usually the difference between the postbooster dose lidocaine concentration and the ultimate steady-state concentration has been reduced by giving the extra dose of drug.

Example 1 BN is a 57-year-old, 50-kg (5 ft 2 in) female with ventricular tachycardia who is receiving therapy with intravenous lidocaine. She has normal liver function and does not have heart failure. After receiving an initial loading dose of lidocaine (75 mg) and a maintenance infusion of lidocaine equal to 2 mg/min for 2 hours, her arrhythmia reappears and a lidocaine concentration is measured at 1.2 μg/mL. Compute a booster dose of lidocaine to achieve a lidocaine concentration equal to 4 μg/mL.

1. *Estimate volume of distribution according to disease states and conditions present in the patient.*

In the case of lidocaine, the population average central volume of distribution equals 0.5 L/kg and this will be used to estimate the parameter for the patient. The patient is nonobese, so her actual body weight will be used in the computation: $V = 0.5 \text{ L/kg} \cdot 50 \text{ kg} = 25 \text{ L}$.

2. *Compute booster dose.*

The booster dose is computed using the following equation: $BD = (C_{desired} - C_{actual})Vc$ = (4 mg/L – 1.2 mg/L)25 L = 70 mg, rounded to 75 mg of lidocaine intravenously over 1.5–3 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for C in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take an additional 3–5 estimated half-lives for new steady-state conditions to be achieved. Lidocaine serum concentrations could be measured at this time. Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current antiarrhythmic and other drug therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with lidocaine exists.

1. VC is a 67-year-old, 72-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver function and does not have heart failure. Suggest an initial oral lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

2. Patient VC (please see problem 1) was prescribed intravenous lidocaine at a rate of 2 mg/min after receiving a loading dose. The current steady-state lidocaine concentration equals 2.5 μg/mL. Compute a new lidocaine infusion rate that will provide a steady-state concentration of 4 μg/mL.

3. EM is a 56-year-old, 81-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 10) and does not have heart failure. Suggest an initial lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 4 μg/mL.

4. Patient EM (please see problem 3) was prescribed intravenous lidocaine at the rate of 2 mg/min. The current steady-state lidocaine concentration equals 6.2 μg/mL. Compute a new intravenous lidocaine continuous infusion that will provide a steady-state concentration of 4 μg/mL.

5. OF is a 71-year-old, 60-kg (5 ft 2 in) female with ventricular fibrillation who requires therapy with intravenous lidocaine. She has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 5 μg/mL.

6. Patient OF (please see problem 5) was prescribed a lidocaine continuous infusion at the rate of 2 mg/min after receiving a loading dose. A steady-state lidocaine serum

concentration was obtained and equaled 6.7 μg/mL. Compute a new intravenous lidocaine continuous infusion that will provide a steady-state concentration of 4 μg/mL.

7. FK is a 67-year-old, 130-kg (5 ft 11 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/mL.

8. Patient FK (please see problem 7) was prescribed intravenous lidocaine. A lidocaine loading dose of 150 mg was given at 1230 H followed by a continuous infusion of 2 mg/min starting at 1245 H. A lidocaine serum concentration was obtained at 1630 H and equaled 6.2 μg/mL. Compute a new lidocaine dose that will provide a steady-state concentration of 4 μg/mL.

9. GP is a 76-year-old, 90-kg (5 ft 11 in) male who suffered a myocardial infarction. Three hours after his heart attack, he developed ventricular tachycardia and requires therapy with intravenous lidocaine. He has normal liver function and does not have heart failure. Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 4 μg/mL.

10. Patient GP (please see problem 9) was prescribed intravenous lidocaine at a rate of 2 mg/min 15 minutes after receiving a 100-mg loading dose at 1520 H. At 1930 H, the lidocaine concentration equals 1.9 μg/mL. Compute a new lidocaine infusion rate that will provide a steady-state concentration of 4 μg/mL.

11. CV is a 69-year-old, 90-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11, total bilirubin = 2.7 mg/dL, albumin = 2.1 gm/dL) and moderate heart failure (NYHA CHF class III). At 0200 H, he received 100 mg of intravenous lidocaine as a loading dose, and a maintenance intravenous infusion of 2 mg/min was started at 0215 H. Because the patient was experiencing mental status changes, the lidocaine infusion rate was decreased to 1 mg/min at 0900 H. A lidocaine serum concentration was measured at 1000 H and equaled 5.4 μg/mL. Suggest a lidocaine continuous infusion rate that would achieve a steady-state concentration equal to 3 μg/mL.

12. FP is a 59-year-old, 90-kg (5 ft 4 in) female with ventricular fibrillation who requires therapy with intravenous lidocaine. She has liver cirrhosis (Child-Pugh score = 9) and has mild heart failure (NYHA CHF class II). At 1130 H, she received 100 mg of intravenous lidocaine as a loading dose, and a maintenance intravenous infusion of 3 mg/min was started at 1200 H. Because the patient was experiencing confusion, agitation, and dysarthria the lidocaine infusion rate was decreased to 1 mg/min at 1500 H. At 2000 H, the patient began experiencing ventricular tachycardia and an additional lidocaine booster dose of 100 mg was given while the continuous infusion was left unchanged. A lidocaine serum concentration was measured at 2200 H and equaled 4.3 μg/mL. Suggest a lidocaine continuous infusion rate that would achieve a steady-state concentration equal to 5 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial lidocaine dose for patient VC would be calculated as follows :

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 1.5 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 1.5\ h = 0.462\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: $Vc = 0.5\ L/kg \cdot 72\ kg = 36\ L$, $V_{area} = 1.5\ L/kg \cdot 72\ kg = 108\ L$. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: $Cl = kV_{area} = 0.462\ h^{-1} \cdot 108\ L = 50\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: $LD = Css \cdot Vc = 3\ mg/L \cdot 36\ L = 108\ mg$, rounded to 100 mg intravenously over 2–4 minutes. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (3\ mg/L \cdot 50\ L/h) / (60\ min/h) = 2.5\ mg/min$.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = $5 \cdot 1.5\ h = 7.5\ h$). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 1–1.5 mg/kg and maintenance infusion of 3–4 mg/min is suggested for a patient without heart failure or liver disease.

2. *Compute dosage regimen.*

Because the desired concentration is in the lower end of the therapeutic range, a dose in the lower end of the suggested ranges will be used. A lidocaine loading dose of 1 mg/kg will be administered: LD = 1 mg/kg · 72 kg = 72 mg, rounded to 75 mg over 1.5–3 minutes. A lidocaine maintenance infusion equal to 3 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = 5 · 1.5 h = 7.5 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

2. *Solution to problem 2* The revised lidocaine dose for patient VC would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 8 hours (5 $t_{1/2}$ = 5 · 1.5 h = 7.5 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.5\ \mu g/mL)\ 2\ mg/min$$
$$= 3.2\ mg/min, \text{ rounded to } 3\ mg/min$$

The new suggested dose would be 3 mg/min of intravenous lidocaine to be started immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = 5 · 1.5 h = 7.5 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters*

The patient would be expected to achieve steady-state conditions after the first 8 hours (5 $t_{1/2}$ = 1.5 · 5 h = 7.5 h) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration Cl = k_0 / Css = (2 mg/min) / (2.5 mg/L) = 0.8 L/min. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: $k_0 = Css \cdot Cl = 4\ mg/L \cdot 0.8\ L/min = 3.2\ mg/min$, round to 3 mg/min.

The new lidocaine infusion rate would be instituted immediately.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 1.5 hours, the lidocaine steady-state concentration could be obtained any time after the first 8 hours of dosing (5 half-lives = 5 · 1.5 h = 7.5 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Computation of Booster Dose (If Needed)

1. *Use central volume of distribution (Vc) to calculate booster dose.*

The booster dose is computed using the following equation (Vc population average estimate used from problem 1): $BD = (C_{desired} - C_{actual})Vc = (4\ mg/L - 2.5\ mg/L)36\ L = 54\ mg$, rounded to 50 mg of lidocaine intravenously over 1–2 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for C in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take an additional 3–5 estimated half-lives for new steady-state conditions to be achieved.

3. *Solution to problem 3* The initial lidocaine dose for patient EM would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: $Vc = 0.6\ L/kg \cdot 81\ kg = 49\ L$, $V_{area} = 2.6\ L/kg \cdot 81\ kg = 211\ L$. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: $Cl = kV_{area} = 0.139\ h^{-1} \cdot 211\ L = 29.3\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: $LD = Css \cdot Vc = 4\ mg/L \cdot 49\ L = 196\ mg$, rounded to 200 mg intravenously over 4–8 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (4\ mg/L \cdot 29.3\ L/h) / (60\ min/h) = 2\ mg/min$.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 1–1.5 mg/kg and maintenance infusion of 1–2 mg/min is suggested for a patient with liver disease.

2. *Compute dosage regimen.*

Because the desired concentration is in the upper end of the therapeutic range, doses in the upper end of the suggested ranges will be used. A lidocaine loading dose of 1.5 mg/kg will be administered: LD = 1.5 mg/kg · 81 kg = 122 mg, rounded to 100 mg over 2–4 minutes. A lidocaine maintenance infusion equal to 2 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

4. *Solution to problem 4* The revised lidocaine dose for patient EM would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after one day ($5\ t_{1/2} = 5 \cdot 5\ h = 25\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old}) D_{old} = (4\ \mu g/mL / 6.2\ \mu g/mL)\ 2\ mg/min$$
$$= 1.3\ mg/min, \text{ rounded to } 1.5\ mg/min$$

The new suggested dose would be 1.5 mg/min of intravenous lidocaine to be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration Cl = k_0 / Css = (2 mg/min)/(6.2 mg/L) = 0.32 L/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: k_0 = Css · Cl = 4 mg/L · 0.32 L/min = 1.3 mg/min, round to 1.5 mg/min.

The new suggested dose would be 1.5 mg/min of intravenous lidocaine to be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

5. *Solution to problem 5* The initial lidocaine dose for patient OF would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 2 hours. The elimination rate constant is computed using the following formula: k = 0.693 / $t_{1/2}$ = 0.693 / 2 h = 0.347 h^{-1}.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: Vc = 0.3 L/kg · 60 kg = 18 L, V_{area} = 1 L/kg · 60 kg = 60 L. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: Cl = kV_{area} = 0.347 h^{-1} · 60 L = 20.8 L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: LD = Css · Vc = 5 mg/L · 18 L = 90 mg, rounded to 100 mg intravenously over 2–4 minutes. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: k_0 = Css · Cl = (5 mg/L · 20.8 L/h) / (60 min/h) = 1.7 mg/min, rounded to 1.5 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 0.5–0.75 mg/kg and maintenance infusion of 1–2 mg/min is suggested for a patient with heart failure.

2. *Compute dosage regimen.*

Because the desired concentration is in the upper end of the therapeutic range, doses in the upper end of the suggested ranges will be used. A lidocaine loading dose of 0.75 mg/kg will be administered: LD = 0.75 mg/kg · 60 kg = 45 mg, rounded to 50 mg over 1–2 minutes. A lidocaine maintenance infusion equal to 2 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

6. *Solution to problem 6* The revised lidocaine dose for patient OF would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 10–12 hours ($5\ t_{1/2} = 5 \cdot 2\ h = 10\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 6.7\ \mu g/mL)\ 2\ mg/min$$
$$= 1.2\ mg/min, \text{ rounded to } 1\ mg/min$$

The new suggested dose would be 1 mg/min of intravenous lidocaine to be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = $5 \cdot 2\ h = 10\ h$). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first 10–12 hours ($5\ t_{1/2} = 5 \cdot 2\ h = 10\ h$) of therapy.

Lidocaine clearance can be computed using a steady-state lidocaine concentration $Cl = k_0 / Css = (2\ mg/min) / (6.7\ mg/L) = 0.30\ L/min$. (Note: $\mu g/mL = mg/L$ and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute lidocaine dose.*

Lidocaine clearance is used to compute the new lidocaine infusion rate: $k_0 = Css \cdot Cl = 4\ mg/L \cdot 0.30\ L/min = 1.2\ mg/min$, round to 1 mg/min.

The new suggested dose would be 1 mg/min of intravenous lidocaine to be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours,

the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

7. *Solution to problem 7* The initial lidocaine dose for patient FK would be calculated as follows :

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 2 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/2\ h = 0.347\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is obese (>30% over ideal body weight), so the estimated lidocaine central volume of distribution (Vc) and the volume of distribution for the entire body (V_{area}) will be based on ideal body weight: IBW_{male} (in kg) = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg, Vc = 0.3 L/kg · 75 kg = 23 L, V_{area} = 1 L/kg · 75 kg = 75 L. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: $Cl = kV_{area} = 0.347\ h^{-1} \cdot 75\ L = 26\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: LD = Css · Vc = 3 mg/L · 23 L = 69 mg, rounded to 75 mg intravenously over 1.5–3 minutes. (Note: µg/mL= mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required). An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (3\ mg/L \cdot 26\ L/h) / (60\ min/h) = 1.3\ mg/min$, rounded to 1.5 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 0.5–0.75 mg/kg and maintenance infusion of 1–2 mg/min is suggested for a patient with heart failure. The patient is obese (>30% over ideal body

weight), so lidocaine doses will be based on ideal body weight: IBW_{male} (in kg) = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg.

2. *Compute dosage regimen.*

Because the desired concentration is in the lower end of the therapeutic range, doses in the lower end of the suggested ranges will be used. A lidocaine loading dose of 0.5 mg/kg will be administered: LD = 0.5 mg/kg · 75 kg = 38 mg, rounded to 50 mg over 1–2 minutes. A lidocaine maintenance infusion equal to 1 mg/min would be administered after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 2 hours, the lidocaine steady-state concentration could be obtained any time after the first 10–12 hours of dosing (5 half-lives = 5 · 2 h = 10 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

8. *Solution to problem 8* The revised lidocaine dose for patient FK would be calculated as follows:

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 2 mg/min infusion rate is equivalent to 120 mg/h (k_0 = 2 mg/min · 60 min/h = 120 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 60 L, a half-life equal to 2.9 h, and a clearance equal to 14.5 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 60 mg/h or 1 mg/min [k_0 = (60 mg/h) / (60 mg/h) = 1 mg/min] will produce a steady-state lidocaine concentration of 4 μg/mL. This infusion rate could be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

9. *Solution to problem 9* The initial lidocaine dose for patient GP would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected lidocaine half-life ($t_{1/2}$) is 4 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 4\ h = 0.173\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated lidocaine central volume of distribution and the volume of distribution for the entire body (V_{area}) will be based on actual body weight: $Vc = 0.5\ L/kg \cdot 90\ kg = 45\ L$, $V_{area} = 1.5\ L/kg \cdot 90\ kg = 135\ L$. Estimated lidocaine clearance is computed by taking the product of V_{area} and the elimination rate constant: $Cl = kV_{area} = 0.173\ h^{-1} \cdot 135\ L = 23.4\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of lidocaine to the patient: $LD = Css \cdot Vc = 4\ mg/L \cdot 45\ L = 180\ mg$, rounded to 200 mg intravenously over 4–8 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous lidocaine is: $k_0 = Css \cdot Cl = (4\ mg/L \cdot 23.4\ L/h) / (60\ min/h) = 1.6\ mg/min$, rounded to 1.5 mg/min.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 4 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = $5 \cdot 4\ h = 20\ h$). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

Literature-Based Recommended Dosing

1. *Choose lidocaine dose based on disease states and conditions present in the patient.*

A lidocaine loading dose of 1–1.5 mg/kg and maintenance infusion of 3–4 mg/min is suggested for a patient without heart failure or liver disease.

2. *Compute dosage regimen.*

Because the desired concentration is in the upper end of the therapeutic range, a dose in the upper end of the suggested ranges will be used. A lidocaine loading dose of 1.5 mg/kg will be administered: $LD = 1.5\ mg/kg \cdot 90\ kg = 135\ mg$, rounded to 150 mg over 3–6 minutes. A lidocaine maintenance infusion equal to 3 mg/min would be administered

after the loading dose was given. An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

A steady-state lidocaine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 4 hours, the lidocaine steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 4 h = 20 h). Lidocaine serum concentrations should also be measured if the patient experiences a return of their ventricular arrhythmia, or if the patient develops potential signs or symptoms of lidocaine toxicity.

10. *Solution to problem 10* The revised lidocaine dose for patient GP would be calculated as follows:

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state, so the Linear Pharmacokinetics method cannot be used. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 2 mg/min infusion rate is equivalent to 120 mg/h (k_0 = 2 mg/min · 60 min/h = 120 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 118 L, a half-life equal to 1.4 hours, and a clearance equal to 57 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 240 mg/h or 4 mg/min [k_0 = (240 mg/h) / (60 mg/h) = 4 mg/min] will produce a steady-state lidocaine concentration of 4.2 μg/mL. This infusion rate would be started immediately.

Computation of Booster Dose (If Needed)

1. *Use central volume of distribution (Vc) to calculate booster dose.*

The booster dose is computed using the following equation (Vc population average estimate used from problem 9): BD = ($C_{desired}$ − C_{actual})Vc = (4.2 mg/L − 1.9 mg/L)45 L = 104 mg, rounded to 100 mg of lidocaine intravenously over 2–4 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for C in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take an additional 3–5 estimated half-lives for new steady-state conditions to be achieved.

11. *Solution to problem 11* The revised lidocaine dose for patient CV would be calculated as follows:

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state and multiple infusion rates have been prescribed, so the linear pharmacokinetics method cannot be used. In addition the patient has two disease states that change lidocaine pharmacokinetics. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 2 mg/min infusion rate is equivalent to 120 mg/h (k_0 = 2 mg/min · 60 min/h = 120 mg/h), and a 1 mg/min infusion rate is equivalent to 60 mg/h (k_0 = 1 mg/min · 60 min/h = 60 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 112 L, a half-life equal to 6 hours, and a clearance equal to 13 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 39 mg/h or 0.7 mg/min [k_0 = (39 mg/h) / (60 mg/h) = 0.7 mg/min] will produce a steady-state lidocaine concentration of 3 μg/mL. This infusion rate could be started immediately. If the patient was experiencing lidocaine side effects, the lidocaine infusion could be held for approximately 1 half-life to allow concentrations to decline, and the new infusion would be started at that time.

12. *Solution to problem 12* The revised lidocaine dose for patient FP would be calculated as follows:

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state and multiple infusion rates and loading doses have been prescribed, so the linear pharmacokinetics method cannot be used. In addition the patient has two disease states that change lidocaine pharmacokinetics. The DrugCalc program requires lidocaine infusion rates be input in terms of mg/h. A 3 mg/min infusion rate is equivalent to 180 mg/h (k_0 = 3 mg/min · 60 min/h = 180 mg/h), and a 1 mg/min infusion rate is equivalent to 60 mg/h (k_0 = 1 mg/min · 60 min/h = 60 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution for the entire body (V_{area}) of 136 L, a half-life equal to 5.6 hours, and a clearance equal to 17 L/h.

3. *Compute dose required to achieve desired lidocaine serum concentrations.*

The continuous intravenous infusion equation used by the program to compute doses indicates that a dose of 83 mg/h or 1.4 mg/min [k_0 = (83 mg/h)/(60 mg/h) = 1.4 mg/min], rounded to 1.5 mg/min, will produce a steady-state lidocaine concentration of 5 μg/mL. This infusion rate could be started immediately.

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8

PROCAINAMIDE/*N*-ACETYL PROCAINAMIDE

INTRODUCTION

Procainamide is an antiarrhythmic agent that is used intravenously and orally. It is classified as a type IA antiarrhythmic agent and can be used for the treatment of supraventricular or ventricular arrhythmias.[1,2] It is a drug of choice for the treatment of stable sustained monomorphic ventricular tachycardia.[3] Procainamide is a useful agent in the treatment of idiopathic repetitive polymorphic ventricular tachycardia in patients with coronary heart disease. It can also be used to treat incessant or recurrent polymorphic ventricular tachycardia secondary to acute myocardial ischemia after revascularizton has been performed and β-blockers have been administered.[3]

The primary treatment for ventricular fibrillation is direct-current cardioversion. Procainamide can be used as an antiarrhythmic for patients that are not converted using electrical shock and intravenous epinephrine or vasopressin. The use of procainamide in this situation is limited due to the long time needed to administer loading doses and lack of evidence-based studies.[4] Given orally, procainamide is used for long-term suppression of ventricular arrhythmias.

Procainamide can be administered for the long-term prevention of chronic supraventricular arrhythmias such as supraventricular tachycardia, atrial flutter, and atrial fibrillation. Ventricular rate control during atrial fibrillation can be accomplished using intravenous procainamide for hemodynamically stable patients with an accessory pathway.[5]

Procainamide inhibits transmembrane sodium influx into the conduction system of the heart thereby decreasing conduction velocity.[1,2] It also increases the duration of the action potential, increases threshold potential toward zero, and decreases the slope of phase 4 of the action potential. Automaticity is decreased during procainamide therapy. The net effect of these cellular changes is that procainamide causes increased refractoriness and

decreased conduction in heart conduction tissue which establishes a bidirectional block in reentrant pathways.

N-acetyl procainamide is an active metabolite of procainamide that has type III antiarrhythmic effects.[1,2] A common characteristic of type III antiarrhythmic agents (bretylium, aminodarone, sotalol) is prolongation of the duration of the action potential resulting in an increased absolute refractory period.

THERAPEUTIC AND TOXIC CONCENTRATIONS

When given intravenously, the serum procainamide concentration/time curve follows a two-compartment model (Figure 8-1).[6] If an intravenous loading dose is followed by a continuous infusion, serum concentrations decline rapidly at first due to distribution of the loading dose from blood to tissues (Figure 8-2).[6] When oral dosage forms are given, absorption occurs more slowly than distribution so a distribution phase is not seen (Figure 8-3).[7–11]

The generally accepted therapeutic range for procainamide is 4–10 μg/mL. Serum concentrations in the upper end of the therapeutic range (≥8 μg/mL) may result in minor side effects such as gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea), weakness, malaise, decreased mean arterial pressure (less than 20%), and a 10–30% prolongation of electrocardiogram intervals (PR and QT intervals, QRS complex). Procainamide serum concentrations above 12 μg/mL can cause increased PR interval, QT interval or QRS complex widening (>30%) on the electrocardiogram, heart block, ventricular conduction disturbances, new ventricular arrhythmias, or cardiac arrest. Procainamide therapy is also associated with Torsade de pointes.[1,2] Torsade de pointes ("twisting of the points") is a form of polymorphic ventricular tachycardia preceded by QT interval prolongation. It is characterized by polymorphic QRS complexes that change in amplitude

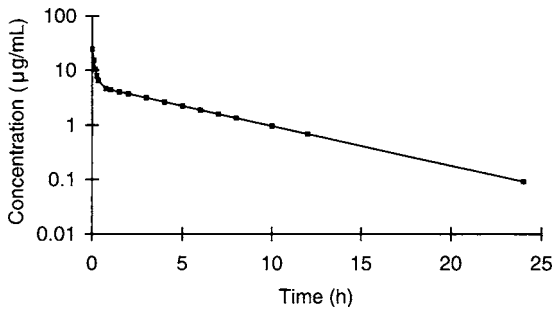

FIGURE 8-1 Procainamide serum concentrations initially drop rapidly after an intravenous bolus as drug distributes from blood into the tissues during the distribution phase. During the distribution phase, drug leaves the blood due to tissue distribution and elimination. After 20–30 minutes, an equilibrium is established between the blood and tissues, and serum concentrations drop more slowly since elimination is the primary process removing drug from the blood. This type of serum concentration/time profile is described by a two-compartment model.

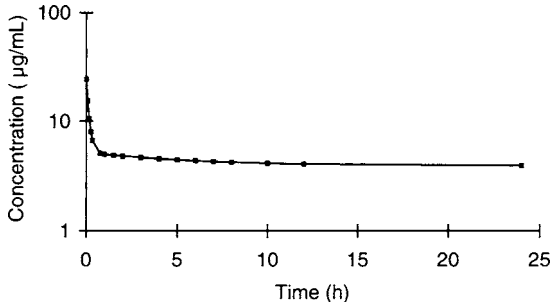

FIGURE 8-2 To maintain therapeutic procainamide concentrations, an intravenous loading dose (over 25–30 minutes) of procainamide is followed by a continuous intravenous infusion of the drug. A distribution phase is still seen due to the administration of the loading dose. Note that the administration of a loading dose may not establish steady-state conditions immediately, and the infusion needs to run 3–5 half-lives until steady-state concentrations are attained.

and length giving the appearance of oscillations around the electrocardiographic baseline. Torsade de pointes can develop into multiple episodes of nonsustained polymorphic ventricular tachycardia, syncope, ventricular fibrillation, or sudden cardiac death.

Nondose or concentration related side effects to procainamide include rash, agranulocytosis, and a systemic lupus-like syndrome. Symptoms of the lupus-like syndrome include rash, photosensitivity, arthralgias, pleuritis, or pericarditis, hemolytic anemia or leukopenia, and a positive antinuclear antibody (ANA) test. Patients who metabolize the drug more rapidly via *N*-acetyltransferase II, known as "rapid acetylators," appear to have a lower incidence of this adverse effect or at least take more time and higher doses for it to appear. While the lupus-like syndrome is usually not life threatening, it does occur in 30–50% of patients taking procainamide for greater than 6–12 months and requires discontinuation of the drug. Most symptoms abate within several weeks to months, but some patients have required a year or more to completely recover. Intravenous procainamide doses must be given no greater than 25–50 mg/min, as faster injection can cause profound hypotension.

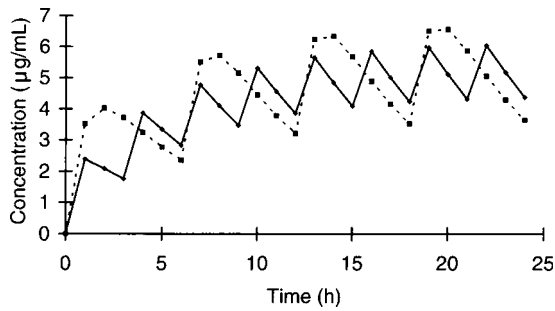

FIGURE 8-3 Serum concentration/time profile for rapid-release procainamide (*solid line,* given every 3 hours) or sustained-release procainamide (*dashed line,* given every 6 hours) oral dosage forms after multiple doses until steady state is achieved. The curves shown would be typical for an adult with normal renal and hepatic function.

An active procainamide metabolite, known as *N*-acetyl procainamide (NAPA) or acecainide, also possesses antiarrhythmic effects.[12–14] Based on limited clinical trials of NAPA, effective concentrations are 10–30 μg/mL. Concentration-dependent adverse effects for NAPA are similar to those given for procainamide. However, NAPA does not appear to cause a systemic lupus-like syndrome. Currently, NAPA is not commercially available in the United States and has been given orphan drug status by the U.S. Food and Drug Administration with an indication for decreasing implantable defibrillator energy requirements.[15] Some laboratories report the sum of procainamide and NAPA concentrations for a patient as the "total procainamide concentration" using the therapeutic range of 10–30 μg/mL. However, because procainamide and NAPA have different antiarrhythmic potency, serum concentrations for each agent should be considered individually. Also, many individuals feel that it is more important to maintain therapeutic procainamide concentrations in patients rather than NAPA or total procainamide levels in the suggested ranges. Clinicians should understand that all patients with "toxic" procainamide or NAPA serum concentrations in the listed ranges will not exhibit signs or symptoms of procainamide toxicity. Rather, procainamide and/or NAPA concentrations in the given ranges increase the likelihood that an adverse effect will occur.

For dose adjustment purposes, procainamide serum concentrations during oral administration are best measured as a predose or trough level at steady state after the patient has received a consistent dosage regimen for 3–5 drug half-lives. If the drug is given as a continuous intravenous infusion, procainamide serum concentrations could be measured at steady state after the patient has received a consistent infusion rate for 3–5 drug half-lives. Procainamide half-life varies from 2.5 to 5 hours in normal adults to 14 hours or more in adult patients with renal failure. Average NAPA half-lives are 6 hours for normal adults and 41 hours for adult patients with renal failure. If procainamide is given orally or intravenously on a stable schedule, steady-state serum concentrations for parent drug and metabolite will be achieved in about 1 day ($5 \cdot 5$ h = 25 h for procainamide and $5 \cdot 6$ h = 30 h for NAPA). For a patient in renal failure, it will take 3 days for steady-state concentrations to occur for procainamide and 9 days for steady-state conditions to be established for NAPA ($5 \cdot 14$ h = 70 h or ~3 days for procainamide, $5 \cdot 41$ h = 205 h or ~9 days for NAPA).

CLINICAL MONITORING PARAMETERS

The electrocardiogram (ECG or EKG) should be monitored to determine the response to procainamide. The goal of therapy is suppression of arrhythmias and avoidance of adverse drug reactions. Electrophysiologic studies using programmed stimulation to replicate the ventricular arrhythmia or 24-hour ECG monitoring using a Holter monitor can be performed in patients while receiving a variety of antiarrhythmic agents to determine effective antiarrhythmic drug therapy.[2]

Because many procainamide therapeutic and side effects are not correlated with its serum concentration, it is often not necessary to obtain serum procainamide concentrations in patients receiving appropriate doses who currently have no arrhythmia or adverse drug effects. However, procainamide serum concentrations should be obtained in patients who have a recurrence of tachyarrhythmias, are experiencing possible procainamide side effects, or are receiving procainamide doses not consistent with disease states and conditions known

to alter procainamide pharmacokinetics (please see Effects of Disease States and Conditions on Procainamide Pharmacokinetics and Dosing section). Serum concentration monitoring can aid in the decision to increase or decrease the procainamide dose. For instance, if an arrhythmia reappears and the procainamide serum concentration is <10 μg/mL, increasing the procainamide dose is a therapeutic option. However, if the procainamide serum concentration is over 10–12 μg/mL, it is less likely a dosage increase will be effective in suppressing the arrhythmia and there is an increased likelihood that drug side effects may occur. Some patients have responded to procainamide serum concentrations as high as 20 μg/mL without experiencing severe adverse effects.[16] Similarly, if a possible concentration-related procainamide adverse drug reaction is noted in a patient and the procainamide serum concentration is <4 μg/mL, it is possible that the observed problem may not be due to procainamide treatment and other sources can be investigated. While receiving procainamide, patients should be monitored for the following adverse drug effects: anorexia, nausea, vomiting, diarrhea, weakness, malaise, decreased blood pressure, electrocardiogram changes (increased PR interval, QT interval, or QRS complex widening >30%), heart block, ventricular conduction disturbances, new ventricular arrhythmias, rash, agranulocytosis, and the systemic lupus-like syndrome.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Procainamide is eliminated by both hepatic metabolism (~50%) and renal elimination of unchanged drug (~50%).[12–14,17,18] Hepatic metabolism is mainly via *N*-acetyltransferase II (NAT-II).[12–14] *N*-acetyl procainamide is the primary active metabolite resulting from procainamide metabolism by *N*-acetyltransferase II. *N*-acetyltransferase II exhibits a bimodal genetic polymorphism that results in "slow acetylator" and "rapid acetylator" phenotypes. If the patient has normal renal function, acetylator status can be estimated using the ratio of NAPA and procainamide (PA) steady-state concentrations: acetylator ratio = NAPA/PA.[19,20] If this ratio is 1.2 or greater, it is likely the patient is a rapid acetylator. If the ratio is 0.8 or less, it is likely the patient is a slow acetylator. The Caucasian and African-American populations appear to be about evenly split between slow and rapid acetylators. Eighty to ninety percent of the Japanese and Eskimo population are rapid acetylators, while only 20% or less of Egyptians and certain Jewish populations are of that phenotype. Obviously, ethnic background can play an important role in the procainamide dose required to achieve a therapeutic effect as well as the potential development of systemic lupus-like adverse effects. Metabolism of procainamide to other metabolites may be mediated by CYP2D6.[21] The ratio of procainamide renal clearance and creatinine clearance is 2–3 implying that net renal tubular secretion is taking place in the kidney.[17,18] The renal secretion probably takes place in the proximal tubule. Although there have been some reports that procainamide follows nonlinear pharmacokinetics, for the purposes of clinical drug dosing in patients, linear pharmacokinetic concepts and equations can be effectively used to compute doses and estimate serum concentrations.[22,23]

The average oral bioavailability of procainamide for both immediate-release and sustained-release dosage forms is 83%.[7–11] A lag time of 20–30 minutes occurs in some patients between oral dosage administration and the time procainamide first appears in the serum. Plasma protein binding of procainamide in normal individuals is only about 15%.

The recommended dose of procainamide is based on the concurrent disease states and conditions present in the patient that can influence procainamide pharmacokinetics. Procainamide pharmacokinetic parameters used to compute doses are given in the following section for specific patient profiles.

EFFECTS OF DISEASE STATES AND CONDITIONS ON PROCAINAMIDE PHARMACOKINETICS AND DOSING

Normal adults without the disease states and conditions given later in this section and with normal liver and renal function have an average procainamide half-life of 3.3 hours (range: 2.5–4.6 hours) and a volume of distribution for the entire body of 2.7 L/kg (V = 2–3.8 L/kg; Table 8-1).[24–26] *N*-acetyltransferase II is the enzyme responsible for conversion of procainamide to NAPA. The genetic polymorphism of *N*-acetyltransferase II produces a bimodal frequency distribution for procainamide half-life and clearance that separates the population into rapid and slow acetylators (Figure 8-4). The mean procainamide half-life for rapid acetylators is 2.7 hours while for slow acetylators it is 5.2 hours. Not all studies conducted with procainamide have separated results from rapid and slow acetylators when analyzing the pharmacokinetic data. Unfortunately, it is not practical to phenotype a patient as a slow or rapid metabolizer before administration of the drug, so an average population half-life and clearance is used for the purpose of initial dosage computation. Disease states and conditions that change procainamide pharmacokinetics and dosage requirements may alter clearance and the volume of distribution. The elimination rate constant ($k = 0.693/t_{1/2}$, where $t_{1/2}$ is the half-life) and clearance ($Cl = kV$) can be computed from the aforementioned pharmacokinetic parameters.

Because about 50% of a procainamide dose is eliminated unchanged by the kidney, renal dysfunction is the most important disease state that effects procainamide pharmacokinetics.[27–29] The procainamide clearance rate decreases as creatinine clearance decreases, but this relationship is not as helpful as it is with other drugs that are primarily renally eliminated. Digoxin, vancomycin, and the aminoglycoside antibiotics are eliminated mostly by glomerular filtration. Creatinine clearance is used as an estimate of glomerular filtration rate in patients because it is relatively easy to calculate or estimate. Since the major route of renal clearance for procainamide is via proximal tubular secretion, creatinine clearance is not as reliable of a parameter to aid in the estimation of procainamide clearance. In patients with renal failure, the average procainamide half-life is 13.9 hours and volume of distribution is 1.7 L/kg.

Uncompensated heart failure reduces procainamide clearance because of decreased hepatic blood flow secondary to compromised cardiac output (Table 8-2).[26,27] Volume of distribution (V = 1.6 L/kg) is decreased in uncompensated heart failure patients as well. Because both clearance and volume of distribution simultaneously decrease the increase in half-life is not as dramatic as might be expected, and patients with uncompensated heart failure have an average procainamide half-life equal to 5.5 hours [$t_{1/2} = (0.693 \cdot \downarrow V)/\downarrow Cl$]. The effect that uncompensated heart failure has on procainamide pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with uncompensated heart failure to have relatively normal or grossly abnormal procainamide clearance and half-life. For uncompensated heart failure patients, initial doses are meant

TABLE 8-1 Disease States and Conditions that Alter Procainamide Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal and liver function	3.3 hours (range: 2.6–4.6 hours)	2.7 L/kg (range: 2–3.8 L/kg)	Procainamide is eliminated about 50% unchanged in the urine and about 50% metabolized. *N*-acetyltransferase II converts procainamide to an active metabolite (*N*-acetyl procainamide or NAPA). Genetically, some individuals are "rapid acetylators" and convert more procainamide to NAPA than "slow acetylators." NAPA is 85% eliminated unchanged by the kidney.
Adult, renal failure (creatinine clearance ≤10 mL/min)	13.9 hours	1.7 L/kg	Because 50% of procainamide and 85% of NAPA is eliminated unchanged by the kidney, the clearance of both agents is reduced in renal failure.
Adult, liver cirrhosis	Not available	Not available	Procainamide is metabolized ~50% by hepatic enzymes (primarily *N*-acetyltransferase II). Clearance of procainamide is decreased in liver cirrhosis patients, but NAPA clearance does not substantially change. Pharmacokinetic parameters highly variable in liver disease patients.

(*Continued*)

TABLE 8-1 ***(Continued)***

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, uncompensated heart failure	5.5 hours	1.6 L/kg	Decreased liver blood flow secondary to reduced cardiac output reduces procainamide clearance. Heart failure results in variable reductions in procainamide clearance.
Adult, obese (>30% over ideal body weight)	According to other disease states/ conditions that affect procainamide pharmacokinetics	According to other disease states/ conditions that affect procainamide pharmacokinetics	Procainamide volume of distribution should be based on ideal body weight for patients who weigh more that 30% over IBW, but clearance should be based on total body weight or (TBW) (0.52 L/h/kg TBW for patients with normal renal function).

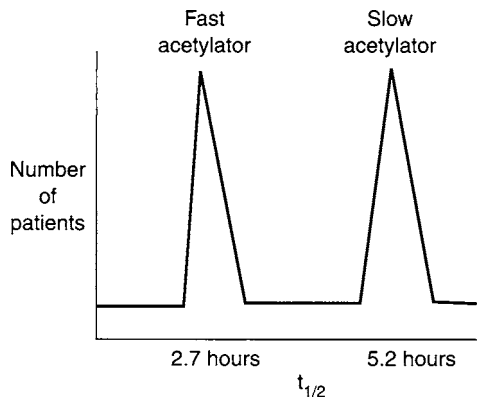

FIGURE 8-4 *N*-acetyltransferase II converts procainamide to its active metabolite, NAPA. Patients can be phenotyped into two groups with regards to their ability to metabolize procainamide to NAPA via acetylation of the parent drug: fast acetylators convert procainamide to NAPA rapidly and have a shorter procainamide half-life, while slow acetylators convert procainamide to NAPA more slowly and have a longer procainamide half-life. This leads to a bimodal distribution of procainamide half-life for adults with normal renal function.

TABLE 8-2 New York Heart Association (NYHA) Functional Classification for Heart Failure[44]

NYHA HEART FAILURE CLASS	DESCRIPTION
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitations of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

as starting points for dosage titration based on patient response and avoidance of adverse effects. Most clinicians reduce initial procainamide doses by 25–50% for patients with uncompensated heart failure (Table 8-3). Patients with compensated heart failure receiving appropriate treatment with good clinical response may have normal procainamide pharmacokinetics.[30] Procainamide serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with heart failure.

Patients with liver cirrhosis or hepatitis have not been adequately studied with regard to procainamide pharmacokinetics. However, the majority of *N*-acetyltransferase II responsible for the conversion of procainamide to NAPA is thought to reside in the liver. Because of this, most clinicians recommend a decrease in initial doses for procainamide in patients with liver disease.[31] An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 8-4).[32] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 8-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score of 8 to 10 is grounds for a decrease of 25% in the initial daily drug dose for procainamide while a score greater than 10 suggests a decrease of 50% (Table 8-4). As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Procainamide serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis or hepatitis.

Studies investigating the impact of obesity (30% over ideal body weight) on procainamide pharmacokinetics have found that volume of distribution correlates best with ideal body weight, but clearance correlates best with total body weight.[33] The volume of distribution for procainamide should be based on ideal body weight for obese individuals according

TABLE 8-3 Literature-Based Recommended Procainamide Initial Dosage Ranges for Various Disease States and Conditions

DISEASE STATE/CONDITION	PROCAINAMIDE, ORAL TABLETS	PROCAINAMIDE, CONTINUOUS INTRAVENOUS INFUSION
Adult, normal renal function (creatinine clearance >50 mL/min)	50 mg/kg/d	2–6 mg/min
Adult, renal dysfunction	Creatinine clearance = 10–50 mL/min: 25–50% dosage decrease Creatinine clearance <10 mL/min: 50–75% dosage decrease	Creatinine clearance = 10–50 mL/min: 25–50% dosage decrease Creatinine clearance <10 mL/min: 50–75% dosage decrease
Adult, uncompensated heart failure	NYHA CHF class II: 25% dosage decrease NYHA CHF class III or IV: 50% dosage decrease	NYHA CHF class II: 25% dosage decrease NYHA CHF class III or IV: 50% dosage decrease
Adult, liver disease	Child-Pugh score = 8–10: 25% dosage decrease Child-Pugh score >10: 50% dosage decrease	Child-Pugh score = 8–10: 25% dosage decrease Child-Pugh score >10: 50% dosage decrease
Adult, obese (>30% over ideal body weight)	Base dose on total body weight according to other disease states/conditions	Base dose on total body weight according to other disease states/conditions

to the other disease states and conditions present in the patient. Clearance should be based on total body weight (TBW) in obese individuals (0.52 L/h/kg TBW for normal renal failure).

Procainamide is significantly removed by hemodialysis but not by peritoneal dialysis.[34] Patients undergoing hemodialysis treatments may receive an additional dose of the usual amount taken after the procedure is finished. Because procainamide has a sieving coefficient equal to 0.86, continuous hemoperfusion removes significant amounts of the drug.[35,36] Appropriate dosage increases should be determined using serum concentration measurements of both procainamide and NAPA.

TABLE 8-4 Child-Pugh Scores for Patients with Liver Disease[32]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

NAPA is primarily eliminated unchanged in the urine via glomerular filtration and renal tubular secretion.[17,18,24,29,37] When NAPA is given orally, 85% of the administered dose is recovered in the urine as unchanged drug. In patients with normal renal and liver function, NAPA has an average half-life of 6 hours.[13] NAPA half-life increases to 41 hours on the average in patients with renal failure.[29,37] The volume of distribution for NAPA in normal individuals is 1.4 L/kg. NAPA is significantly removed by hemodialysis but not by peritoneal dialysis.[37] In most patients with renal dysfunction, the ratio of NAPA to procainamide steady-state concentration exceeds 1, even if the patient is a slow acetylator. The reason for this is NAPA elimination is much more dependent on renal function, so NAPA concentrations accumulate more than procainamide concentrations do in patients with renal dysfunction. Thus, in patients with renal failure NAPA may be the predominant antiarrhythmic agent present in the serum.

DRUG INTERACTIONS

Procainamide has serious drug interactions with other drugs that are capable of inhibiting its renal tubular secretion.[38–40] Cimetidine, trimethoprim, ofloxacin, levofloxacin, and ciprofloxacin are all drugs that compete for tubular secretion with procainamide and NAPA. When given with these other agents, procainamide renal clearance decreases by 30–50% and NAPA renal clearance decreases by 10–30%. Amiodarone increases the steady-state concentrations of procainamide and NAPA by 57% and 32%, respectively.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate procainamide therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of procainamide. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of procainamide is to compute the best dose possible for the patient given their set of disease states and conditions that influence procainamide pharmacokinetics and the arrhythmia being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Depending on the acetylator status of the patient, procainamide is almost equally metabolized by the liver and eliminated unchanged by the kidney in patients with normal hepatic and renal function. Unfortunately, there is no good way to estimate the elimination

characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated by glomerular filtration. Additionally, creatinine clearance does not accurately reflect the renal elimination of procainamide because the mechanism of elimination is active tubular secretion. Because of this, a patient is categorized according to the disease states and conditions that are known to change procainamide half-life, and the half-life previously measured in these studies is used as an estimate of the current patient's half-life (Table 8-1). For a patient with moderate heart failure (NYHA CHF class III), procainamide half-life would be assumed to equal 5.5 hours, while a patient with renal failure would be assigned an estimated half-life of 13.9 hours. To produce the most conservative procainamide doses in patients with multiple concurrent disease states or conditions that affect procainamide pharmacokinetics, the disease state or condition with the longest half-life should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible. Once the correct half-life is identified for the patient, it can be converted into the procainamide elimination rate constant (k) using the following equation: $k = 0.693/t_{1/2}$.

VOLUME OF DISTRIBUTION ESTIMATE

As with the half-life estimate, the procainamide volume of distribution is chosen according to the disease states and conditions that are present (Table 8-1). The volume of distribution is used to help compute procainamide clearance, and is assumed to equal 1.7 L/kg for renal failure patients, 1.6 L/kg for uncompensated heart failure patients, and 2.7 L/kg for all other patients. For obese patients (>30% above ideal body weight), ideal body weight is used to compute procainamide volume of distribution. Thus, for a nonobese 80-kg patient without heart failure or liver disease, the estimated procainamide volume of distribution would be 216 L: $V = 2.7\ L/kg \cdot 80\ kg = 216\ L$. For a 150-kg obese patient with an ideal body weight of 60 kg and normal cardiac and liver function, the estimated procainamide volume of distribution is 162 L: $V = 2.7\ L/kg \cdot 60\ kg = 162\ L$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given orally, procainamide follows a one-compartment pharmacokinetic model (Figure 8-3). Because procainamide has such a short half-life, most patients receive oral procainamide therapy using sustained-release dosage forms. Procainamide sustained-release dosage forms provide good bioavailability (F = 0.83), supply a continuous release of procainamide into the gastrointestinal tract, and provided a smooth procainamide serum concentration/time curve that emulates an intravenous infusion when doses are given 2–4 times daily. In the United States, 2 different sustained-release dosage forms have been approved that provide every 6-hour or every 12-hour dosing. Because of this, a very simple pharmacokinetic equation that computes the average procainamide steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation: $Css \cdot [F(D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau) / F$, where F is the bioavailability fraction for the oral dosage form (F = 0.83 for most oral procainamide sustained-release products), D is the dose of procainamide in mg, and τ is the dosage interval in hours. Cl is procainamide clearance in L/h and is computed using estimates of procainamide elimination rate constant (k) and volume of distribution: Cl = kV. For example, for a patient with an estimated elimination rate constant equal to 0.210 h^{-1} and an estimated volume of distribution equal to 189 L, the estimated clearance would equal 39.7 L/h: $Cl = 0.210\ h^{-1} \cdot 189\ L = 39.7\ L/h$.

When intravenous therapy is required, a similar pharmacokinetic equation that computes the procainamide steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows dosage calculation for a continuous infusion: $Css = k_0/Cl$ or $k_0 = Css \cdot Cl$, where k_0 is the dose of procainamide in mg/min, Cl is procainamide clearance in L/min and is computed using estimates of procainamide elimination rate constant (k) and volume of distribution: $Cl = kV$.

The equation used to calculate an intravenous loading dose (LD in mg) is based on a simple one-compartment model: $LD = Css \cdot V$, where Css is the desired procainamide steady-state concentration in μg/mL which is equivalent to mg/L, and V is the procainamide volume of distribution. Intravenous procainamide loading doses should be infused no faster than 25–50 mg/min to avoid severe hypotension. Two methods are used to administer procainamide loading doses. One method administers 100 mg every 5 minutes to a maximum of 500 mg; a 10 minute waiting period to allow drug distribution to tissues is utilized if more than 500 mg is needed to abate the arrhythmia. The other method administers the loading dose as a short-term infusion at a rate of 20 mg/min over 25–30 minutes, not to exceed a total dose of 17 mg/kg.

STEADY-STATE CONCENTRATION SELECTION

The general accepted therapeutic range for procainamide is 4–10 μg/mL. If procainamide + NAPA or "total procainamide" concentrations are used, the usual therapeutic range is 10–30 μg/mL, keeping in mind that procainamide and NAPA are not equipotent antiarrhythmics. However, procainamide therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with oral procainamide sustained-release tablets. He has normal liver and cardiac function. Suggest an initial oral procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected procainamide half-life ($t_{1/2}$) for an individual with normal hepatic and renal function is 3.3 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/3.3\ h = 0.210\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: $V = 2.7\ L/kg \cdot 75\ kg = 203\ L$. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.210\ h^{-1} \cdot 203\ L = 42.6\ L/h$

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). Because the patient has a rapid procainamide clearance and short half-life, the initial dosage interval (τ) will be set to 6 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is $D = (Css \cdot Cl \cdot \tau)/F = (4\ mg/L \cdot 42.6\ L/h \cdot 6\ h)/0.83 = 1231\ mg$, rounded to 1250 mg every 6 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady-state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral procainamide. He has renal failure with an estimated creatinine clearance = 9 mL/min. Suggest an initial extended-release procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe renal disease have highly variable procainamide pharmacokinetics and dosage requirements. Renal failure decreases procainamide renal clearance, and the expected procainamide half-life ($t_{1/2}$) is 13.9 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/13.9\ h = 0.050\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 1.7 L/kg · 85 kg = 145 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.050\ h^{-1} \cdot 145\ L = 7.25$ L/h.

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is $D = (Css \cdot Cl \cdot \tau) / F = (4\ mg/L \cdot 7.25\ L/h \cdot 12\ h) / 0.83 = 419$ mg, rounded to 500 mg every 12 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after 3–9 days of dosing (5 half-lives = 5 · 13.9 h = 69.5 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

To illustrate the differences and similarities between oral and intravenous procainamide dosage regimen design, the same cases will be used to compute intravenous procainamide loading doses and continuous infusions.

Example 3 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous procainamide. He has normal liver and cardiac function. Suggest an intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected procainamide half-life ($t_{1/2}$) for an individual with normal hepatic and renal function is 3.3 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/3.3\ h = 0.210\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: $V = 2.7\ L/kg \cdot 75\ kg = 203\ L$. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.210\ h^{-1} \cdot 203\ L = 42.6\ L/h$.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of procainamide to the patient: $LD = Css \cdot V = 4\ mg/L \cdot 203\ L = 812\ mg$, rounded to 800 mg intravenously. Initially, a maximum dose of 600 mg over 25–30 minutes will be given, and the additional 200 mg given, if needed, at a rate of 20 mg/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

A procainamide continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous procainamide is $k_0 = Css \cdot Cl = (4\ mg/L \cdot 42.6\ L/h) / (60\ min/h) = 2.8\ mg/h$, rounded to 3 mg/min.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = $5 \cdot 3.3\ h$ = 16.5 h for procainamide, 5 half-lives = $5 \cdot 6\ h = 30\ h$ for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 4 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with intravenous procainamide. He has renal failure with an estimated creatinine clearance = 9 mL/min. Suggest an initial intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe renal disease have highly variable procainamide pharmacokinetics and dosage requirements. Renal failure decreases procainamide renal clearance, and the expected procainamide half-life ($t_{1/2}$) is 13.9 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 13.9\ h = 0.050\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 1.7 L/kg · 85 kg = 145 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: Cl = kV = 0.050 h^{-1} · 145 L = 7.25 L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of procainamide to the patient: LD = Css · V = 4 mg/L · 145 L = 580 mg, rounded to 600 mg intravenously over 25–30 minutes. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

A procainamide continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous procainamide is k_0 = Css · Cl = (4 mg/L · 7.25 L/h) / (60 min/h)= 0.48 mg/h, rounded to 0.5 mg/min.

Steady-state procainamide and NAPA serum concentrations could be measured after steady-state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after 3–9 days of dosing (5 half-lives = 5 · 13.9 h = 69.5 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in procainamide pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard procainamide doses for various situations are warranted. The original computation of these doses was based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. In general, the procainamide steady-state serum concentration expected from the lower end of the dosage range was 4–6 µg/mL and 6–10 µg/mL for the upper end of the dosage range. Suggested procainamide maintenance doses are given in Table 8-3. A 25–50% reduction in initial procainamide dose is suggested for patients with moderate-to-severe liver disease (Child-Pugh score ≥8) or moderate-to-severe heart failure (NYHA class II or greater). A 25–75% decrease is indicated with renal dysfunction. When more than one disease state or condition is present in a patient, choosing the lowest daily dose will result in the safest, most conservative dosage recommendation.

Pediatric doses are similar to those given to adults when adjusted for differences in body weight.[41] The recommended intravenous loading dose is 2–6 mg/kg over 5 minutes (maximum dose 100 mg), repeating as necessary every 5–10 minutes to a maximum dose of 15 mg/kg (no more than 500 mg should be given within a 30-minute time period). For patients with ventricular tachycardia and poor perfusion, 15 mg/kg infused over 30–60 minutes as a single dose can be considered if cardioversion is ineffective. Intravenous maintenance

infusion rates equal 20–80 μg/kg/min (maximum dose 2 g/d). Oral maintenance doses are 15–50 mg/kg/d. The dosage interval chosen should be appropriate for dosage form administered to the patient.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with oral procainamide sustained-release tablets. He has normal liver and cardiac function. Suggest an initial oral procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide maintenance dose of 50 mg/kg/d is suggested for a patient without heart failure or liver disease requiring a procainamide steady-state serum concentration in the lower end of the therapeutic range. The suggested initial dose would be 3750 mg/d (50 mg/kg/d · 75 kg = 3750 mg/d), rounded to 4000 mg/d or 1000 mg every 6 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral procainamide. He has renal failure with an estimated creatinine clearance = 9 mL/min. Suggest an initial extended-release procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide maintenance dose of 12.5 mg/kg/d (50 mg/kg/d · 0.25 = 12.5 mg/kg/d) is suggested for a patient with renal failure requiring a procainamide steady-state serum concentration in the lower end of the therapeutic range. The suggested initial dose would be 1063 mg/d (12.5 mg/kg/d · 85 kg = 1063 mg/d), rounded to 1000 mg/d or 500 mg every 12 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after 3–9 days of dosing (5 half-lives = 5 · 13.9 h = 69.5 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

To illustrate the differences and similarities between oral and intravenous procainamide dosage regimen design, the same cases will be used to compute intravenous procainamide loading doses and continuous infusions.

Example 3 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous procainamide. He has normal liver and cardiac function. Suggest an intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

A procainamide maintenance dose of 2–4 mg/min is suggested for a patient without heart failure or liver disease requiring a procainamide steady-state serum concentration in the lower end of the therapeutic range. The suggested initial continuous infusion would be 3 mg/min. If needed, a loading dose of 500 mg infused over 25–30 minutes would also be given.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 4 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with intravenous procainamide. He has renal failure with an estimated creatinine clearance = 9 mL/min. Suggest an initial intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide maintenance dose of 1–2 mg/min is suggested for a patient with renal failure requiring a procainamide steady-state serum concentration in the lower end of the therapeutic range. The suggested initial dose would be 1 mg/min. If needed, a loading dose of 500 mg infused over 25–30 minutes would also be given.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after 3–9 days of dosing (5 half-lives = 5 · 13.9 h = 69.5 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

USE OF PROCAINAMIDE AND *N*-ACETYLPROCAINAMIDE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce procainamide or NAPA serum concentrations that are expected or desirable. Because of

pharmacokinetic variability, the narrow therapeutic index of procainamide, and the desire to avoid of procainamide adverse side effects, measurement of procainamide and NAPA serum concentrations can be a useful adjunct for patients to ensure that therapeutic, nontoxic levels are present. In addition to procainamide serum concentrations, important patient parameters (electrocardiogram, clinical signs and symptoms of the arrhythmia, potential procainamide side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When procainamide and NAPA serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change procainamide doses assuming the drug follows *linear pharmacokinetics*. Thus, assuming linear pharmacokinetics is adequate for dosage adjustments in most patients.

Sometimes, it is useful to compute procainamide pharmacokinetic constants for a patient and base dosage adjustments on these parameters. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the procainamide dose.

In some situations, it may be necessary to compute procainamide pharmacokinetic parameters as soon as possible for the patient before steady-state conditions occur and utilize these parameters to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where serum concentrations are obtained at suboptimal times or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because procainamide follows linear, dose-proportional pharmacokinetics in most patients, steady-state procainamide and NAPA serum concentrations change in proportion to dose according to the following equation: $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or $D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantage of this method is that it is quick and simple. The disadvantage is steady-state concentrations are required. Because nonlinear pharmacokinetics for procainamide has been observed in some patients, suggested dosage increases greater than 75% using this method should be scrutinized by the prescribing clinician, and the risk versus benefit for the patient assessed before initiating large dosage increases (>75% over current dose).

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with procainamide sustained-release tablets. He has normal liver and cardiac function. The current steady-state procainamide and NAPA concentrations equal 2.2 μg/mL and 1.5 μg/mL, respectively, (total procainamide concentration = 3.7 μg/mL) at a dose of 1000 mg every 12 hours. Compute a procainamide dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 3.3$ h = 17 h for procainamide, $5\ t_{1/2} = 5 \cdot 6$ h = 30 h for NAPA) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 1000 mg/dose · 2 dose/day = 2000 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.2\ \mu g/mL)\ 2000\ mg/d$$
$$= 3636\ mg/d, \text{ rounded to } 4000\ mg/d \text{ or } 2000\ mg \text{ every } 12 \text{ hours}$$

The new suggested dose would be 2000 mg every 12 hours of oral procainamide to be started immediately.

The expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (4000\ mg/d / 2000\ mg/d)\ 1.5\ \mu g/mL = 3\ \mu g/mL$$

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 3.3 hours and NAPA half-life equal to 6 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 17 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral procainamide sustained-release tablets. He has renal failure with an estimated creatinine clearance = 9 mL/min. The current steady-state procainamide and NAPA concentrations equal 13.1 μg/mL and 25.2 μg/mL, respectively, (total procainamide concentration = 38.3 μg/mL) at a dose of 1000 mg every 12 hours. Compute a procainamide dose that will provide a steady-state concentration of 6 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the ninth day ($5\ t_{1/2} = 5 \cdot 13.9$ h = 70 h, or 3 days for procainamide, $5\ t_{1/2} = 5 \cdot 41$ h = 205 h, or 9 days for NAPA) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 1000 mg/dose · 2 dose/day = 2000 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (6\ \mu g/mL / 13.1\ \mu g/mL)\ 2000\ mg/d$$
$$= 916\ mg/d, \text{ rounded to } 1000\ mg/d \text{ or } 500\ mg \text{ every } 12 \text{ hours}$$

The new suggested dose would be 500 mg every 12 hours of oral procainamide to be started immediately.

The expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (1000\ mg/d / 2000\ mg/d)\ 25.2\ \mu g/mL = 12.6\ \mu g/mL$$

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 13.9 hours and NAPA half-life equal to 41 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous procainamide. He has moderate heart failure (NYHA CHF class III). The current steady-state procainamide and NAPA concentrations equal 4.5 μg/mL and 7.9 μg/mL, respectively, (total procainamide concentration = 12.4 μg/mL), at a dose of 1 mg/min. Compute a procainamide dose that will provide a steady-state concentration of 8 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 5.5 h = 28 h for procainamide, 5 $t_{1/2}$ = 5 · 6 h = 30 h, for NAPA assuming normal renal function) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (8\ \mu g/mL / 4.5\ \mu g/mL)\ 1\ mg/min$$
$$= 1.8\ mg/min, \text{ rounded to } 2\ mg/min$$

The new suggested dose would be 2 mg/min of intravenous procainamide to be started immediately.

The expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (2\ mg/min / 1\ mg/min)\ 7.9\ \mu g/mL = 15.8\ \mu g/mL$$

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 5.5 hours and NAPA half-life equal to 6 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 28 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a

dose that achieves desired procainamide concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state procainamide concentration (Css). During a continuous intravenous infusion, the following equation is used to compute procainamide clearance (Cl): $Cl = k_0 / Css$, where k_0 is the dose of procainamide in mg/min. If the patient is receiving oral procainamide therapy, procainamide clearance (Cl) can be calculated using the following formula: $Cl = [F(D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 0.83 for most oral procainamide products), D is the dose of procainamide in mg, Css is the steady-state procainamide concentration, and τ is the dosage interval in hours. For both oral and intravenous procainamide routes of administration, the expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase: $C_{ss,new} = (D_{new} / D_{old})C_{ss,old}$ where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. Because this method also assumes linear pharmacokinetics, procainamide doses computed using the pharmacokinetic parameter method and the linear pharmacokinetic method should be identical.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with procainamide sustained-release tablets. He has normal liver and cardiac function. The current steady-state procainamide and NAPA concentrations equal 2.2 μg/mL and 1.5 μg/mL, respectively, (total procainamide concentration = 3.7 μg/mL) at a dose of 1000 mg every 12 hours. Compute a procainamide dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 3.3$ h = 17 h for procainamide, $5\ t_{1/2} = 5 \cdot 6$ h = 30 h for NAPA) of therapy.

Procainamide clearance can be computed using a steady-state procainamide concentration: $Cl = [F(D/\tau)] / Css = [0.83\ (1000\ mg/12\ h)] / (2.2\ mg/L) = 31.4$ L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (4\ mg/L \cdot 31.4\ L/h \cdot 12\ h)/0.83 = 1816$ mg, rounded to 2000 mg every 12 hours.

The expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (4000\ mg/d / 2000\ mg/d)\ 1.5\ \mu g/mL = 3\ \mu g/mL$$

The new procainamide dose would be instituted immediately.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 3.3 hours and NAPA half-life equal to 6 hours, procainamide and

NAPA steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 17 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 2 OI is a 60-year-old, 85-kg (height 6 ft 1 in) male with atrial fibrillation who requires therapy with oral procainamide sustained-release tablets. He has renal failure with an estimated creatinine clearance = 9 mL/min. The current steady-state procainamide and NAPA concentrations equal 13.1 μg/mL and 25.2 μg/mL, respectively, (total procainamide concentration = 38.3 μg/mL) at a dose of 1000 mg every 12 hours. Compute a procainamide dose that will provide a steady-state concentration of 6 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the ninth day (5 $t_{1/2}$ = 5 · 13.9 h = 70 h, or 3 days for procainamide, 5 $t_{1/2}$ = 5 · 41 h = 205 h, or 9 days for NAPA) of therapy.

Procainamide clearance can be computed using a steady-state procainamide concentration: Cl = [F(D/τ)] / Css = [0.83 (1000 mg/12 h)] / (13.1 mg/L) = 5.28 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (6 mg/L · 5.28 L/h · 12 h) / 0.83 = 458 mg, rounded to 500 mg every 12 hours.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage change:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (1000 \text{ mg/d} / 2000 \text{ mg/d})\ 25.2 \text{ μg/mL} = 12.6 \text{ μg/mL}$$

If the patient was experiencing side effects, the new dosage regimen would be held for one estimated half-life. Otherwise, the new procainamide dose would be instituted immediately.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 13.9 hours and NAPA half-life equal to 41 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with intravenous procainamide. He has moderate heart failure (NYHA CHF class III). The current steady-state procainamide and NAPA concentrations

equal 4.5 μg/mL and 7.9 μg/mL, respectively, (total procainamide concentration = 12.4 μg/mL) at a dose of 1 mg/min. Compute a procainamide dose that will provide a steady-state concentration of 8 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 5.5 h = 28 h for procainamide, 5 $t_{1/2}$ = 5 · 6 h = 30 h, for NAPA (assuming normal renal function) of therapy.

Procainamide clearance can be computed using a steady-state procainamide concentration: Cl = k_0/Css = (1 mg/min)/(4.5 mg/L) = 0.22 L/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new dose: k_0 = Css Cl = 8 mg/L · 0.22 L/min = 1.8 mg/min, rounded to 2 mg/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

The expected NAPA steady-state serum concentration would increase in proportion to the procainamide dosage increase:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (2 \text{ mg/min} / 1 \text{ mg/min})\ 7.9 \text{ μg/mL} = 15.8 \text{ μg/mL}$$

The new procainamide dose would be instituted immediately.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 5.5 hours and NAPA half-life equal to 6 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 28 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

CHIOU METHOD

For some patients, it is desirable to individualize procainamide infusion rates as rapidly as possible before steady state is achieved.[42] Examples of these cases include patients with renal dysfunction, heart failure, or hepatic cirrhosis who have variable procainamide pharmacokinetic parameters and long procainamide half-lives. In this situation, two procainamide serum concentrations obtained at least 4–6 hours apart during a continuous infusion can be used to compute procainamide clearance and dosing rates. In addition to this requirement, the only way procainamide can be entering the patient's body must be via intravenous infusion. Thus, the last dose of sustained-release procainamide must have been administered no less than 12–16 hours before this technique is used, or some residual

oral procainamide will still be absorbed from the gastrointestinal tract and cause computation errors.

The following equation is used to compute procainamide clearance (Cl) using the procainamide concentrations:

$$Cl = \frac{2k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

where k_0 is the infusion rate of procainamide, V is procainamide volume of distribution (chosen according to disease states and conditions present in the patient, Table 8-1), C_1 and C_2 are the first and second procainamide serum concentrations, and t_1 and t_2 are the times that C_1 and C_2 were obtained. Once procainamide clearance (Cl) is determined, it can be used to adjust the procainamide salt infusion rate (k_0) using the following relationship: $k_0 = Css \cdot Cl$.

Example 1 JB is a 50-year-old, 60-kg (5 ft 7 in) male with heart failure (NYHA CHF class III) started on a 5 mg/min procainamide infusion after being administered an intravenous loading dose. The procainamide concentration was 10.6 μg/mL at 1000 H and 14.3 μg/mL at 1400 H. What procainamide infusion rate is needed to achieve Css = 8 μg/mL?

1. *Compute procainamide clearance and dose.*

$$Cl = \frac{2k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2(5\,mg/min)}{10.6\,mg/L + 14.3\,mg/L} + \frac{2(1.6\,L/kg \cdot 60\,kg)(10.6\,mg/L - 14.3\,mg/L)}{(10.6\,mg/L + 14.3\,mg/L)\,240\,min}$$
$$= 0.28\,L/min$$

(Note: μg/mL = mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1, in minutes, was determined and placed directly in the calculation.)

$$k_0 = Css \cdot Cl = 8\,mg/L \cdot 0.28\,L/h = 2.2\,mg/min\ of\ procainamide$$

Example 2 YU is a 64-year-old, 80-kg (5 ft 9 in) male started on a 3 mg/min procainamide infusion after being administered an intravenous loading dose at 0800 H. The procainamide concentration was 10.3 μg/mL at 1000 H and 7.1 μg/mL at 1600 H. What procainamide infusion rate is needed to achieve Css = 10 μg/mL?

1. *Compute procainamide clearance and dose.*

$$Cl = \frac{2k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2(3\,mg/min)}{10.3\,mg/L + 7.1\,mg/L} + \frac{2(2.7\,L/kg \cdot 80\,kg)(10.3\,mg/L - 7.1\,mg/L)}{(10.3\,mg/L + 7.1\,mg/L)\,360\,min}$$
$$= 0.57\,L/min$$

(Note: μg/mL= mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1, in minutes, was determined and placed directly in the calculation.)

$$k_0 = Css \cdot Cl = 10 \text{ mg/L} \cdot 0.57 \text{ L/min} = 5.7 \text{ mg/min of procainamide}$$

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[43]

Example 1 OY is a 57-year-old, 79-kg (5 ft 8 in) male with ventricular tachycardia who requires therapy with oral procainamide. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 gm/dL), renal (serum creatinine = 1.0 mg/dL), and cardiac function. He started taking procainamide sustained-release tablets 500 mg four times daily at 0700, 1200, 1800, and 2200 H. The procainamide serum concentration equals 2.1 μg/mL at 2130 H before the third dose is given on the first day of therapy. Compute a procainamide dose that will provide a steady-state concentration of 6 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 152 L, a half-life equal to 3.1 hours, and a clearance equal to 33.9 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 2000 mg of procainamide every 6 hours will produce a steady-state trough concentration of 6.1 μg/mL. This dose would be started immediately.

Example 2 SL is a 71-year-old, 82-kg (5 ft 10 in) male with atrial fibrillation who requires therapy with oral procainamide. He has liver cirrhosis (Child-Pugh score = 12, bilirubin = 3.2 mg/dL, albumin = 2.5 gm/dL) and normal cardiac function. He began procainamide sustained-release tablets 500 mg every 12 hours at 0700 H. On the second day of therapy before the morning dose is administered, the procainamide serum concentration equals 4.5 μg/mL at 0700 H. Compute a procainamide dose that will provide a steady-state concentration of 5 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 110 L, a half-life equal to 15.5 hours, and a clearance equal to 4.93 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 250 mg of procainamide sustained-release tablets every 8 hours will produce a steady-state trough concentration of 5.5 μg/mL. This dose would be started immediately.

Example 3 TR is a 75-year-old, 85-kg (5 ft 8 in) male with atrial flutter who requires therapy with procainamide sustained-release tablets. He has moderate heart failure (NYHA CHF class III). Yesterday, he was prescribed procainamide 500 mg four times daily, and received the first two doses at 0800 H and 1200 H. Because he felt that his arrhythmia may have returned, the patient phoned his physician who advised him to increase the dose to 1000 mg (1800 H and 2200 H). The procainamide serum concentration equals 10.7 μg/mL at 1000 H, 2 hours after the morning dose (at 0800 H, 1000 mg procainamide). Compute a procainamide sustained-release tablet dose that will provide a steady-state trough concentration of 6 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 114 L, a half-life equal to 7.3 hours, and a clearance equal to 10.8 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 500 mg of procainamide immediate-release tablets every 6 hours will produce a steady-state trough concentration of 5.9 μg/mL. This dose would be started immediately.

USE OF PROCAINAMIDE BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

If a patient has a subtherapeutic procainamide serum concentration in an acute situation, it may be desirable to increase the procainamide concentration as quickly as possible. In this setting, it would not be acceptable to simply increase the maintenance dose and wait 3–5 half-lives for therapeutic serum concentrations to be established in the patient. A rational way to increase the serum concentrations rapidly is to administer a booster dose of procainamide, a process also known as "reloading" the patient with procainamide, computed using pharmacokinetic techniques. A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current procainamide concentration present in the patient: $BD = (C_{desired} - C_{actual})V$, where $C_{desired}$ is the desired procainamide concentration, C_{actual} is the actual current procainamide concentration for the patient, and V is the volume of distribution for procainamide. If the volume of distribution for procainamide is known for the patient, it can be used in the calculation. However, this value is not usually known and is assumed to equal the population average for the disease states and conditions present in the patient (Table 8-1).

Concurrent with the administration of the booster dose, the maintenance dose of procainamide is usually increased. Clinicians need to recognize that the administration of a booster dose does not alter the time required to achieve steady-state conditions when a

new procainamide dosage rate is prescribed. It still requires 3–5 half-lives to attain steady state when the dosage rate is changed. However, usually the difference between the post-booster dose procainamide concentration and the ultimate steady-state concentration has been reduced by giving the extra dose of drug.

Example 1 BN is a 42-year-old, 50-kg (5 ft 2 in) female with atrial flutter who is receiving therapy with intravenous procainamide. She has normal liver and cardiac function. After receiving an initial loading dose of procainamide (300 mg) and a maintenance infusion of procainamide equal to 4 mg/min for 16 hours, her procainamide concentration is measured at 2.1 μg/mL and her atrial rate continues to be rapid. Compute a booster dose of procainamide to achieve a procainamide concentration equal to 6 μg/mL.

1. *Estimate volume of distribution according to disease states and conditions present in the patient.*

In the case of procainamide, the population average volume of distribution equals 2.7 L/kg and this will be used to estimate the parameter for the patient. The patient is nonobese, so her actual body weight will be used in the computation: V = 2.7 L/kg · 50 kg = 135 L.

2. *Compute booster dose.*

The booster dose is computed using the following equation: $BD = (C_{desired} - C_{actual})V$ = (6 mg/L − 2.1 mg/L)135 L = 527 mg, rounded to 500 mg of procainamide infused over 25–30 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take an additional 3–5 estimated half-lives for new steady-state conditions to be achieved. Procainamide serum concentrations can be measured at this time.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Tables 8-5.

TABLE 8-5 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/ equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

CONVERSION OF PROCAINAMIDE DOSES FROM INTRAVENOUS TO ORAL ROUTE OF ADMINISTRATION

Occasionally there is a need to convert a patient stabilized on procainamide therapy from the oral route of administration to an equivalent continuous infusion or vice versa. In general, oral procainamide dosage forms, including most sustained-release tablets and capsules, have a bioavailability equal to 0.83. Assuming that equal procainamide serum concentrations are desired, this makes conversion between the intravenous ($k_0 = Css \cdot Cl$) and oral [$D = (Css \cdot Cl \cdot \tau) / F$] routes of administration simple since equivalent doses of drug are prescribed: $k_0 = FD_{po} / (60 \text{ min/h} \cdot \tau)$ or $D_{po} = (k_0 \cdot \tau \cdot 60 \text{ min/h}) / F$, where k_0 is the equivalent intravenous infusion rate for the procainamide in mg/min, D_{po} is equivalent dose of oral procainamide in mg, τ is the dosage interval, and F is the bioavailability fraction for oral procainamide.

Example 1 JH is currently receiving oral sustained-release procainamide 1000 mg every 6 hours. She is responding well to therapy, has no adverse drug effects, and has a steady-state procainamide and NAPA concentrations of 8.3 μg/mL and 14.7 μg/mL, respectively. Suggest an equivalent dose of procainamide given as an intravenous infusion for this patient.

1. *Calculate equivalent intravenous dose of procainamide.*

The equivalent intravenous procainamide dose would be: $k_0 = FD_{po} / (60 \text{ min/h} \cdot \tau) = (0.83 \cdot 1000 \text{ mg})/(60 \text{ min/h} \cdot 6 \text{ h}) = 2.3$ mg/min of procainamide as a continuous intravenous infusion.

Example 2 LK is currently receiving a continuous infusion of procainamide at the rate of 5 mg/min. He is responding well to therapy, has no adverse drug effects, and has steady-state procainamide and NAPA concentrations of 6.2 μg/mL and 4.3 μg/mL, respectively. Suggest an equivalent dose of sustained-release oral procainamide for this patient.

1. *Calculate equivalent oral dose of procainamide.*

The equivalent oral sustained-release procainamide dose using a 12-hour dosage interval would be: $D_{po} = (k_0 \cdot \tau \cdot 60 \text{ min/h}) / F = (5 \text{ mg/min} \cdot 12 \text{ h} \cdot 60 \text{ min/h}) / 0.83 = 4337$ mg, rounded to 4000 mg. The patient would be prescribed procainamide sustained-release tablets 4000 mg orally every 12 hours.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current antiarrhythmic and other drug therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with procainamide exists.

1. NJ is a 67-year-old, 72-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with oral procainamide. He has normal renal and liver function, and does not have uncompensated heart failure. Suggest an initial oral procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

2. Patient NJ (please see problem 1) was prescribed procainamide sustained-release tablets 1000 mg orally every 6 hours. The current steady-state procainamide and NAPA concentrations equal 4.2 μg/mL and 2.5 μg/mL, respectively, (total procainamide concentration = 6.7 μg/mL). Compute a new oral procainamide dose that will provide a procainamide steady-state concentration of 6 μg/mL.

3. GF is a 56-year-old, 81-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral procainamide. He has renal failure (estimated creatinine clearance = 10 mL/min) and normal liver function. Suggest an initial procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

4. Patient GF (please see problem 3) was prescribed procainamide sustained-release tablets 1000 mg orally every 12 hours. The current steady-state procainamide and NAPA concentrations equal 9.5 μg/mL and 32.5 μg/mL, respectively, (total procainamide concentration = 42 μg/mL). Compute a new oral procainamide dose that will provide a procainamide steady-state concentration of 6 μg/mL.

5. YU is a 71-year-old, 60-kg (5 ft 2 in) female with paroxysmal atrial tachycardia who requires therapy with oral procainamide. She has severe uncompensated heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 5 μg/mL.

6. Patient YU (please see problem 5) was prescribed procainamide sustained-release tablets 1000 mg orally every 12 hours. The procainamide and NAPA concentrations obtained just before the third dose of this regimen equaled 11.4 μg/mL and 10.1 μg/mL, respectively, (total procainamide concentration = 21.5 μg/mL). Assuming the procainamide concentration was zero before the first dose, compute a new oral procainamide dose that will provide a steady-state concentration of 8 μg/mL.

7. WE is a 54-year-old, 55-kg (5 ft 5 in) female with atrial fibrillation who requires therapy with oral procainamide. She has severe liver cirrhosis (Child-Pugh score = 13). Suggest an initial oral procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 5 μg/mL.

8. Patient WE (please see problem 7) was prescribed procainamide sustained-release tablets 1000 mg orally every 12 hours. The procainamide and NAPA concentrations obtained just before the third dose of this regimen equaled 9.5 μg/mL and 7.2 μg/mL, respectively, (total procainamide concentration = 16.7 μg/mL). Assuming the procainamide concentration was zero before the first dose, compute a new oral procainamide dose that will provide a steady-state concentration of 7 μg/mL.

9. IO is a 62-year-old, 130-kg (5 ft 11 in) male with atrial flutter who requires therapy with oral procainamide. He has normal liver and renal function. Suggest an initial procainamide sustained-release dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

10. Patient IO (please see problem 9) was prescribed procainamide sustained-release tablets 2000 mg orally every 12 hours. After the first dose, the patient's arrhythmia returned, and his clinician advised a dosage increase to 3000 mg every 12 hours.

Procainamide and NAPA serum concentrations were obtained just before the third dose (i.e., after one 2000 mg and one 3000 mg dose) and equaled 2.8 μg/mL. Assuming the procainamide concentration was zero before the first dose, compute a new oral procainamide dose that will provide a steady-state concentration of 4 μg/mL.

11. LG is a 53-year-old, 69-kg (5 ft 10 in) male with atrial flutter who requires therapy with intravenous procainamide. He has normal liver and cardiac function. Suggest an initial procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

12. Patient LG (please see problem 11) was prescribed intravenous procainamide 3 mg/min. The procainamide and NAPA concentrations obtained after 24 hours of this regimen equaled 4.5 μg/mL and 2.5 μg/mL, respectively, (total procainamide concentration = 7 μg/mL). Compute a new intravenous procainamide infusion and a procainamide booster dose that will provide a steady-state concentration of 8 μg/mL.

13. CV is a 69-year-old, 90-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with intravenous procainamide. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 5 μg/mL.

14. Patient CV (please see problem 13) was prescribed intravenous procainamide 3 mg/min and administered a loading dose of procainamide 500 mg over 30 minutes before the continuous infusion began. A procainamide serum concentration was obtained after 12 hours of the infusion and equaled 11.2 μg/mL. Compute a new intravenous procainamide infusion that will provide a steady-state concentration of 6 μg/mL.

15. PE is a 61-year-old, 67-kg (5 ft 6 in) female with atrial fibrillation who requires therapy with intravenous procainamide. She has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial intravenous procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/mL.

16. Patient PE (please see problem 15) was prescribed intravenous procainamide 4 mg/min and administered a loading dose of procainamide 500 mg over 30 minutes before the continuous infusion began. Procainamide serum concentrations were obtained 4 hours and 8 hours after the infusion began and equaled 4.3 μg/mL and 8.8 μg/mL, respectively. Compute a new intravenous procainamide infusion that will provide a steady-state concentration of 6 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial procainamide dose for patient NJ would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected procainamide half-life ($t_{1/2}$) is 3.3 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693 / 3.3\ h = 0.210\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 2.7 L/kg · 72 kg = 194 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: Cl = kV = 0.210 h^{-1} · 194 L = 40.7 L/h.

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). Because the patient has a rapid procainamide clearance and half-life, the initial dosage interval (τ) will be set to 6 hours. (Note: μg/mL= mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is D = (Css · Cl · τ) / F = (4 mg/L · 40.7 L/h · 6 h) / 0.83 = 1177 mg, rounded to 1000 mg every 6 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide dose of 50 mg/kg/d is suggested by Table 8-3 for an adult with normal renal and hepatic function.

2. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient every 6 hours: D = procainamide dose · Wt = 50 mg/kg/d · 72 kg = 3600 mg/d, rounded to 4000 mg/d or 1000 mg every 6 hours. This dose is identical to that suggested by the pharmacokinetic dosing method.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours for procainamide and 6 hours for NAPA, the steady-state concentrations could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

2. *Solution to problem 2* The revised procainamide dose for patient NJ would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 3.3 h = 17 h for procainamide, 5 $t_{1/2}$ = 5 · 6 h = 30 h for NAPA) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 1000 mg/dose · 4 doses/day = 4000 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (6\ \mu g/mL / 4.2\ \mu g/mL)\ 4000\ mg/d$$
$$= 5714\ mg/d, \text{ rounded to } 6000\ mg/d \text{ or } 1500\ mg \text{ every } 6 \text{ hours}$$

The new suggested dose would be 1500 mg every 6 hours of oral procainamide to be started immediately.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (6000\ mg/d / 4000\ mg/d)\ 2.5\ \mu g/mL = 3.8\ \mu g/mL$$

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 3.3 hours and NAPA half-life equal to 6 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 3.3 h = 17 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 3.3 h = 17 h for procainamide, 5 $t_{1/2}$ = 5 · 6 h = 30 h for NAPA) of therapy.

Procainamide clearance can be computed using a steady-state procainamide concentration: $Cl = [F(D/\tau)] / Css = [0.83\ (1000\ mg/6\ h)] / (4.2\ mg/L) = 32.9\ L/h$. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (6\ mg/L \cdot 32.9\ L/h \cdot 6\ h) / 0.83 = 1427\ mg$, rounded to 1500 mg every 6 hours.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (6000\ mg/d / 4000\ mg/d)\ 2.5\ \mu g/mL = 3.8\ \mu g/mL$$

The new procainamide dose would be instituted immediately.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a procainamide half-life equal to 3.3 hours and NAPA half-life equal to 6 hours, procainamide and NAPA steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 3.3 h = 17 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

3. *Solution to problem 3* The initial procainamide dose for patient GF would be calculated as follows :

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected procainamide half-life ($t_{1/2}$) is 13.9 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/13.9\ h = 0.050\ h^{-1}$.

2*. Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 1.7 L/kg · 81 kg = 138 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.050\ h^{-1} \cdot 138\ L = 6.9$ L/h.

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). Because the patient has a slow procainamide clearance and long half-life, the initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is $D = (Css \cdot Cl \cdot \tau) / F = (4\ mg/L \cdot 6.9\ L/h \cdot 12\ h) / 0.83 = 399$ mg, rounded to 500 mg every 12 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide dose of 12.5 mg/kg/d (50 mg/kg/d normal dose, reduced by 75%) is suggested by the Table 8-3 for an adult with severe renal failure.

2. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient every 12 hours: D = procainamide dose · Wt = 12.5 mg/kg/d · 81 kg = 1013 mg/d, rounded to 1000 mg/d or 500 mg every 12 hours. This dose is identical to that suggested by the pharmacokinetic dosing method.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

4. *Solution to problem 4* The revised procainamide dose for patient GF would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA).

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 1000 mg/dose · 2 doses/day = 2000 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (6\ \mu g/mL / 9.5\ \mu g/mL)\ 2000\ mg/d$$
$$= 1263\ mg/d, \text{ rounded to } 1500\ mg/d \text{ or } 750\ mg \text{ every } 12 \text{ hours}$$

The new suggested dose would be 750 mg every 12 hours of oral procainamide to be started immediately if no adverse effects are present. If side effects are observed, the new dosage regimen could be held for one procainamide half-life before being instituted.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (1500\ mg/d / 2000\ mg/d)\ 32.5\ \mu g/mL = 24.4\ \mu g/mL$$

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA).

Procainamide clearance can be computed using a steady-state procainamide concentration: Cl = [F(D/τ)] / Css = [0.83 (1000 mg/12 h)] / (9.5 mg/L) = 7.3 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (6 mg/L · 7.3 L/h · 12 h) / 0.83 = 633 mg, rounded to 750 mg every 12 hours.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (1500 \text{ mg/d} / 2000 \text{ mg/d})\ 32.5\ \mu\text{g/mL} = 24.4\ \mu\text{g/mL}$$

The new suggested dose would be 750 mg every 12 hours of oral procainamide to be started immediately if no adverse effects are present. If side effects are observed, the new dosage regimen could be held for one procainamide half-life before being instituted.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 13.9 hours for procainamide and 41 hours for NAPA, the steady-state concentrations could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 13.9 h = 70 h for procainamide, 5 half-lives = 5 · 41 h = 205 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

5. *Solution to problem 5* The initial procainamide dose for patient YU would be calculated as follows:

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe uncompensated heart failure have highly variable procainamide pharmacokinetics and dosage requirements. Heart failure patients have decreased cardiac output which leads to decreased liver blood flow, and the expected procainamide half-life ($t_{1/2}$) is 5.5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5.5 \text{ h} = 0.126 \text{ h}^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 1.6 L/kg · 60 kg = 96 L. Estimated procainamide clearance

is computed by taking the product of the volume of distribution and the elimination rate constant: Cl = kV = 0.126 h^{-1} · 96 L = 12.1 L/h.

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is D = (Css · Cl · τ) / F = (5 mg/L · 12.1 L/h · 12 h) / 0.83 = 875 mg, rounded to 750 mg every 12 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.5 hours for procainamide and 6 hours for NAPA (assuming heart failure has no effect on NAPA pharmacokinetics), the steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 27.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and procainamide clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and procainamide clearance. Thus, patients with heart failure receiving procainamide therapy must be monitored very carefully.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide dose of 25 mg/kg/d (50 mg/kg/d normal dose, reduced by 50%) is suggested by Table 8-3 for an adult with severe renal failure.

2. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient every 12 hours: D = procainamide dose · Wt = 25 mg/kg/d · 60 kg = 1500 mg/d, 750 mg every 12 hours. This dose is identical to that suggested by the pharmacokinetic dosing method.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.5 hours for procainamide and 6 hours for NAPA (assuming heart failure has no effect on NAPA pharmacokinetics), the steady-state concentrations could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 27.5 h for procainamide, 5 half-lives = 5 · 6 h = 30 h for NAPA). Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's cardiac status changes. If heart

failure improves, cardiac output will increase resulting in increased liver blood flow and procainamide clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and procainamide clearance. Thus, patients with heart failure receiving procainamide therapy must be monitored very carefully.

6. *Solution to problem 6* The revised procainamide dose for patient YU would be calculated as follows:

The patient has severe heart failure and would be expected to achieve steady-state conditions after the second day (5 $t_{1/2} = 5 \cdot 5.5$ h = 27.5 h) of therapy. Because the serum procainamide serum concentration was obtained just before the third dose, it is unlikely that steady state has been attained, so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 75 L, a half-life equal to 13.8 hours, and a clearance equal to 3.8 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 500 mg every 12 hours will produce a steady-state procainamide concentration of 8 μg/mL.

7. *Solution to problem 7* The initial procainamide dose for patient WE would be calculated as follows:

Pharmacokinetic Dosing Method

Detailed pharmacokinetic studies have not been done in patients with severe liver disease, so this method cannot be used.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide dose of 25 mg/kg/d (50 mg/kg/d normal dose, reduced by 50%) is suggested by Table 8-3 for an adult with severe liver disease.

2. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient every 12 hours: D = procainamide dose · Wt = 25 mg/kg/d · 55 kg = 1375 mg/d, rounded to 1500 mg or 750 mg every 12 hours.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's hepatic status changes. Thus, patients with heart failure receiving procainamide therapy must be monitored very carefully.

8. *Solution to problem 8* The revised procainamide dose for patient WE would be calculated as follows:

The patient has abnormal hepatic function and would be expected to have a prolonged half-life. Because the serum procainamide serum concentration was obtained before the third dose, it is unlikely that the serum concentration was obtained at steady state so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 91 L, a half-life equal to 14 hours, and a clearance equal to 4.5 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 500 mg every 12 hours will produce a steady-state procainamide concentration of 6.7 μg/mL.

9. *Solution to problem 9* The initial procainamide dose for patient IO would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

For an obese individual, a value of clearance is used to compute procainamide doses.

2. *Estimate volume of distribution and clearance.*

The patient is obese [IBW_{male} (in kg) = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg, patient >30% over ideal body weight], so the estimated procainamide clearance will be based on total body weight and the population clearance value: Cl = 0.52 L/h/kg · 130 kg = 67.6 L/h.

3. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this

concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral procainamide is D = (Css · Cl · τ) / F = (4 mg/L · 67.6 L/h · 12 h) / 0.83 = 3909 mg, rounded to 4000 or 2000 mg every 12 hours.

A steady-state trough procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 17 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide dose of 50 mg/kg/d is suggested by Table 8-3 for an adult with normal renal and hepatic function. Because the patient is obese [IBW_{male} (in kg) = 50 kg + 2.3 (Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg, patient >30% over ideal body weight], total body weight will be used to compute doses.

2. *Compute dosage regimen.*

Oral sustained-release procainamide tablets will be prescribed to this patient. The initial dosage interval will be set to 12 hours: D = procainamide dose · Wt = 50 mg/kg/d · 130 kg = 6500 mg, rounded to 6000 or 3000 mg every 12 hours. (Note: Dose is rounded down to avoid possible overdosage.)

A steady-state trough procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 17 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's cardiac status changes.

10. *Solution to problem 10* The revised procainamide dose for patient IO would be calculated as follows:

The patient has mild heart failure and would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5.5 h = 27.5 h) of therapy. Because the serum procainamide serum concentration was obtained on the second day of therapy, but two different doses were given on day 1, it is unlikely that the serum concentration was obtained at steady state so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 235 L, a half-life equal to 5.1 hours, and a clearance equal to 31.8 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 4000 mg every 12 hours will produce a steady-state procainamide concentration of 4.4 μg/mL.

A steady-state trough procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.1 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5.1 h = 25.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

11. *Solution to problem 11* The initial procainamide dose for patient LG would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected procainamide half-life ($t_{1/2}$) is 3.3 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/3.3\ h = 0.210\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 2.7 L/kg · 69 kg = 186 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.210\ h^{-1} \cdot 186\ L = 39.1$ L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of procainamide to the patient: LD = Css · V = 4 mg/L · 186 L = 744 mg, rounded to 750 mg. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

A procainamide continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous procainamide is $k_0 = Css \cdot Cl = (4\ mg/L \cdot 39.1\ L/h) / (60\ min/h) = 2.6$ mg/min, rounded to 3 mg/min.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide loading dose of 500 mg over 25–30 minutes would be administered followed by a continuous infusion. A procainamide dose of 2–6 mg/min is suggested by Table 8-3 for an adult with normal hepatic and renal function. A dose of 3 mg/min would be expected to attain a steady-state concentration in the lower end of the therapeutic range.

A procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

12. *Solution to problem 12* The revised procainamide dose for patient LG would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 3.3 h = 16.5 h) of therapy.

Using linear pharmacokinetics, the new infusion rate to attain the desired concentration should be proportional to the old infusion rate that produced the measured concentration:

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (8\ \mu g/mL / 4.5\ \mu g/mL)\ 3\ mg/min$$
$$= 5.3\ mg/min, \text{ rounded to } 5\ mg/min$$

The new suggested infusion rate would be 5 mg/min of procainamide.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (5\ mg/min / 3\ mg/min)\ 2.5\ \mu g/mL = 4.2\ \mu g/mL$$

A booster dose of procainamide would be computed using an estimated volume of distribution for the patient (2.7 L/kg · 69 kg = 186 L): $BD = (C_{desired} - C_{actual})V =$

(8 mg/L − 4.5 mg/L) 186 L = 651 mg, rounded to 600 mg of procainamide over 25–30 minutes. The booster dose would be given to the patient before the infusion rate was increased to the new value.

A steady-state trough procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 3.3 h = 16.5 h) of therapy.

Procainamide clearance can be computed using a steady-state procainamide concentration Cl = k_0 / Css = (3 mg/min) / (4.5 mg/L) = 0.67 L/min. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute procainamide dose.*

Procainamide clearance is used to compute the new procainamide infusion rate: k_0 = Css · Cl = 8 mg/L · 0.67 L/min = 5.4 mg/min, rounded to 5 mg/min.

The new suggested infusion rate would be 5 mg/min of procainamide.

The expected NAPA steady-state serum concentration would change in proportion to the procainamide dosage alteration:

$$C_{ss,new} = (D_{new} / D_{old})C_{ss,old} = (5 \text{ mg/min} / 3 \text{ mg/min})\ 2.5 \text{ µg/mL} = 4.2 \text{ µg/mL}$$

A booster dose of procainamide would be computed using an estimated volume of distribution for the patient (2.7 L/kg · 69 kg = 186 L): BD = $(C_{desired} - C_{actual})V$ = (8 mg/L − 4.5 mg/L) 186 L = 651 mg, rounded to 600 mg of procainamide over 25–30 minutes. The booster dose would be given to the patient before the infusion rate was increased to the new value.

A steady-state trough procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.3 hours, the procainamide steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 3.3 h = 16.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity.

13. *Solution to problem 13* The initial procainamide dose for patient CV would be calculated as follows:

Pharmacokinetic Dosing Method

Detailed pharmacokinetic studies have not been done in patients with severe liver disease, so this method cannot be used.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide loading dose of 500 mg over 25–30 minutes would be administered followed by a continuous infusion. A procainamide dose of 1–3 mg/min (2–6 mg/min normal dose, reduced by 50%) is suggested by Table 8-3 for an adult with severe liver disease. A dose in the lower end of this range should result in a procainamide steady-state concentration in the lower end of the therapeutic range. A dose of 1 mg/min would be prescribed to the patient.

Steady-state procainamide and NAPA serum concentrations could be measured after steady state is attained in 3–5 half-lives. Procainamide and NAPA serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's hepatic status changes. Thus, patients with liver failure receiving procainamide therapy must be monitored very carefully.

14. *Solution to problem 14* The revised procainamide dose for patient CV would be calculated as follows:

The patient has liver cirrhosis and may not have achieved steady-state conditions after 12 hours of therapy. Because of this, it is unlikely that the serum concentration was obtained at steady state even though a loading dose was given so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program*

Note: DrugCalc requires procainamide infusion rates to be entered in the units of mg/h (3 mg/min · 60 min/h = 180 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 139 L, a half-life equal to 8.2 hours, and a clearance equal to 11.8 L/h.

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The one-compartment model infusion equations used by the program to compute doses indicate that a procainamide infusion of 71 mg/h or 1.2 mg/min (71 mg/h /

60 min/h = 1.2 mg/min) will produce a steady-state procainamide concentration of 6 μg/mL. This dose would be started immediately if no adverse effects were noted. However, if the patient was experiencing drug side effects, the new infusion rate would be started after holding the infusion for 8 hours (~one half-life) to allow procainamide serum concentrations to decrease by one half.

15. *Solution to problem 15* The initial procainamide dose for patient PE would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe heart failure have highly variable procainamide pharmacokinetics and dosage requirements. Heart failure patients have decreased cardiac output which leads to decreased liver blood flow, and the expected procainamide half-life ($t_{1/2}$) is 5.5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5.5\ h = 0.126\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated procainamide volume of distribution will be based on actual body weight: V = 1.6 L/kg · 67 kg = 107 L. Estimated procainamide clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.126\ h^{-1} \cdot 107\ L = 13.5$ L/h.

3. *Compute dosage regimen.*

Therapy will be started by administering an intravenous loading dose of procainamide to the patient: LD = Css · V = 4 mg/L · 107 L = 428 mg, rounded to 400 mg. A loading dose of 400 mg given intravenously over 25–30 minutes would be given. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

A procainamide continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous procainamide is $k_0 = Css \cdot Cl = (4\ mg/L \cdot 13.5\ L/h) / (60\ min/h) = 0.9$ mg/min, rounded to 1 mg/min.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.5 hours, the procainamide steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 27.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and procainamide clearance. Alternatively, if heart failure worsens, cardiac output

will decrease further resulting in decreased liver blood flow and procainamide clearance. Thus, patients with heart failure that receive procainamide therapy must be monitored very carefully.

Literature-Based Recommended Dosing

1. *Choose procainamide dose based on disease states and conditions present in the patient.*

A procainamide loading dose of 500 mg over 25–30 minutes would be administered followed by a continuous infusion. A procainamide dose of 1–3 mg/min (2–6 mg/min normal dose, reduced by 50%) is suggested by Table 8-3 for an adult with severe heart failure. A dose in the lower end of this range should result in a procainamide steady-state concentration in the lower end of the therapeutic range. A dose of 1 mg/min would be prescribed to the patient.

A steady-state procainamide serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.5 hours, the procainamide steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 5.5 h = 27.5 h). Procainamide serum concentrations should also be measured if the patient experiences an exacerbation of their arrhythmia, or if the patient develops potential signs or symptoms of procainamide toxicity. Procainamide pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and procainamide clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and procainamide clearance. Thus, patients with heart failure that receive procainamide therapy must be monitored very carefully.

16. *Solution to problem 16* The revised procainamide dose for patient PE would be calculated as follows:

The patient has severe heart failure and would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 5.5 h = 27.5 h) of therapy. Because the serum procainamide serum concentrations were obtained after 4 hours and 8 hours of therapy, it is unlikely that the serum concentrations were obtained at steady state even though a loading dose was given so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Chiou Method

1. *Compute procainamide clearance.*

$$Cl = \frac{2k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2(4\ \text{mg/min})}{4.3\ \text{mg/L} + 8.8\ \text{mg/L}} + \frac{2(1.6\ \text{L/kg} \cdot 67\ \text{kg})(4.3\ \text{mg/L} - 8.8\ \text{mg/L})}{(4.3\ \text{mg/L} + 8.8\ \text{mg/L})\,240\ \text{min}}$$

$$= 0.30\ \text{L/min}$$

(Note: μg/mL= mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1, in minutes, was determined and placed directly in the calculation.)

$$k_0 = Css \cdot Cl = 6 \text{ mg/L} \cdot 0.30 \text{ L/min} = 1.8 \text{ mg/min of procainamide}$$

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this case, the patient is not at steady state so the linear pharmacokinetics method cannot be used. DrugCalc requires procainamide continuous infusions to be entered in terms of mg/h (4 mg/min · 60 min/h = 240 mg/h).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 246 L, a half-life equal to 13.9 hours, and a clearance equal to 12.3 L/h or 0.21 L/min (12.3 L/h / 60 min/h = 0.21 L/h).

3. *Compute dose required to achieve desired procainamide serum concentrations.*

The one-compartment model infusion equations used by the program to compute doses indicates that a procainamide infusion of 74 mg/h or 1.2 mg/min (74 mg/h / 60 min/h = 1.2 mg/min) will produce a steady-state procainamide concentration of 6 μg/mL.

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9

QUINIDINE

INTRODUCTION

Quinidine was one of the first agents used for its antiarrhythmic effects. It is classified as a type IA antiarrhythmic agent and can be used for the treatment of supraventricular or ventricular arrhythmias.[1,2] After ventricular rate has been controlled, quinidine therapy can be used to chemically convert atrial fibrillation to normal sinus rhythm for a patient. Because of its side effect profile, quinidine is considered by many clinicians to be a second-line antiarrhythmic choice. Quinidine inhibits transmembrane sodium influx into the conduction system of the heart thereby decreasing conduction velocity.[1,2] It also increases the duration of the action potential, increases threshold potential toward zero, and decreases the slope of phase 4 of the action potential. Automaticity is decreased during quinidine therapy. The net effect of these cellular changes is that quinidine causes increased refractoriness and decreased conduction in heart conduction tissue which establishes a bidirectional block in reentrant pathways.

THERAPEUTIC AND TOXIC CONCENTRATIONS

When given intravenously, the serum quinidine concentration/time curve follows a two-compartment model.[3–6] However, due to marked hypotension and tachycardia when given intravenously to some patients, the oral route of administration is far more common. When oral quinidine is given as a rapidly absorbed dosage form such as quinidine sulfate tablets, a similar distribution phase is also observed with a duration of 20–30 minutes.[3,4,7,8] If extended-release oral dosage forms are given, absorption occurs more slowly than distribution so a distribution phase is not seen (Figure 9-1).[9–13]

The generally accepted therapeutic range for quinidine is 2–6 μg/mL. Quinidine serum concentrations above the therapeutic range can cause increased QT interval or QRS complex widening (>35–50%) on the electrocardiogram, cinchonism, hypotension, high-degree atrioventricular block, and ventricular arrhythmias. Cinchonism is a collection of

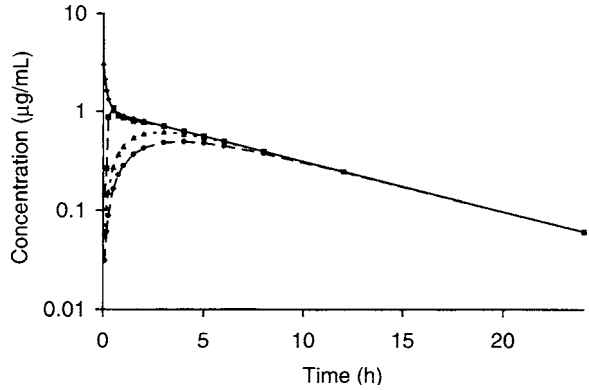

FIGURE 9-1 Quinidine serum concentrations after an intravenous dose *(diamonds with solid line)* and three different oral tablets (doses normalized to provide 200 mg of quinidine base systemically). After an intravenous dose, quinidine serum concentrations decline according to a two-compartment model which demonstrates a distribution phase that lasts for 20–30 minutes postinjection. Immediate-release quinidine tablets *(squares with dashed line)* are rapidly absorbed and also show a distinct distribution phase. Extended-release quinidine gluconate *(triangles with dotted line)* and quinidine sulfate *(circles with dashed line)* have slower absorption profiles, so the drug has an opportunity to distribute to tissues while absorption is occurring. Because of this, no distribution phase is observed for these dosage forms.

symptoms that includes tinnitus, blurred vision, lightheadedness, tremor, giddiness, and altered hearing which decreases in severity with lower quinidine concentrations. Gastrointestinal adverse effects such as anorexia, nausea, vomiting, diarrhea are the most common side effects of quinidine therapy, can occur after both oral and intravenous quinidine routes of administration, but are not strongly correlated with specific serum levels. Quinidine therapy is also associated with syncope and torsade de pointes. Quinidine syncope occurs when ventricular tachycardia, ventricular fibrillation, or a prolongation of QT intervals occurs in a nondose dependent manner. Torsade de pointes ("twisting of the points") is a form of polymorphic ventricular tachycardia preceded by QT-interval prolongation. It is characterized by polymorphic QRS complexes that change in amplitude and length giving the appearance of oscillations around the electrocardiographic baseline. Torsade de pointes can develop into multiple episodes of nonsustained polymorphic ventricular tachycardia, syncope, ventricular fibrillation, or sudden cardiac death. Hypersensitivity reactions to quinidine include rash, drug fever, thrombocytopenia, hemolytic anemia, asthma, respiratory depression, a systemic lupus-like syndrome, hepatitis, and anaphylactic shock.

Quinidine metabolites (3-hydroxyquinidine, 2′-quinidinone, quinidine-*N*-oxide, *O*-desmethylquinidine) all have antiarrhythmic effects in animal models.[14–17] Of these compounds, 3-hydroxyquinidine is the most potent (60–80% compared to the parent drug) and achieves high enough serum concentrations in humans that its antiarrhythmic effects probably contribute to the clinical effects observed during quinidine treatment. Dihydroquinidine is an impurity contained in commercially available quinidine products that also has antiarrhythmic effects.[18–20] Most products contain less than 10% of the labeled quinidine amount as dihydroquinidine. Clinicians should understand that all patients with

"toxic" quinidine serum concentrations in the listed ranges will not exhibit signs or symptoms of quinidine toxicity. Rather, quinidine concentrations in the given ranges increase the likelihood that an adverse effect will occur.

For dose adjustment purposes, quinidine serum concentrations are best measured as a predose or trough level at steady state after the patient has received a consistent dosage regimen for 3–5 drug half-lives. Quinidine half-life varies from 6–8 hours in normal adults to 9–10 hours or more in adult patients with liver failure. If quinidine is given orally or intravenously on a stable schedule, steady-state serum concentrations will be achieved in about 2 days ($5 \cdot 8$ h = 40 h).

CLINICAL MONITORING PARAMETERS

The electrocardiogram (ECG or EKG) should be monitored to determine the response to quinidine. The goal of therapy is suppression of arrhythmias and avoidance of adverse drug reactions. Electrophysiologic studies using programmed stimulation to replicate the ventricular arrhythmia or 24-hour ECG monitoring using a Holter monitor can be performed in patients while receiving a variety of antiarrhythmic agents to determine effective antiarrhythmic drug therapy.[2]

Because many quinidine therapeutic and side effects are not correlated with its serum concentration, it is often not necessary to obtain serum quinidine concentrations in patients receiving appropriate doses who currently have no arrhythmia or adverse drug effects. However, quinidine serum concentrations should be obtained in patients who have a recurrence of tachyarrhythmias, are experiencing possible quinidine side effects, or are receiving quinidine doses not consistent with disease states and conditions known to alter quinidine pharmacokinetics (please see Effects of Disease States and Conditions on Quinidine Pharmacokinetics and Dosing section). Serum concentration monitoring can aid in the decision to increase or decrease the quinidine dose. For instance, if an arrhythmia reappears and the quinidine serum concentration is <6 μg/mL, increasing the quinidine dose is a therapeutic option. However, if the quinidine serum concentration is over 6 μg/mL, it is unlikely a dosage increase will be effective in suppressing the arrhythmia and there is an increased likelihood that drug side effects may occur. Similarly, if a possible concentration-related quinidine adverse drug reaction is noted in a patient and the quinidine serum concentration is <2 μg/mL, it is possible that the observed problem may not be due to quinidine treatment and other sources can be investigated. While receiving quinidine, patients should be monitored for the following adverse drug effects: anorexia, nausea, vomiting, diarrhea, cinchonism, syncope, increased QT interval or QRS complex widening (>35–50%) on the electrocardiogram, hypotension, high-degree atrioventricular block, ventricular arrhythmias, and hypersensitivity reactions (rash, drug fever, thrombocytopenia, hemolytic anemia, asthma, respiratory depression, a lupus-like syndrome, hepatitis, anaphylactic shock).

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Quinidine is almost completely eliminated by hepatic metabolism (~80%).[4,7] Hepatic metabolism is mainly via the CYP3A enzyme system. 3-Hydroxyquinidine is the primary active metabolite resulting from quinidine metabolism while dihydroquinidine is an

active compound that is found as an impurity in most quinidine dosage forms. The hepatic extraction ratio of quinidine is about 30%, so quinidine is typically classified as an intermediate extraction ratio drug. Because of this, it is expected that liver blood flow, unbound fraction of drug in the blood, and intrinsic clearance will all be important factors influencing the clearance of quinidine. After oral administration, quinidine is subject to moderate first-pass metabolism by CYP3A contained in the liver and intestinal wall. Quinidine is also a substrate for P-glycoprotein. Approximately 20% of a quinidine dose is eliminated unchanged in the urine. Although there have been some reports that quinidine follows nonlinear pharmacokinetics, for the purposes of clinical drug dosing in patients, linear pharmacokinetic concepts and equations can be effectively used to compute doses and estimate serum concentrations.[21]

Three different salt forms of quinidine are available. Quinidine sulfate contains 83% quinidine base, quinidine gluconate contains 62% quinidine base, and quinidine polygalacturonate contains 60% quinidine base. The gluconate salt is available for intravenous injection and oral use. Quinidine sulfate and polygalacturonate are available only for oral use. The oral bioavailability of all three quinidine-based drugs is moderate and generally equals 70% reflecting first-pass metabolism in the intestinal wall and liver.[3,7] Although quinidine injection can be given intramuscularly, this route of administration may lead to erratic absorption and serum concentrations.[6]

Plasma protein binding of quinidine in normal individuals is about 80–90%.[22–24] The drug binds to both albumin and α_1-acid glycoprotein (AGP). AGP is classified as an acute phase reactant protein that is present in lower amounts in all individuals but is secreted in large amounts in response to certain stresses and disease states such as trauma, heart failure, and myocardial infarction. In patients with these disease states, quinidine binding to AGP can be even larger resulting in an unbound fraction as low as 8%.

The recommended dose of quinidine is based on the concurrent disease states and conditions present in the patient that can influence quinidine pharmacokinetics. Quinidine pharmacokinetic parameters used to compute doses are given in the following section for specific patient profiles.

EFFECTS OF DISEASE STATES AND CONDITIONS ON QUINIDINE PHARMACOKINETICS AND DOSING

Normal adults without the disease states and conditions given later in this section and with normal liver function have an average quinidine half-life of 7 hours (range: 6–8 hours) and a volume of distribution for the entire body of 2.4 L/kg (V = 2–3 L/kg; Table 9-1).[3–6,9,25–27] Disease states and conditions that change quinidine pharmacokinetics and dosage requirements may alter clearance and the volume of distribution. The elimination rate constant ($k = 0.693 / t_{1/2}$, where $t_{1/2}$ is the half-life) and clearance ($Cl = kV$) can be computed from the aforementioned pharmacokinetic parameters.

Patients with liver cirrhosis have increased quinidine clearance and volume of distribution which results in a prolonged average quinidine half-life of 9 hours.[28,29] Clearance and volume of distribution are larger in patients with liver disease because albumin and AGP concentrations are lower in these patients and result in reduced quinidine plasma protein binding (average V = 3.8 L/kg). The increased unbound

TABLE 9-1 Disease States and Conditions That Alter Quinidine Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal liver function	7 hours (range: 6–8 hours)	2.4 L/kg (range: 2–3 L/kg)	Quinidine has a moderate hepatic extraction ratio of ~30%, so liver blood flow, unbound fraction of drug in the blood, and intrinsic clearance are all important factors in clearance rate. ~20% of quinidine eliminated unchanged in urine.
Adult, liver cirrhosis	9 hours	3.8 L/kg	Quinidine is metabolized ~80% by hepatic microsomal enzymes (primarily CYP3A) and is a substrate for P-glycoprotein. Clearance of total drug increased in cirrhosis patients, but intrinsic clearance is decreased. Pharmacokinetic parameters highly variable in liver disease patients. Volume of distribution is larger due to decreased α_1-acid glycoprotein and albumin production by liver which decreases drug binding in the plasma.
Adult, heart failure	7 hours	1.7 L/kg	Decreased liver blood flow secondary to reduced cardiac output reduces quinidine clearance. Volume of distribution is smaller due to increased α_1-acid glycoprotein drug binding in the plasma. Heart failure results in large and variable

(*Continued*)

TABLE 9-1 ***(Continued)***

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, heart failure *(continued)*			reductions in quinidine clearance. Cardiac status must be monitored closely in heart failure patients since quinidine clearance changes with acute changes in cardiac output.
Adult, obese (>30% over ideal body weight)	According to other disease states/ conditions that affect quinidine pharmacokinetics	According to other disease states/ conditions that affect quinidine pharmacokinetics	Quinidine doses should be based on ideal body weight for patients who weigh more that >30% over IBW.

fraction in the plasma allows more quinidine to enter the liver parenchyma where hepatic drug metabolizing enzymes are present and leads to increased drug clearance. Decreased plasma protein binding also leads to higher unbound levels for a given total quinidine serum concentration. For example, a quinidine total serum concentration of 3 μg/mL would yield an unbound concentration of 0.3 μg/mL in a patient with normal plasma protein binding (3 μg/mL · 0.1 unbound fraction = 0.3 μg/mL), but an unbound concentration of 0.6 μg/mL in a cirrhosis patient with decreased plasma protein binding (3 μg/mL · 0.2 unbound fraction = 0.6 μg/mL). The significance of this difference in unbound concentrations has not been assessed in cirrhosis patients, but clinicians should bear it in mind when monitoring quinidine levels as only total serum concentrations are available from laboratories. The exact effect that liver disease has on quinidine pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with liver disease to have relatively normal or grossly abnormal quinidine clearance, volume of distribution, and half-life. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 9-2).[30] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 9-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for quinidine. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Quinidine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

TABLE 9-2 Child-Pugh Scores for Patients with Liver Disease[30]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

Heart failure reduces quinidine clearance because of decreased hepatic blood flow secondary to compromised cardiac output (Table 9-3).[7,8,31,32] Volume of distribution (V = 1.7 L/kg) is decreased because heart failure patients have elevated AAG serum concentrations which leads to increased quinidine plasma protein binding and decreased quinidine unbound fraction. Because both clearance and volume of distribution simultaneously decrease, patients with heart failure have an average quinidine half-life equal to 7 hours which is similar to a normal individual [$t_{1/2} = (0.693 \cdot \downarrow V) / \downarrow Cl$]. Increased plasma protein binding also leads to lower unbound levels for a given total quinidine serum concentration. For example, a quinidine total serum concentration of 3 μg/mL would yield an unbound concentration of 0.3 μg/mL in a patient with normal plasma protein binding (3 μg/mL · 0.1 unbound fraction = 0.3 μg/mL), but an unbound concentration of 0.15 μg/mL in a heart failure patient with increased plasma protein binding (3 μg/mL · 0.05 unbound fraction = 0.15 μg/mL). The clinical significance of this difference in unbound concentrations has not been assessed in heart failure patients. Obviously, the

TABLE 9-3 New York Heart Association (NYHA) Functional Classification for Heart Failure[41]

NYHA HEART FAILURE CLASS	DESCRIPTION
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitations of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

effect that heart failure has on quinidine pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with heart failure to have relatively normal or grossly abnormal quinidine clearance and half-life. For heart failure patients, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Quinidine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with heart failure.

Patients with myocardial infarction may develop serious arrhythmias that require therapy with quinidine. After a myocardial infarction, serum AAG concentrations increase up to 50% over a 12–72 hour time period. As AAG serum concentrations increase, plasma protein binding of quinidine increases and the unbound fraction of quinidine decreases. Because quinidine is considered a moderate hepatic extraction ratio drug, a decline in the unbound fraction of quinidine in the plasma decreases quinidine clearance.

Patient age has an effect on quinidine clearance and half-life.[15,33] For elderly patients over the age of 65, studies indicate that quinidine clearance is reduced, the volume of distribution is unchanged, and half-life is longer (average half-life = 10 hours) compared to younger subjects. A confounding factor found in quinidine pharmacokinetic studies conducted in older adults is the possible accidental inclusion of subjects that have subclinical or mild cases of the disease states associated with reduced quinidine clearance (heart failure, liver disease, etc.). Additionally, most patients with serious arrhythmias studied in all of the previously mentioned investigations are older and those results include any influence of age. Thus, in most cases elderly patients are treated with quinidine according to the other disease states or conditions present that influence quinidine pharmacokinetics.

Because detailed studies have not been conducted in obese patients, ideal body weight should be used to compute initial doses of quinidine to avoid accidental overdose in overweight individuals (>30% above ideal body weight or IBW). Since only 20% of a quinidine dose is eliminated unchanged by the kidney, dosage adjustments for renal failure patients are usually not required.[14,32] Quinidine is not appreciably removed by hemodialysis or peritoneal dialysis.[34,35]

DRUG INTERACTIONS

Quinidine has serious drug interactions with other drugs that are capable of inhibiting the CYP3A enzyme system.[36] Because this isozyme is present in the intestinal wall and liver, quinidine serum concentrations may increase due to decreased clearance, decreased first-pass metabolism, or a combination of both. P-glycoprotein is also inhibited by quinidine so drug transport may be decreased and cause drug interactions. Erythromycin, ketoconazole, and verapamil have been reported to increase quinidine serum concentrations or area under the concentration/time curve (AUC) by >30–50%. Other macrolide antibiotics (such as clarithromycin) or azole antifungals (such as fluconazole, miconazole, and itraconazole) that inhibit CYP3A probably cause similar drug interactions with quinidine. Cimetidine and aminodarone also have been reported to cause increases in quinidine concentrations or AUC of a similar magnitude. Drugs that induce CYP3A (phenytoin, phenobarbital, rifampin, rifabutin) decrease quinidine serum concentrations by increasing quinidine clearance and first-pass metabolism. It is important to remember that phenytoin has antiarrhythmic effects and is also classified as a type IB antiarrhythmic agent.

Because of this, phenytoin and quinidine may have additive pharmacologic effects that could result in a pharmacodynamic drug interaction.

Although it is not a substrate for the enzyme, quinidine is a potent inhibitor of the CYP2D6 enzyme system.[36–39] As little as 50 mg of quinidine can effectively turn an "extensive metabolizer" into a "poor metabolizer" for this isozyme. Because poor metabolizers of CYP2D6 substrates have little to none of this enzyme in their liver, the administration of quinidine does not result in a drug interaction in these individuals. Quinidine can markedly decrease the clearance β-adrenergic receptor blockers eliminated via CYP2D6 by 30% or more. Propranolol, metoprolol, and timolol have decreased clearance due to quinidine coadministration. Tricyclic antidepressants (nortriptyline, imipramine, desipramine), haloperidol, and dextromethorphan also have increased serum concentrations when given with quinidine. Codeine is a prodrug with no analgesic effect that relies on conversion to morphine via the CYP2D6 enzyme system to decrease pain. When quinidine is given concomitantly with codeine, the conversion from codeine to morphine does not take place, and patients do not experience analgesia. A similar drug interaction may occur with dihydrocodeine and hydrocodone. Although it may not be reported in the literature for a specific compound, clinicians should consider that a drug interaction is possible between quinidine and any CYP2D6 substrate.

Quinidine increases digoxin serum concentrations 30–50% by decreasing digoxin renal and nonrenal clearance as well as digoxin volume of distribution.[36] The probable mechanisms of this drug interaction are inhibition of digoxin renal and hepatic P-glycoprotein (PGP) elimination and tissue binding displacement of digoxin by quinidine. Antacids can increase urinary pH leading to increased renal tubular reabsorption of unionized quinidine and decreased quinidine renal clearance. Kaolin-pectin administration results in physical adsorption of quinidine in the gastrointestinal tract and decreased quinidine oral absorption. The pharmacologic effects of warfarin and neuromuscular blockers have been enhanced when given with quinidine.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate quinidine therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of quinidine. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of quinidine is to compute the best dose possible for the patient given their set of disease states and conditions that influence quinidine pharmacokinetics and the arrhythmia being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Quinidine is predominately metabolized by liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change quinidine half-life, and the half-life previously measured in these studies is used as an estimate of the current patient's half-life (Table 9-1). For a patient with moderate heart failure (NYHA CHF class III), quinidine half-life would be assumed to equal 7 hours, while a patient with severe liver disease (Child-Pugh score = 12) would be assigned an estimated half-life of 9 hours. To produce the most conservative quinidine doses in patients with multiple concurrent disease states or conditions that affect quinidine pharmacokinetics, the disease state or condition with the longest half-life should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible. Once the correct half-life is identified for the patient, it can be converted into the quinidine elimination rate constant (k) using the following equation: $k = 0.693 / t_{1/2}$.

VOLUME OF DISTRIBUTION ESTIMATE

As with the half-life estimate, the quinidine volume of distribution is chosen according to the disease states and conditions that are present (Table 9-1). The volume of distribution is used to help compute quinidine clearance, and is assumed to equal 3.8 L/kg for liver disease patients, 1.7 L/kg for heart failure patients, and 2.4 L/kg for all other patients. For obese patients (>30% above ideal body weight), ideal body weight is used to compute quinidine volume of distribution. Thus, for a nonobese 80-kg patient without heart failure or liver disease, the estimated quinidine volume of distribution would be 192 L: $V = 2.4\ L/kg \cdot 80\ kg = 192\ L$. For a 150-kg obese patient with an ideal body weight of 60 kg and normal cardiac and liver function, the estimated quinidine volume of distribution is 144 L: $V = 2.4\ L/kg \cdot 60\ kg = 144\ L$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given orally, quinidine follows a one- or two-compartment pharmacokinetic model (Figure 9-1). When oral therapy is required, most clinicians utilize a sustained-release dosage form that has good bioavailability (F = 0.7), supplies a continuous release of quinidine into the gastrointestinal tract, and provides a smooth quinidine serum concentration/time curve that emulates an intravenous infusion when given every 8–12 hours. Because of this, a very simple pharmacokinetic equation that computes the average quinidine steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation: $Css = [F \cdot S\ (D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau) / (F \cdot S)$, where F is the bioavailability fraction for the oral dosage form (F = 0.7 for most oral quinidine products), S is the fraction of the quinidine salt form that is active quinidine (S = 0.83 for sulfate, immediate-release tablets = 100 mg, 200 mg, 300 mg, extended-release tablets = 300 mg; S = 0.62 for gluconate, extended-release tablets = 324 mg; S = 0.60 for polygalacturonate, immediate-release tablets = 275 mg), D is the dose of quinidine salt in mg, and τ is the dosage interval in hours. Cl is quinidine clearance in L/h and is computed using estimates of quinidine elimination rate constant (k) and volume of distribution: $Cl = kV$. For example, for a patient with an estimated elimination rate constant equal

to 0.099 h^{-1} and an estimated volume of distribution equal to 168 L, the estimated clearance would equal 16.6 L/h: Cl = 0.099 h^{-1} · 168 L = 16.6 L/h.

STEADY-STATE CONCENTRATION SELECTION

The general accepted therapeutic range for quinidine is 2–6 μg/mL. However, quinidine therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with oral quinidine gluconate. He has normal liver and cardiac function. Suggest an initial oral quinidine dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 7 hours. The elimination rate constant is computed using the following formula: k = 0.693 / $t_{1/2}$ = 0.693 / 7 h = 0.099 h^{-1}.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: V = 2.4 L/kg · 75 kg = 180 L. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: Cl = kV = 0.099 h^{-1} · 180 L = 17.8 L/h.

3. *Compute dosage regimen.*

Oral extended-release quinidine gluconate tablets will be prescribed to this patient (F = 0.7, S = 0.62). The initial dosage interval (τ) will be set to 8 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: D = (Css · Cl · τ) / (F · S) = (3 mg/L · 17.8 L/h · 8 h) / (0.7 · 0.62) = 984 mg, rounded to 972 mg every 8 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral quinidine sulfate. He has liver cirrhosis (Child-Pugh score = 11). Suggest an initial extended-release quinidine sulfate dosage regimen designed to achieve a steady-state quinidine concentration equal to 2 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 9 hours. The elimination rate constant is computed using the following formula: k = 0.693 / $t_{1/2}$ = 0.693 / 9 h = 0.077 h^{-1}.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: V = 3.8 L/kg · 85 kg = 323 L. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: Cl = kV = 0.077 h^{-1} · 323 L = 24.9 L/h.

3. *Compute dosage regimen.*

Oral extended-release quinidine sulfate tablets will be prescribed to this patient (F = 0.7, S = 0.83). The initial dosage interval (τ) will be set to 8 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: D = (Css · Cl · τ) / (F · S) = (2 mg/L · 24.9 L/h · 8 h) / (0.7 · 0.83) = 686 mg, rounded to 600 mg every 8 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral quinidine. He has moderate heart failure (NYHA CHF class III). Suggest an initial extended-release quinidine gluconate dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 7 hours. The elimination rate constant is computed using the following formula: k = 0.693 / $t_{1/2}$ = 0.693 / 7 h = 0.099 h^{-1}.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: V = 1.7 L/kg · 78 kg = 133 L. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: Cl = kV = 0.099 h^{-1} · 133 L = 13.2 L/h.

3. *Compute dosage regimen.*

Oral extended-release quinidine gluconate tablets will be prescribed to this patient (F = 0.7, S = 0.62). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: D = (Css · Cl · τ) / (F · S) = (3 mg/L · 13.2 L/h · 8 h) / (0.7 · 0.62) = 730 mg, rounded to 648 mg every 8 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours,

the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in quinidine pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard quinidine doses for various situations are warranted. The original computation of these doses was based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. In general, the quinidine steady-state serum concentration expected from the lower end of the dosage range was 2–4 μg/mL and 4–6 μg/mL for the upper end of the dosage range. Suggested quinidine maintenance doses for adults and children are given in Table 9-4. A 25–50% reduction in initial quinidine dose is suggested for patients with moderate-to-severe liver disease (Child-Pugh score ≥8) or moderate-to-severe heart failure (NYHA class II or greater). When more than one disease state or condition is present in a patient, choosing the lowest daily dose will result in the safest, most conservative dosage recommendation.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with oral quinidine gluconate. He has normal liver and cardiac function.

TABLE 9-4 Literature-Based Recommended Oral Quinidine Initial Dosage Ranges for Various Disease States and Conditions

DISEASE STATE/ CONDITION	QUINIDINE SULFATE, IMMEDIATE-RELEASE TABLETS	QUINIDINE SULFATE, EXTENDED-RELEASE TABLETS	QUINIDINE GLUCONATE, EXTENDED-RELEASE TABLETS	QUINIDINE POLYGALACTURONATE TABLETS
Adult, normal liver function	200–300 mg every 6–8 hours	600 mg every 8–12 hours	324–648 mg every 8–12 hours	275–413 mg every 6–8 hours
Adult, liver cirrhosis or heart failure	100–200 mg every 6–8 hours	300 mg every 8–12 hours	324 mg every 8–12 hours	138–275 mg every 6–8 hours
Children, normal liver function*	15–60 mg/kg/d given every 6 hours	——	——	——

*For intravenous use, the dose of quinidine gluconate injection is 2–10 mg/kg/dose administered every 3–6 hours, as needed. A 2 mg/kg test dose of oral quinidine sulfate or injectable quinidine gluconate (IM or IV) is recommended to determine if an idiosyncratic adverse effect will occur (maximum test dose 200 mg).[42]

Suggest an initial oral quinidine dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine gluconate maintenance dose of 628 mg every 12 hours (1256 mg/d) is suggested for a patient without heart failure or liver disease requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral quinidine sulfate. He has liver cirrhosis (Child-Pugh score = 11). Suggest an initial immediate-release quinidine sulfate dosage regimen designed to achieve a steady-state quinidine concentration equal to 2 μg/mL.

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine sulfate maintenance dose of 100 mg every 6 hours (400 mg/d) is suggested for a patient with liver disease requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral quinidine. He has moderate heart failure (NYHA CHF class III). Suggest an initial extended-release quinidine gluconate dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine gluconate maintenance dose of 324 mg every 12 hours (648 mg/d) is suggested for a patient with heart failure requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

USE OF QUINIDINE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce quinidine serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the narrow therapeutic index of quinidine, and the desire to avoid quinidine adverse side effects, measurement of quinidine serum concentrations can be a useful adjunct for patients to ensure that therapeutic, nontoxic levels are present. In addition to quinidine serum concentrations, important patient parameters (electrocardiogram, clinical signs and symptoms of the arrhythmia, potential quinidine side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When quinidine serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change quinidine doses assuming the drug follows *linear pharmacokinetics*. Thus, assuming linear pharmacokinetics is adequate for dosage adjustments in most patients.

Sometimes, it is useful to compute quinidine pharmacokinetic constants for a patient and base dosage adjustments on these parameters. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the quinidine dose.

In some situations, it may be necessary to compute quinidine pharmacokinetic parameters as soon as possible for the patient before steady-state conditions occur and utilize these parameters to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where serum concentrations are obtained at suboptimal times or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because quinidine follows linear, dose-proportional pharmacokinetics in most patients, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or $D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required. Because nonlinear pharmacokinetics for quinidine has been observed in some patients, suggested dosage increases greater than 75% using this method should be scrutinized by the prescribing clinician, and the risk versus benefit for the patient assessed before initiating large dosage increases (>75% over current dose).

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with quinidine gluconate. He has normal liver and cardiac function. The current steady-state quinidine concentration equals 2.2 μg/mL at a dose of 324 mg

every 8 hours. Compute a quinidine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 324 mg/dose · 3 dose/day = 972 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.2\ \mu g/mL)\ 972\ mg/d$$
$$= 1767\ mg/d, \text{ rounded to } 1944\ mg/d \text{ or } 648\ mg \text{ every } 8 \text{ hours}$$

The new suggested dose would be 648 mg every 8 hours of oral quinidine gluconate to be started immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral quinidine sulfate extended-release tablets. He has liver cirrhosis (Child-Pugh score = 11). The current steady-state quinidine concentration equals 7.4 μg/mL at a dose of 600 mg every 12 hours. Compute a quinidine dose that will provide a steady-state concentration of 3 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 2 days (5 $t_{1/2}$ = 5 · 9 h = 45 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 600 mg/dose · 2 dose/day = 1200 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (3\ \mu g/mL / 7.4\ \mu g/mL)\ 1200\ mg/d$$
$$= 486\ mg/d, \text{ rounded to } 600\ mg/d$$

The new suggested dose would be 300 mg every 12 hours of quinidine sulfate extended-release tablets. If the patient was experiencing adverse drug effects, the new dosage regimen could be held for 1–2 estimated half-lives ($t_{1/2}$ = 9 h).

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be

measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral quinidine sulfate immediate-release tablets. He has moderate heart failure (NYHA CHF class III). The current steady-state quinidine concentration equals 2.2 μg/mL at a dose of 100 mg every 6 hours. Compute a quinidine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 2 days (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose = 100 mg/dose · 4 doses/day = 400 mg/d.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.2\ \mu g/mL)\ 400\ mg/d$$

$$= 727\ mg/d, \text{ rounded to } 800\ mg/d \text{ or } 200\ mg \text{ every } 6 \text{ hours}$$

The new suggested dose would be 200 mg every 6 hours of quinidine sulfate immediate-release tablets to begin immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired quinidine concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state quinidine concentration (Css). If the patient is receiving oral quinidine therapy, quinidine clearance (Cl) can be calculated using the following formula: $Cl = [F \cdot S\ (D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 0.7 for most oral quinidine products), S is the fraction of the quinidine salt form that is active quinidine (S = 0.83 for quinidine sulfate, S = 0.62 for quinidine gluconate, S = 0.60 for quinidine polygalacturonate), D is the dose of quinidine salt in mg, Css is the steady-state quinidine concentration, and τ is the dosage interval in hours. Because this method also assumes linear pharmacokinetics, quinidine doses computed using the pharmacokinetic parameter method and the linear pharmacokinetic method should be identical.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with quinidine gluconate. He has normal liver and cardiac function.

The current steady-state quinidine concentration equals 2.2 μg/mL at a dose of 324 mg every 8 hours. Compute a quinidine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.62 (324 mg/8 h)] / (2.2 mg/L) = 7.99 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (4 mg/L · 7.99 L/h · 8 h) / (0.7 · 0.62) = 589 mg, rounded to 648 mg every 8 hours.

The new quinidine dose would be instituted immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with atrial fibrillation who requires therapy with oral quinidine sulfate extended-release tablets. He has liver cirrhosis (Child-Pugh score = 11). The current steady-state quinidine concentration equals 7.4 μg/mL at a dose of 600 mg every 12 hours. Compute a quinidine dose that will provide a steady-state concentration of 3 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 9 h = 45 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.83 (600 mg/12 h)] / (7.4 mg/L) = 3.93 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (3 mg/L · 3.93 L/h · 12 h) / (0.7 · 0.83) = 244 mg, rounded to 300 mg every 12 hours.

The new quinidine dose would be instituted immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours,

the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Example 3 MN is a 64-year-old, 78-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral quinidine sulfate immediate-release tablets. He has moderate heart failure (NYHA CHF class III). The current steady-state quinidine concentration equals 2.2 μg/mL at a dose of 100 mg every 6 hours. Compute a quinidine dose that will provide a steady-state concentration of 4 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.83 (100 mg/6 h)] / (2.2 mg/L) = 4.40 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (4 mg/L · 4.40 L/h · 6 h) / (0.7 · 0.83) = 182 mg, rounded to 200 mg every 6 hours.

The new quinidine dose would be instituted immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic

parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[40]

Example 1 OY is a 57-year-old, 79-kg (5 ft 8 in) male with ventricular tachycardia who requires therapy with oral quinidine gluconate. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) and cardiac function. He started taking quinidine gluconate 648 mg every 12 hours at 0800 H. The quinidine serum concentration equals 2.1 μg/mL at 0730 H before the morning dose is given on the second day of therapy. Compute a quinidine gluconate dose that will provide a steady-state concentration of 4 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 648 mg of quinidine gluconate is equivalent to 400 mg of quinidine base (400-mg quinidine base = 648-mg quinidine gluconate · 0.62).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 181 L, a half-life equal to 15.2 h, and a clearance equal to 8.21 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 972 mg of quinidine gluconate every 12 hours will produce a steady-state

trough concentration of 4.7 μg/mL. (Note: DrugCalc uses salt form A and sustained-action options for quinidine gluconate.) This dose would be started immediately.

Example 2 SL is a 71-year-old, 82-kg (5 ft 10 in) male with atrial fibrillation who requires therapy with oral quinidine. He has liver cirrhosis (Child-Pugh score = 12, bilirubin = 3.2 mg/dL, albumin = 2.5 g/dL) and normal cardiac function. He began quinidine sulfate extended-release tablets 600 mg every 12 hours at 0700 H. On the second day of therapy before the morning dose is administered, the quinidine serum concentration equals 4.5 μg/mL at 0700 H. Compute a quinidine sulfate dose that will provide a steady-state concentration of 4 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 600 mg of quinidine sulfate is equivalent to 500 mg of quinidine base (500-mg quinidine base = 600-mg quinidine sulfate · 0.83).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 161 L, a half-life equal to 21.4 hours, and a clearance equal to 5.24 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 300 mg of quinidine sulfate extended-release tablets every 12 hours will produce a steady-state trough concentration of 4.1 μg/mL. (Note: DrugCalc uses salt form B and sustained-action options for quinidine sulfate extended-release tablets.) This dose would be started immediately.

Example 3 TR is a 75-year-old, 85-kg (5 ft 8 in) male with atrial flutter who requires therapy with quinidine sulfate immediate-release tablets. He has moderate heart failure (NYHA CHF class III). Yesterday, he was prescribed quinidine sulfate 200 mg four times daily, and received the first two doses at 0800 H and 1200 H. Because he felt that his arrhythmia may have returned, the patient phoned his physician who advised him to increase the dose to 400 mg (1800 H and 2200 H). The quinidine serum concentration equals 4.7 μg/mL at 1000 H, 2 hours after the morning dose (at 0800 H, 400 mg quinidine sulfate). Compute a quinidine sulfate dose that will provide a steady-state trough concentration of 4 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 200 mg of quinidine sulfate is equivalent to 165 mg of quinidine base while 400 mg of quinidine sulfate is equivalent to 330 mg of quinidine base (165-mg quinidine base = 200-mg quinidine sulfate · 0.83, 330-mg quinidine base = 400-mg quinidine sulfate · 0.83).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 126 L, a half-life equal to 11.6 h, and a clearance equal to 7.53 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 300 mg of quinidine sulfate immediate-release tablets every 6 hours will produce a steady-state trough concentration of 4.2 μg/mL. (Note: DrugCalc uses salt form B and oral options for quinidine sulfate immediate-release tablets.) This dose would be started immediately.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 9-5.

CONVERSION OF QUINIDINE DOSES FROM ONE SALT FORM TO ANOTHER

Occasionally there is a need to convert a patient stabilized on quinidine therapy from one salt form to an equivalent amount of quinidine base using another salt form. In general, oral quinidine dosage forms, including most sustained-release tablets, have a bioavailability equal to 0.7. Assuming that equal quinidine serum concentrations are desired, this makes conversion between the two salt forms simple since equivalent doses of drug are prescribed: $D_{new} = (D_{old} \cdot S_{old}) / S_{new}$, where D_{new} is the equivalent quinidine base dose for the new quinidine salt dosage form in mg/d, D_{old} is the dose of oral quinidine salt old dosage form in mg/d, and S_{old} and S_{new} are the fraction of the old and new quinidine salt dosage forms that is active quinidine.

TABLE 9-5 Dosing Strategies

DOSING APPROACH/PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concepts	Literature-based recommended dosing	Linear pharmacokinetics method
Computerized	Bayesian computer programs	Bayesian computer programs

Example 1 JH is currently receiving oral extended-release quinidine sulfate 600 mg every 12 hours. She is responding well to therapy, has no adverse drug effects, and has a steady-state quinidine concentration of 4.7 μg/mL. Suggest an equivalent dose of extended-release quinidine gluconate given every 8 hours for this patient.

1. *Calculate equivalent oral dose of quinidine.*

The patient is currently receiving 600 mg every 12 hours or 1200 mg/d (600 mg/dose · 2 doses/d = 1200 mg/d) of quinidine sulfate. The equivalent quinidine gluconate dose would be: $D_{new} = (D_{old} \cdot S_{old}) / S_{new} = (1200 \text{ mg/d} \cdot 0.83) / 0.62 = 1606$ mg/d, rounded to 1620 mg/d of quinidine gluconate, or 648 mg at 0700 H, 324 mg at 1500 H, and 648 mg at 2300 H.

Example 2 LK is currently receiving oral extended-release quinidine gluconate 648 mg every 12 hours. He is responding well to therapy, has no adverse drug effects, and has a steady-state quinidine concentration of 3.3 μg/mL. Suggest an equivalent dose of immediate-release oral quinidine sulfate for this patient.

1. *Calculate equivalent oral dose of quinidine.*

The patient is currently receiving 648 mg every 12 hours or 1296 mg/d (648 mg/dose · 2 doses/d = 1296 mg/d) of quinidine gluconate. The equivalent quinidine sulfate dose would be: $D_{new} = (D_{old} \cdot S_{old}) / S_{new} = (1296 \text{ mg/d} \cdot 0.62) / 0.83 = 968$ mg/d, rounded to 800 mg/d of quinidine sulfate, or 200 mg every 6 hours.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current antiarrhythmic and other drug therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with quinidine exists.

1. VC is a 67-year-old, 72-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with oral quinidine. He has normal liver function and does not have heart failure. Suggest an initial extended-release quinidine gluconate dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.
2. Patient VC (please see problem 1) was prescribed oral quinidine gluconate 648 mg every 12 hours. The current steady-state quinidine concentration equals 2.5 μg/mL. Compute a new quinidine gluconate dose that will provide a steady-state concentration of 4 μg/mL.
3. EM is a 56-year-old, 81-kg (5 ft 9 in) male with ventricular tachycardia who requires therapy with oral quinidine. He has liver cirrhosis (Child-Pugh score = 10) and does not have heart failure. Suggest an initial quinidine gluconate extended-release tablet dosage regimen designed to achieve a steady-state quinidine concentration equal to 2 μg/mL.
4. Patient EM (please see problem 3) was prescribed oral quinidine gluconate extended-release tablets 648 mg every 8 hours. The current steady-state quinidine concentration equals 5.1 μg/mL, and the patient is experiencing symptoms that could be adverse

effects related to quinidine therapy. Compute a new quinidine gluconate dose that will provide a steady-state concentration of 3 μg/mL.

5. OF is a 71-year-old, 60-kg (5 ft 2 in) female with paroxysmal atrial tachycardia who requires therapy with oral quinidine. She has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial quinidine sulfate extended-release dosage regimen designed to achieve a steady-state quinidine concentration equal to 4 μg/mL.

6. Patient OF (please see problem 5) was prescribed quinidine sulfate extended-release tablets 600 mg orally every 12 hours. A steady-state quinidine serum concentration was obtained and equaled 6.7 μg/mL. Compute a new quinidine sulfate dose that will provide a steady-state concentration of 4 μg/mL.

7. FK is a 67-year-old, 130-kg (5 ft 11 in) male with ventricular tachycardia who requires therapy with oral quinidine. He has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial quinidine sulfate immediate-release dosage regimen designed to achieve a steady-state quinidine concentration equal to 3 μg/mL.

8. Patient FK (please see problem 7) was prescribed oral quinidine. Immediate-release quinidine sulfate tablets 300 mg every 8 hours were prescribed starting at 0700 H. A quinidine serum concentration was obtained just before the third dose at 2300 H and equaled 1.7 μg/mL. Compute a new dose that will provide a steady-state concentration of 4 μg/mL.

9. CV is a 69-year-old, 90-kg (6 ft 1 in) male with ventricular tachycardia who requires therapy with quinidine. He has liver cirrhosis (Child-Pugh score = 11, total bilirubin = 2.7 mg/dL, albumin = 2.1 g/dL) and moderate heart failure (NYHA CHF class III). At 0200 H, he received 500 mg of intravenous quinidine gluconate over 2 hours as a loading dose. At 0800 H, quinidine gluconate 648 mg orally every 12 hours was started. A quinidine serum concentration was measured before the third dose at 0800 H the next day and equaled 5.4 μg/mL. Suggest an oral quinidine gluconate dosage regimen that would achieve a steady-state trough concentration equal to 4 μg/mL.

10. FP is a 59-year-old, 90-kg (5 ft 4 in) female with atrial fibrillation who requires therapy with oral quinidine. She has liver cirrhosis (Child-Pugh score = 9) and has mild heart failure (NYHA CHF class II). She received 600 mg of quinidine sulfate sustained-release every 12 hours at 0600 H and 1800 H for 9 doses. Because the patient was experiencing anorexia, nausea, vomiting, and at 40% widening of the ORS complex, the quinidine doses were held after the ninth dose. A quinidine serum concentration was measured at 0800 H the next morning and equaled 7.1 μg/mL. Suggest a quinidine sulfate immediate-release tablet dose that would achieve a steady-state trough concentration equal to 4 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial quinidine dose for patient VC would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 7 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 7\ h = 0.099\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: $V = 2.4\ L/kg \cdot 72\ kg = 173\ L$. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: $Cl = kV = 0.099\ h^{-1} \cdot 173\ L = 17.1\ L/h$.

3. *Compute dosage regimen.*

Oral extended-release quinidine gluconate tablets will be prescribed to this patient ($F = 0.7$, $S = 0.62$). The initial dosage interval (τ) will be set to 8 hours. (Note: $\mu g/mL = mg/L$ and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: $D = (Css \cdot Cl \cdot \tau) / (F \cdot S) = (3\ mg/L \cdot 17.1\ L/h \cdot 8\ h) / (0.7 \cdot 0.62) = 945\ mg$, rounded to 972 mg every 8 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 7\ h = 35\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Literature-Based Recommended Dosing

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine gluconate maintenance dose of 324 mg every 12 hours (684 mg/d) is suggested for a patient without heart failure or liver disease requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 7\ h = 35\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

2. *Solution to problem 2* The revised quinidine dose for patient VC would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 2 days ($5\ t_{1/2} = 5 \cdot 7\ h = 35\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose is 1296 mg/d = 648 mg/d · 2 doses/day.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 2.5\ \mu g/mL)\ 1296\ mg/d$$
$$= 2074\ mg/d, \text{ rounded to } 1944\ mg/d \text{ or } 648\ mg \text{ every } 8 \text{ hours}$$

The new suggested dose would be 648 mg every 8 hours of quinidine gluconate to be started immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the 2 days of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.62 (648 mg/12 h)] / (2.5 mg/L) = 9.37 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (4 mg/L · 9.37 L/h · 8 h) / (0.7 · 0.62) = 691 mg, rounded to 648 mg every 8 hours.

The new quinidine dose would be instituted immediately.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

3. *Solution to problem 3* The initial quinidine dose for patient EM would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 9 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 9\ h = 0.077\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: $V = 3.8\ L/kg \cdot 81\ kg = 308\ L$. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: $Cl = kV = 0.077\ h^{-1} \cdot 308\ L = 23.7\ L/h$.

3. *Compute dosage regimen.*

Oral extended-release quinidine gluconate tablets will be prescribed to this patient ($F = 0.7$, $S = 0.62$). The initial dosage interval (τ) will be set to 8 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: $D = (Css \cdot Cl \cdot \tau) / (F \cdot S) = (2\ mg/L \cdot 23.7\ L/h \cdot 8\ h) / (0.7 \cdot 0.62) = 873\ mg$, rounded to 972 mg every 8 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 9\ h = 45\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Literature-Based Recommended Dosing

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine gluconate maintenance dose of 324 mg every 12 hours (648 mg/d) is suggested for a patient with liver disease requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 9\ h = 45\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

4. *Solution to problem 4* The revised quinidine dose for patient EM would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 2 days ($5\ t_{1/2} = 5 \cdot 9\ h = 45\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose is 1944 mg/d = 648 mg/d · 3 doses/day.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (3\ \mu g/mL / 5.1\ \mu g/mL)\ 1944\ mg/d$$
$$= 1144\ mg/d, \text{ rounded to } 1296\ mg/d \text{ or } 648\ mg \text{ every } 12 \text{ hours}$$

The new suggested dose would be 648 mg every 12 hours of quinidine gluconate to be started in 1–2 half-lives (9–18 hours) to allow time for possible side effects to subside.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the 2 days of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 9 h = 45 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.62 (648 mg/8 h)] / (5.1 mg/L) = 6.89 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (3 mg/L · 6.89 L/h · 12 h) / (0.7 · 0.62) = 572 mg, rounded to 648 mg every 12 hours.

The new suggested dose would be 648 mg every 12 hours of quinidine gluconate to be started in 1–2 half-lives (9–18 hours) to allow time for possible side effects to subside.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the quinidine steady-state concentration could be obtained any time after the 2 days of dosing (5 half-lives = 5 · 9 h = 45 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

5. *Solution to problem 5* The initial quinidine dose for patient OF would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 7 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 7\ h = 0.099\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated quinidine volume of distribution will be based on actual body weight: $V = 1.7\ L/kg \cdot 60\ kg = 102\ L$. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: $Cl = kV = 0.099\ h^{-1} \cdot 102\ L = 10.1\ L/h$.

3. *Compute dosage regimen.*

Oral extended-release quinidine sulfate tablets will be prescribed to this patient ($F = 0.7$, $S = 0.83$). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: $D = (Css \cdot Cl \cdot \tau) / (F \cdot S) = (4\ mg/L \cdot 10.1\ L/h \cdot 12\ h) / (0.7 \cdot 0.83) = 834\ mg$, rounded to 900 mg every 12 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 7\ h = 35\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Literature-Based Recommended Dosing

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine sulfate maintenance dose of 300 mg every 8 hours (900 mg/d) is suggested for a patient with heart failure requiring a quinidine steady-state serum concentration in the upper end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = $5 \cdot 7\ h = 35\ h$). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

6. *Solution to problem 6* The revised quinidine dose for patient OF would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after 2 days ($5\ t_{1/2} = 5 \cdot 7\ h = 35\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration. (Note: Total daily dose is 1200 mg/d = 600 mg/dose · 2 doses/day.)

$$D_{new} = (C_{ss,new} / C_{ss,old})D_{old} = (4\ \mu g/mL / 6.7\ \mu g/mL)\ 1200\ mg/d$$

$$= 716\ mg/d, \text{ rounded to } 600\ mg/d \text{ or } 300\ mg \text{ every } 12 \text{ hours}$$

The new suggested dose would be 300 mg every 12 hours of quinidine sulfate extended-release tablets to be started in 1–2 half-lives (7–14 hours) to allow time for serum concentrations to decline.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the 2 days of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 7 h = 35 h) of therapy.

Quinidine clearance can be computed using a steady-state quinidine concentration: Cl = [F · S (D/τ)] / Css = [0.7 · 0.83 (600 mg/12 h)] / (6.7 mg/L) = 4.34 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute quinidine dose.*

Quinidine clearance is used to compute the new dose: D = (Css · Cl · τ) / (F · S) = (4 mg/L · 4.34 L/h · 12 h) / (0.7 · 0.83) = 359 mg, rounded to 300 mg every 12 hours.

The new suggested dose would be 300 mg every 12 hours of quinidine sulfate extended-release tablets to be started in 1–2 half-lives (7–14 hours) to allow time for possible side effects to subside.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the 2 days of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

7. *Solution to problem 7* The initial quinidine dose for patient FK would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected quinidine half-life ($t_{1/2}$) is 7 hours. The elimination rate constant is computed using the following formula: $k = 0.693 / t_{1/2} = 0.693 / 7\ h = 0.099\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is obese (>30% over ideal body weight), so the estimated quinidine volume of distribution will be based on ideal body weight: IBW_{male} (in kg) = 50 kg + 2.3 (Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg, V = 1.7 L/kg · 75 kg = 128 L. Estimated quinidine clearance is computed by taking the product of V and the elimination rate constant: $Cl = kV = 0.099\ h^{-1} \cdot 128\ L = 12.7\ L/h$.

3. *Compute dosage regimen.*

Oral immediate-release quinidine sulfate tablets will be prescribed to this patient (F = 0.7, S = 0.83). The initial dosage interval (τ) will be set to 6 hours. (Note: μg/mL= mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral quinidine is: $D = (Css \cdot Cl \cdot \tau) / (F \cdot S) = (3\ mg/L \cdot 12.7\ L/h \cdot 6\ h) / (0.7 \cdot 0.83) = 393\ mg$, rounded to 400 mg every 6 hours.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

Literature-Based Recommended Dosing

1. *Choose quinidine dose based on disease states and conditions present in the patient.*

A quinidine sulfate maintenance dose of 100 mg every 6 hours (400 mg/d) is suggested for a patient with heart failure requiring a quinidine steady-state serum concentration in the lower end of the therapeutic range.

A steady-state quinidine serum concentration could be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 7 hours, the quinidine steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 7 h = 35 h). Quinidine serum concentrations should also be measured if the patient experiences a return of their arrhythmia, or if the patient develops potential signs or symptoms of quinidine toxicity.

8. *Solution to problem 8* The revised quinidine dose for patient FK would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 300-mg dose of quinidine sulfate is equivalent to 250 mg of quinidine base (250-mg quinidine base = 300-mg quinidine sulfate · 0.83).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 171 L, a half-life equal to 16.1 hours, and a clearance equal to 7.36 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 300 mg of quinidine sulfate immediate-release tablets every 6 hours will produce a steady-state trough concentration of 4.7 μg/mL. (Note: DrugCalc uses salt form B and oral options for quinidine sulfate immediate-release tablets.) This dose would be started immediately.

9. *Solution to problem 9* The revised quinidine dose for patient CV would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 500-mg dose of quinidine gluconate is equivalent to 300 mg of quinidine base while a 648-mg dose of quinidine gluconate is equal to 400 mg of quinidine base (300-mg quinidine base = 500-mg quinidine gluconate · 0.62, 400-mg quinidine base = 648-mg quinidine gluconate · 0.62).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 130 L, a half-life equal to 23.6 hours, and a clearance equal to 3.83 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 324 mg of quinidine gluconate extended-release tablets every 12 hours will produce a steady-state trough concentration of 4.2 μg/mL. (Note: DrugCalc uses salt form B and sustained-release options for quinidine gluconate extended-release tablets.) This dose could be held for 1 half-life (1 day) if adverse drug effects were occurring or started immediately.

10. *Solution to problem 10* The revised quinidine dose for patient FP would be calculated as follows:

Bayesian Pharmacokinetic Computer Program Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. The DrugCalc program requires quinidine salt doses be input in terms of quinidine base. A 600-mg dose of quinidine sulfate is equivalent to 500 mg of quinidine base (500-mg quinidine base = 600-mg quinidine sulfate · 0.83).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 238 L, a half-life equal to 51.3 hours, and a clearance equal to 3.21 L/h.

3. *Compute dose required to achieve desired quinidine serum concentrations.*

The oral one-compartment model equation used by the program to compute doses indicates that 200 mg of quinidine sulfate immediate-release tablets every 12 hours will produce a steady-state trough concentration of 3.6 μg/mL. (Note: DrugCalc uses salt form B and oral options for quinidine sulfate immediate-release tablets.) This dose could be held for 1 half-life (2 days) if adverse drug effects continued to occur or started immediately.

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Part IV

ANTICONVULSANTS

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10

PHENYTOIN

INTRODUCTION

Phenytoin is a hydantoin compound related to the barbiturates that are used for the treatment of seizures. It is an effective anticonvulsant for the chronic treatment of tonic-clonic (grand mal) or partial seizures and the acute treatment of generalized status epilepticus (Table 10-1).[1,2] After generalized status epilepticus has been controlled with intravenous benzodiazepine therapy and supportive measures have been instituted, phenytoin therapy is usually immediately instituted with the administration of intravenous phenytoin or fosphenytoin. Orally administered phenytoin is used chronically to provide prophylaxis against tonic-clonic or partial seizures. Phenytoin is a type 1B antiarrhythmic and is also used in the treatment of trigeminal neuralgia.

The antiseizure activity of phenytoin is related to its ability to inhibit the repetitive firing of action potentials caused by prolonged depolarization of neurons.[3,4] Additionally, phenytoin stops the spread of abnormal discharges from epileptic foci thereby decreasing the spread of seizure activity throughout the brain. Posttetanic potentiation at synaptic junctions are blocked which alters synaptic transmission. At the cellular level, the mechanism of action for phenytoin appears related to its ability to prolong the inactivation of voltage-activated sodium ion channels and reduction of the ability of neurons to fire at high frequencies.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The usual therapeutic range for total (unbound + bound) phenytoin serum concentrations when the drug is used in the treatment of seizures is 10–20 μ/mL. Since phenytoin is highly bound (~90%) to albumin, it is prone to plasma protein binding displacement due to a large variety of factors. Because of this, unbound or "free" phenytoin concentrations are widely available. Although there is clinical data to support the therapeutic range for total phenytoin concentrations, the suggested therapeutic range for unbound phenytoin

TABLE 10-1 International Classification of Epileptic Seizures with Treatment Recommendations

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	*Drugs of choice* Carbamazepine Phenytoin Lamotrigine Oxcarbazepine *Alternatives* Valproic acid Gabapentin Topiramate Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)	*Drugs of choice* Ethosuximide Valproic acid *Alternatives* Lamotrigine Clonazepam Zonisamide Levetiracetam
	2. Tonic-clonic seizures (also known as grand mal seizures)	*Drugs of choice* Valproic acid Phenytoin Carbamazepine *Alternatives* Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

concentrations is based on the usual unbound fraction (10%) of phenytoin in individuals with normal plasma protein binding. Thus, the generally accepted therapeutic range for unbound phenytoin concentrations is 1–2 μg/mL, which is simply 10% of the lower and upper bounds for the total concentration range, respectively.

In the upper end of the therapeutic range (>15 μg/mL) some patients will experience minor central nervous system depression side effects such as drowsiness or fatigue.[3,4] At total phenytoin concentrations above 20 μg/mL, nystagmus may occur and can be especially prominent upon lateral gaze. When total concentrations exceed 30 μg/mL, ataxia, slurred speech, and/or incoordination similar to ethanol intoxication can be observed. If total phenytoin concentrations are above 40 μg/mL, mental status changes, including decreased mentation, severe confusion or lethargy, and coma are possible. Drug-induced seizure activity has been observed at concentrations over 50–60 μg/mL. Because phenytoin follows nonlinear or saturable metabolism pharmacokinetics, it is possible to attain excessive drug concentrations much easier than for other compounds that follow linear pharmacokinetics. Clinicians should understand that all patients with "toxic" phenytoin serum concentrations in the listed ranges will not exhibit signs or symptoms of phenytoin toxicity. Rather, phenytoin concentrations in the ranges given increase the likelihood that an adverse drug effect will occur.

CLINICAL USEFULNESS OF UNBOUND PHENYTOIN CONCENTRATIONS

Unbound phenytoin concentrations are an extremely useful monitoring tool when used correctly. The relationship between total concentration (C), unbound or "free" concentration (C_f), and unbound or "free" fraction (f_B) is $C_f = f_B C$. For routine therapeutic drug monitoring purposes, total phenytoin serum concentrations are still the mainstream way to gauge therapy with the anticonvulsant. In most patients without known or identifiable plasma protein binding abnormalities, the unbound fraction of phenytoin will be normal (~10%) and unbound drug concentration measurement is unnecessary. At present, unbound drug concentrations are 50–100% more expensive than total concentrations, take longer to conduct by the laboratory and have results returned to clinicians, and are not available at all laboratories. Generally, unbound phenytoin serum concentration monitoring should be restricted to those patients with known reasons to have altered drug plasma protein binding. Exceptions to this approach are patients with an augmented or excessive pharmacologic response compared to their total phenytoin concentration. For example, if a patient has a satisfactory anticonvulsant response to a low total phenytoin concentration, one possible reason would be abnormal plasma protein binding ($f_B = 20\%$) for some unidentified reason, so that even though the total concentration was low (5 μg/mL), a therapeutic unbound concentration was present in the patient ($C_f = f_B C = 0.2 \cdot 5$ μg/mL = 1 μg/mL). Conversely, if a patient has a possible phenytoin-related adverse drug reaction and the total phenytoin concentration is within the therapeutic range, a possible reason could be abnormal protein binding (20%) for an unidentified reason, so that even though the total concentration appeared to be appropriate (15 μg/mL), a toxic unbound concentration was present in the patient ($C_f = f_B C = 0.2 \cdot 15$ μg/mL = 3 μg/mL).

Unbound phenytoin serum concentrations should be measured in patients with factors known to alter phenytoin plasma protein binding. These factors fall into three broad categories:

TABLE 10-2 Disease States and Conditions that Alter Phenytoin Plasma Protein Binding

INSUFFICIENT ALBUMIN CONCENTRATION (HYPOALBUMINEMIA)	DISPLACEMENT BY ENDOGENOUS COMPOUNDS	DISPLACEMENT BY EXOGENOUS COMPOUNDS
Liver disease	Hyperbilirubinemia	Drug interactions
Nephrotic syndrome	Jaundice	Warfarin
Pregnancy	Liver disease	Valproic acid
Cystic fibrosis	Renal dysfunction	Aspirin (>2 g/d)
Burns		NSAIDs with high albumin binding
Trauma		
Malnourishment		
Elderly		

(1) lack of binding protein where there are insufficient plasma concentrations of albumin, (2) displacement of phenytoin from albumin binding sites by endogenous compounds, and (3) displacement of phenytoin from albumin binding sites by exogenous compounds (Table 10-2).[5–23] When multiple factors that decrease phenytoin plasma protein binding are present in a patient, the free fraction can be as high as 30–40%.[24]

Low albumin concentrations, known as hypoalbuminemia, can be found in patients with liver disease or the nephrotic syndrome, pregnant women, cystic fibrosis patients, burn patients, trauma patients, malnourished individuals, and the elderly. Albumin concentrations below 3 g/dL are associated with high phenytoin unbound fractions in the plasma. Patients with albumin concentrations between 2.5–3 g/dL typically have phenytoin unbound fractions of 15–20%, while patients with albumin concentrations between 2.0–2.5 g/dL often have unbound phenytoin fractions >20%. Albumin is manufactured by the liver so patients with hepatic disease may have difficulty synthesizing the protein. Patients with nephrotic syndrome waste albumin by eliminating it in the urine. Malnourished patients can be so nutritionally deprived that albumin production is impeded. Malnourishment is the reason for hypoalbuminemia in some elderly patients, although there is a general downtrend in albumin concentrations in older patients. While recovering from their injuries, burn and trauma patients can become hypermetabolic and albumin concentrations decrease if enough calories are not supplied during this phase of their disease state. Albumin concentrations may decline during pregnancy as maternal reserves are shifted to the developing fetus and are especially prevalent during the third trimester.

Displacement of phenytoin from plasma protein binding sites by endogenous substances can occur in patients with hepatic or renal dysfunction. The mechanism is competition for albumin plasma protein binding sites between the exogenous substances and phenytoin. Bilirubin (a byproduct of heme metabolism) is broken down by the liver, so patients with hepatic disease can have excessive bilirubin concentrations. Total bilirubin concentrations in excess of 2 mg/dL are associated with abnormal phenytoin plasma protein binding. End-stage renal disease patients (creatinine clearance <10–15 mL/min) with uremia (blood urea nitrogen concentrations >80–100 mg/dL) accumulate unidentified compound(s) in their blood that displace phenytoin from plasma protein binding sites. Abnormal phenytoin binding persists in these patients even when dialysis procedures are instituted.

Phenytoin plasma protein binding displacement can also occur due to exogenously administered compounds such as drugs. In this case, the mechanism is competition for albumin binding sites between phenytoin and other agents. Other drugs that are highly bound to albumin and cause plasma protein binding displacement drug interactions with phenytoin include warfarin, valproic acid, aspirin (>2 g/d), and some highly bound nonsteroidal antiinflammatory agents.

Once the free fraction (f_B) has been determined for a patient with altered phenytoin plasma protein binding ($f_B = C_f/C$, where C is the total concentration and C_f is the unbound concentration), it is often not necessary to obtain additional unbound drug concentrations. If the situations that caused altered plasma protein binding are stable (albumin or bilirubin concentration, hepatic or renal function, other drug doses, etc.), total phenytoin concentrations can be converted to concurrent unbound values and used for therapeutic drug monitoring purposes. For example, an end-stage renal failure patient is receiving phenytoin therapy as well as valproic acid and warfarin. The concurrently measured total and unbound phenytoin concentrations are 5 μg/mL and 1.5 μg/mL, respectively, yielding an unbound fraction of 30% [$f_B = C_f/C = (1.5\ \mu g/mL / 5\ \mu g/mL) = 0.30$]. The next day, a total phenytoin concentration is measured and equals 6 μg/mL. The estimated unbound concentration using this information would be 1.8 μg/mL: $C_f = f_B C = 0.30 \cdot 6\ \mu g/mL = 1.8\ \mu g/mL$. Of course, if the disease state status or drug therapy changes, a new unbound phenytoin fraction will be present and need to be remeasured using an unbound/total phenytoin concentration pair.

When unbound phenytoin concentrations are unavailable, several methods have been suggested to estimate the value or a surrogate measure of the value. The most common surrogate is an estimation of the equivalent total phenytoin concentration that would provide the same unbound phenytoin concentration if the patient had a normal unbound fraction value of 10%. These calculations "normalize" the total phenytoin concentration so that it can be compared to the usual phenytoin therapeutic range of 10–20 μg/mL and used for dosage adjustment purposes. The equation for hypoalbuminemia is: $C_{\text{Normal Binding}} = C/(X \cdot \text{Alb} + 0.1)$, where $C_{\text{Normal Binding}}$ is the normalized total phenytoin concentration in μg/mL, C is the actual measured phenytoin concentration in μg/mL, X is a constant equal to 0.2 if protein binding measurements were conducted at 37°C or 0.25 if conducted at 25°C, and Alb is the albumin concentration in g/dL.[25,26] If the patient has end-stage renal disease (creatinine clearance <10–15 mL/min), the same equation is used with a different constant value (X = 0.1).[25] [Note: In most experimental laboratories protein binding is determined at normal body temperature (37°C), in most clinical laboratories protein binding is determined at room temperature (25°C)]. Because these methods assume that the normal unbound fraction of phenytoin is 10%, the estimated unbound phenytoin concentration ($C_{f_{EST}}$) is computed using the following formula: $(C_{f_{EST}}) = 0.1\ C_{\text{Normal Binding}}$. A different approach is taken by the equations used for patients with concurrent valproic acid administration. In this case, the unbound phenytoin concentration ($C_{f_{EST}}$) is estimated using simultaneously measured total phenytoin (PHT in μg/mL) and valproic acid (VPA in μg/mL) concentrations: $C_{f_{EST}} = (0.095 + 0.001 \cdot \text{VPA})\text{PHT}$.[27,28] This value is compared to the usual therapeutic range for unbound phenytoin concentrations (1–2 μg/mL) and used for dosage adjustment purposes. It should be noted that these equations only provide estimates of their respective concentrations, and actual unbound phenytoin concentrations should be measured whenever possible in patients with suspected abnormal phenytoin plasma protein binding.

Example 1 JM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His total phenytoin concentration is 7.5 μg/mL. Assuming that any unbound concentrations performed by the clinical laboratory will be conducted at 25°C, compute an estimated normalized phenytoin concentration for this patient.

1. *Choose appropriate equation to estimate normalized total phenytoin concentration at the appropriate temperature.*

$$C_{\text{Normal Binding}} = C/(0.25 \cdot \text{Alb} + 0.1) = (7.5\ \mu\text{g/mL}) / (0.25 \cdot 2.2\ \text{g/dL} + 0.1) = 11.5\ \mu\text{g/mL}$$

$$C_{f_{EST}} = 0.1\ C_{\text{Normal Binding}} = 0.1 \cdot 11.5\ \mu\text{g/mL} = 1.2\ \mu\text{g/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 11.5 μg/mL for a patient with normal drug protein binding ($C_{f_{EST}}$ = 1.2 μg/mL). Because the estimated total value is within the therapeutic range of 10–20 μg/mL, it is likely that the patient has an unbound phenytoin concentration within the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

Example 2 LM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and poor renal function (creatinine clearance = 10 mL/min). His total phenytoin concentration is 7.5 μg/mL. Compute an estimated normalized phenytoin concentration for this patient.

1. *Choose appropriate equation to estimate normalized total phenytoin concentration.*

$$C_{\text{Normal Binding}} = C/(0.1 \cdot \text{Alb} + 0.1) = (7.5\ \mu\text{g/mL}) / (0.1 \cdot 2.2\ \text{g/dL} + 0.1) = 23.4\ \mu\text{g/mL}$$

$$C_{f_{EST}} = 0.1\ C_{\text{Normal Binding}} = 0.1 \cdot 23.4\ \mu\text{g/mL} = 2.3\ \mu\text{g/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 23.4 μg/mL for a patient with normal drug protein binding ($C_{f_{EST}}$ = 2.3 μg/mL). Because the estimated total value is above the therapeutic range of 10–20 μg/mL, it is likely that the patient has an unbound phenytoin concentration above the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

Example 3 PM is an epileptic patient being treated with phenytoin and valproic acid. He has a normal albumin concentration (albumin = 4.2 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His steady-state total phenytoin and valproic acid concentrations are 7.5 μg/mL and 100 μg/mL, respectively. Compute an estimated unbound phenytoin concentration for this patient.

1. *Choose appropriate equation to estimate unbound phenytoin concentration.*

$$C_{f_{EST}} = (0.095 + 0.001 \cdot \text{VPA})\text{PHT} = (0.095 + 0.001 \cdot 100\ \mu\text{g/mL})7.5\ \mu\text{g/mL} = 1.5\ \mu\text{g/mL}$$

This patient's estimated unbound phenytoin concentration is expected to be within the therapeutic range for unbound concentrations. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects.[3] While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (drowsiness, fatigue, nystagmus, ataxia, slurred speech, incoordination, mental status changes, decreased mentation, confusion, lethargy, coma) as well as adverse reactions associate with long-term use (behavioral changes, cerebellar syndrome, connective tissue changes, coarse facies, skin thickening, folate deficiency, gingival hyperplasia, lymphadenopathy, hirsutism, osteomalacia). Idiosyncratic side effects include skin rash, Stevens-Johnson syndrome, bone marrow suppression, systemic lupus-like reactions, and hepatitis.

Phenytoin serum concentrations should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Phenytoin serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum. Because phenytoin follows nonlinear or saturable pharmacokinetics, it is fairly easy to attain toxic concentrations with modest changes in drug dose.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Phenytoin is primarily eliminated by hepatic metabolism (>95%). Hepatic metabolism is mainly via the CYP2C9 enzyme system with a smaller amount metabolized by CYP2C19. About 5% of a phenytoin dose is recovered in the urine as unchanged drug. Phenytoin follows Michaelis-Menten or saturable pharmacokinetics.[29,30] This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug. When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase (Figure 10-1). In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems: rate of metabolism = $(V_{max} \cdot C) / (K_m + C)$, where V_{max} is the maximum rate of metabolism in mg/d, C is the phenytoin concentration in mg/L, K_m is the substrate concentration in mg/L, and where the rate of metabolism = $V_{max}/2$.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of phenytoin is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent. As the dose or concentration of phenytoin increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions: $Cl = V_{max} / (K_m + C)$. This is the reason concentrations increase disproportionately after a phenytoin dosage increase. For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of V_{max} = 500 mg/d and K_m = 4 mg/L. The therapeutic range of phenytoin is 10–20 µg/mL. As the steady-state concentration of phenytoin increases from 10 µg/mL to 20 µg/mL, clearance decreases from 36 L/d to 21 L/d: $Cl = V_{max}/(K_m + C)$; Cl = (500 mg/d) / (4 mg/L + 10 mg/L) = 36 L/d; Cl = (500 mg/d) / (4 mg/L

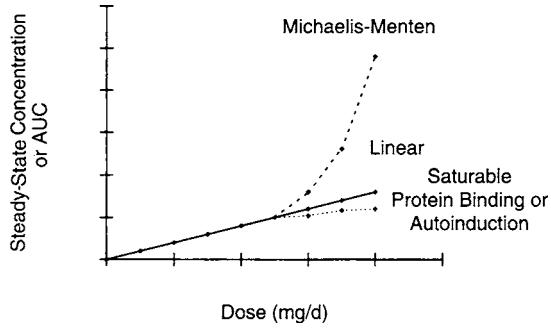

FIGURE 10-1 If a drug follows linear pharmacokinetics, Css or AUC increases proportionally with dose resulting in a straight line on the plot. Nonlinear pharmacokinetics occurs when the Css or AUC versus dose plot results in something other than a straight line. If a drug follows Michaelis-Menten pharmacokinetics (e.g., phenytoin, aspirin), as steady-state drug concentrations approach K_m serum concentrations increase more than expected due to dose increases. If a drug follows nonlinear protein binding (e.g., valproic acid, disopyramide), total steady-state drug concentrations increase less than expected as dose increases.

+ 20 mg/L) = 21 L/d. (Note: µg/mL = mg/L and this substitution was directly made to avoid unnecessary unit conversion.) Unfortunately, there is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for phenytoin (typically V_{max} = 100–1000 mg/d and K_m = 1–15 µg/mL) that dosing the drug is extremely difficult.

Phenytoin volume of distribution (V = 0.7 L/kg) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T): $V = V_B + (f_B/f_T)V_T$. Also, half-life ($t_{1/2}$) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t_{1/2} = (0.693 \cdot V)/Cl$. However, since clearance is dose- or concentration-dependent, half-life also changes with phenytoin dosage or concentration changes. As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug: $\uparrow t_{1/2} = (0.693 \cdot V) / \downarrow Cl$. Using the above example for clearance and the volume of distribution for a 70-kg person (V = 0.7 L/kg · 70 kg ≈ 50 L), half-life changes from 1 d ($t_{1/2}$ = [0.693 · V] / Cl = [0.693 · 50 L] / 36 L/d = 1 d) to 1.7 d ($t_{1/2}$ = [0.693 · 50 L] / 21 L/d = 1.7 d) as phenytoin serum concentrations increase from 10 µg/mL to 20 µg/mL. The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is longer as the dose or concentration is increased for phenytoin. On average, the time to steady-state serum concentrations is approximately 5 days at a dosage rate of 300 mg/d and 15 days at a dosage rate of 400 mg/d.[29]

Under steady-state conditions the rate of drug administration equals the rate of drug removal.[31] Therefore, the Michaelis-Menten equation can be used to compute the maintenance dose (MD in mg/d) required to achieve a target steady-state phenytoin serum concentration (Css in µg/mL or mg/L):

$$MD = \frac{V_{max} \cdot Css}{K_m + Css}$$

Or, solved for Css:

$$Css = \frac{K_m \cdot MD}{V_{max} - MD}$$

When phenytoin steady-state concentrations are far below the K_m value for a patient, this equation simplifies to: $MD = (V_{max}/K_m)Css$ or, since V_{max}/K_m is a constant, $MD = Cl \cdot Css$. Therefore, when $K_m >> Css$, phenytoin follows linear pharmacokinetics. When phenytoin steady-state concentrations are far above the K_m value for a patient, the rate of metabolism becomes a constant equal to V_{max}. Under these conditions only a fixed amount of phenytoin is metabolized per day because the enzyme system is completely saturated and cannot increase its metabolic capacity. This situation is also known as zero-order pharmacokinetics. First-order pharmacokinetics is another name for linear pharmacokinetics.

For parenteral use, phenytoin is available in two different dosage forms. Phenytoin sodium, the sodium salt of phenytoin, contains 92% phenytoin by weight. Even though it is a salt of phenytoin, the drug is still relatively insoluble in water. To facilitate dissolution, ethanol and propylene glycol are added to the vehicle, and the pH of the solution is adjusted to between 10–12. When given intramuscularly, phenytoin sodium injections are very painful.[32] Some of the drug probably precipitates in the muscle injection site, and this results in prolonged absorption of drug over several days. When given intravenously, injection rates should not exceed 50 mg/min to avoid hypotension. Even at lower infusion rates, profound hypotension can result in patients with unstable blood pressure or shock. Phenytoin sodium injection can be given by slow intravenous push of undiluted drug, or added to normal saline at a concentration of 10 mg/mL or less and infused <50 mg/min. When added to normal saline, the drug should be given as soon as possible after being mixed to avoid precipitation, and a 0.22-μm in-line filter should be used to remove any drug crystals before they reach the patient.

To avoid many of the problems associated with phenytoin sodium injection, a water-soluble phosphate ester prodrug of phenytoin, fosphenytoin, has been developed. Conversion of fosphenytoin to phenytoin is rapid, with a fosphenytoin half-life of approximately 15 minutes. To avoid confusion, fosphenytoin is prescribed in terms of phenytoin sodium equivalents (PE). Thus, 100 mg PE of fosphenytoin is equivalent to 100 mg of phenytoin sodium. Hypotension during intravenous administration fosphenytoin is much less of a problem than with phenytoin sodium. The maximal intravenous infusion rate is 150 mg PE/min. Transient pruritus and paresthesia are associated with this route of administration. Intramuscular absorption is rapid with a peak concentration about 30 minutes after injection, and bioavailability via this route of administration is 100%. However, fosphenytoin is much more expensive than phenytoin sodium injection, and this has limited its widespread use. Because of this, most clinicians have reserved fosphenytoin use to patients requiring intramuscular phenytoin, or to patients with unstable or low blood pressure requiring intravenous phenytoin therapy.

For oral use, capsules contain phenytoin sodium (92% phenytoin, by weight) while tablets and suspension contain phenytoin. Phenytoin sodium capsules are labeled as extended phenytoin sodium capsules or prompt phenytoin capsules. Extended phenytoin capsules release phenytoin slowly from the gastrointestinal tract into the systemic circulation. The extended-release characteristics of this dosage form are due to the slow dissolution

of the drug in gastric juices and not the result of extended-release dosage form technology. Prompt phenytoin sodium capsules are absorbed fairly quickly from the gastrointestinal tract because they contain microcrystalline phenytoin sodium which dissolves quicker in gastric juices. As a result of their sustained-release properties, phenytoin doses given as extended phenytoin sodium capsules can be given every once or twice daily, but prompt phenytoin sodium capsules must be given multiple times daily. Extended phenytoin sodium capsules are available in 30 mg, 100 mg, 200 mg, and 300 mg strengths.

Phenytoin tablets (50 mg, chewable) and suspension (125 mg/5 mL) for oral use are available as the acid form of the drug. Both the tablet and suspension dosage forms are absorbed more rapidly than extended phenytoin sodium capsules, and once daily dosing with these may not be possible in some patients. The suspension is thick, and the drug is difficult to disperse evenly throughout the liquid. If not shaken well before dispensing a dose, the drug can flocculate out into the bottom of the bottle. When this occurs, phenytoin concentrations near the top of the bottle will be less than average, and doses given when the bottle is $^2/_3$ or more full will contain less phenytoin. Conversely, phenytoin concentrations near the bottom of the bottle will be greater than average, and doses given when the bottle is $^1/_3$ or less full will contain more phenytoin. This problem can be avoided to a large extent if the dispensing pharmacist shakes the bottle very well (several minutes) before giving to the patient.

For most drugs, the 8% difference in dose between dosage forms containing phenytoin (suspension and tablets, 100 mg = 100 mg phenytoin) and phenytoin sodium (capsules and injection, 100 mg = 92 mg phenytoin) would be trivial and could easily be ignored. However, because phenytoin follows nonlinear pharmacokinetics, an 8% difference in dose can result in major changes in phenytoin serum concentrations. For example, if a patient is stabilized on a dose of intravenous phenytoin sodium 300 mg/d (300 mg/d phenytoin sodium × 0.92 = 276 mg phenytoin) with a steady-state concentration of 17 μg/mL, switching the patient to phenytoin suspension 300 mg/d could result in steady-state phenytoin concentrations exceeding 20 μg/mL (15–30% increase or more) and result in toxicity. Conversely, if a different patient is stabilized on a dose of phenytoin suspension 300 mg/d with a steady-state concentration of 12 μg/mL, switching the patient to intravenous phenytoin sodium 300 mg/d (300 mg/d phenytoin sodium × 0.92 = 276 mg phenytoin) could result in steady-state phenytoin concentrations below 10 μg/mL (15–30% decrease or more) and result in loss of efficacy. Usually, phenytoin doses are not fine-tuned to the point of directly accounting for the difference in phenytoin content (i.e., 276 mg of phenytoin suspension would not be prescribed for the patient receiving 300 mg of phenytoin sodium injection). Rather, clinicians are aware that when phenytoin dosage forms are changed, phenytoin content may change and anticipate that the drug concentration may increase or decrease because of this. Because of this, most individuals recheck phenytoin serum concentrations after a dosage form change is instituted.

The oral bioavailability of phenytoin is very good for capsule, tablet, and suspension dosage forms and approximates 100%.[33–36] At larger amounts, there is some dose-dependency on absorption characteristics.[37] Single oral doses of 800 mg or more produce longer times for maximal concentrations to occur (T_{max}) and decreased bioavailability. Since larger oral doses also produce a higher incidence of gastrointestinal side effects (primarily nausea and vomiting due to local irritation), it is prudent to break maintenance doses larger than 800 mg/d into multiple doses. If oral phenytoin loading doses are given,

a common total dose is 1000 mg given as 400 mg, 300 mg, and 300 mg separated by 2- to 6-hour time intervals. Enteral feedings given by nasogastric tube interfere with phenytoin absorption.[38–41] Possible mechanisms include decreased gastrointestinal transit time which reduces absorption contact time, binding of phenytoin to proteins contained in the feedings, and adherence of phenytoin to the lumen of the feeding tube. The solution to this problem is to stop the feedings, when possible, for 1–2 hours before and after phenytoin administration, and increase the oral phenytoin dose.[40] It is not unusual for phenytoin oral dosage requirements to double or triple while the patient receives concurrent nasogastric feedings (e.g., usual dose of 300–400 mg/d increasing to 600–1200 mg/d while receiving nasogastric feedings). Of course, intravenous or intramuscular phenytoin or fosphenytoin doses could also be substituted while nasogastric feedings were being administered. Although poorly documented, phenytoin oral malabsorption may also occur in patients with severe diarrhea, malabsorption syndromes, or gastric resection.

The typical recommended loading dose for phenytoin is 15–20 mg/kg resulting in 1000 mg for most adult patients. Usual initial maintenance doses are 5–10 mg/kg/d for children (6 months–16 years old) and 4–6 mg/kg/d for adults. For adults the most prescribed dose is 300–400 mg/d of phenytoin. Because of an increased incidence of adverse effects in older patients (>65 years old), many clinicians prescribe a maximum of 200 mg/d as an initial dose for these individuals.[42,43]

IMPACT OF ALTERED PLASMA PROTEIN BINDING ON PHENYTOIN PHARMACOKINETICS

The pharmacokinetic alterations that occur with altered plasma protein binding result in complex changes for total and unbound steady-state phenytoin concentrations and drug response. As previously discussed (please see Chapter 3), hepatic drug metabolism is described by the following equation:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance. For drugs such as phenytoin with a low hepatic extraction ratio (≤30%), the numeric value of liver blood flow is much greater than the product of unbound fraction of drug in the blood and the intrinsic clearance of the compound ($LBF >> f_B \cdot Cl'_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [$LBF \approx LBF + (f_B \cdot Cl'_{int})$]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF} = f_B \cdot Cl'_{int}$$

In order to illustrate the differences that may occur in steady-state drug concentrations and pharmacologic effects for patients with altered phenytoin plasma protein binding, a graphical technique will be used (Figure 10-2A). The example assumes that phenytoin is

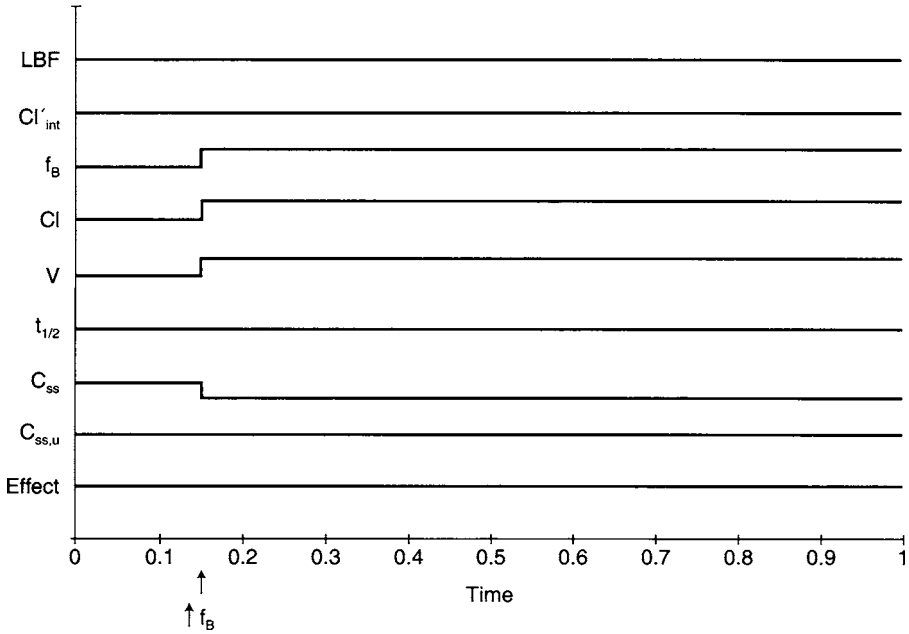

FIGURE 10-2A Schematic representation of physiologic (*LBF* = liver blood flow, Cl'_{int} = intrinsic or unbound clearance, f_B = unbound fraction of drug in blood/plasma), pharmacokinetic (*Cl* = clearance; *V* = volume of distribution; $t_{1/2}$ = half-life; *Css* = total steady-state drug concentration; Css,u = unbound steady-state drug concentration), and pharmacodynamic (Effect = pharmacodynamic effect) changes that occur with decreased protein binding of phenytoin (*arrow* denotes $\uparrow f_B$).

being given to a patient as a continuous intravenous infusion, and that all physiologic, pharmacokinetic, and drug effect parameters (shown on the y-axis) are initially stable. However, the same changes occur for average total and unbound steady-state concentrations when the drug is given on a continuous dosage schedule (every 8 hours, 12 hours, 24 hours, and so on) or orally. On the x-axis, an arrow indicates that phenytoin plasma protein binding decreases and unbound fraction increases in the patient; an assumption made for this illustration is that any changes in the parameters are instantaneous. An increase in the parameter is denoted as an uptick in the line while a decrease in the parameter is shown as a downtick in the line.

For a drug with a low hepatic extraction ratio, plasma protein binding displacement drug interactions cause major pharmacokinetic alterations but are not clinically significant because the pharmacologic effect of the drug does not change (Figure 10-2A). Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent, a decrease in plasma protein binding and increase in unbound fraction will increase clearance ($\uparrow Cl = \uparrow f_B Cl'_{int}$) and volume of distribution [$\uparrow V = V_B + (\uparrow f_B / f_T) V_T$]. Since half-life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change [$t_{1/2} = (0.693 \cdot \uparrow V) / \uparrow Cl$]. However, it is possible that if either clearance or volume of distribution changes disproportionately, half-life will change. The

total steady-state concentration will decline because of the increase in clearance ($\downarrow Css = k_0/\uparrow Cl$, where k_0 is the infusion rate of drug). But, the unbound steady-state concentration will remain unaltered because the free fraction of drug in the blood is higher than it was before the increase in unbound fraction occurred ($Css,u = \uparrow f_B \downarrow Css$). The pharmacologic effect of the drug does not change because the free concentration of drug in the blood is unchanged. This can be an unexpected outcome for the decrease in plasma protein binding, especially because the total steady-state concentration of the drug decreased. Clinicians need to be on the outlook for situations like this because the total drug concentration (bound + unbound) can be misleading and cause an unwarranted increase in drug dosage. Unbound drug concentrations should be used to convince clinicians that a drug dosage increase is not needed even though total concentrations decline as a result of this interaction.

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

Adults without the disease states and conditions given later in this section, with normal liver and renal function as well as normal plasma protein binding (~90%), have an average phenytoin V_{max} of 7 mg/kg/d (range: 1.5–14 mg/kg/d) and K_m of 4 μg/mL (range: 1–15 μg/mL).[30] Michaelis-Menten parameters for younger children (6 months–6 years) are V_{max} = 12 mg/kg/d and K_m = 6 μg/mL while for older children (7–16 years) V_{max} = 9 mg/kg/d and K_m = 6 μg/mL.[44–49] The most difficult and frustrating aspect of phenytoin dosage determination is the 10- to 15-fold variation in Michaelis-Menten pharmacokinetic parameters which creates a huge amount of variability in dose requirements. An individualized dosage regimen for each patient prescribed phenytoin must be determined to accomplish therapeutic goals. Unfortunately, measurement of V_{max} and K_m for phenytoin is very difficult to accomplish for research or clinical purposes. Because of this, the effects of disease states and conditions on these parameters are largely unknown. By necessity, this discussion must be done in qualitative terms for phenytoin.

Patients with liver cirrhosis or acute hepatitis have reduced phenytoin clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of CYP2C9 and CYP2C19 available to metabolize the drug and decreases V_{max}. The volume of distribution is larger because of reduced plasma protein binding. Protein binding is reduced and unbound fraction is increased due to hypoalbuminemia and/or hyperbilirubinemia (especially albumin ≤3 g/dL and/or total bilirubin ≥2 mg/dL). However, the effects that liver disease has on phenytoin pharmacokinetics are highly variable and difficult to accurately predict. It is possible for a patient with liver disease to have relatively normal or grossly abnormal phenytoin clearance and volume of distribution. For example, a liver disease patient who has relatively normal albumin and bilirubin concentrations can have a normal volume of distribution for phenytoin. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 10-3).[50] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal)–3 (severely abnormal; Table 10-3), and the scores for the five areas are summed. The Child-Pugh score for a

TABLE 10-3 Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for phenytoin. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Phenytoin serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Other patients are also prone to hypoalbuminemia, including patients with the nephrotic syndrome, cystic fibrosis patients, and malnourished individuals. Unbound phenytoin concentration monitoring should be considered in these patients especially when albumin concentrations are ≤3 g/dL. High bilirubin concentrations can also be found in patients with biliary tract obstruction or hemolysis. Unbound phenytoin concentration monitoring should be considered in these patients especially when total bilirubin concentrations are ≥2 mg/dL.

Trauma and burn patients have an increased ability to metabolize phenytoin beginning 3–7 days after their initial injury.[51,52] At this time, these patients become hypermetabolic in order to repair damaged tissue, and the V_{max} for phenytoin increases due to this general increase in metabolic rate. If caloric needs are not met during this phase of recovery for trauma patients, many become hypoalbuminemic, and phenytoin plasma protein binding decreases resulting in an increased unbound fraction. Phenytoin dosage requirements are increased while trauma patients are in their hypermetabolic phase, and unbound concentration monitoring is indicated when patients have low albumin concentrations (especially for albumin levels ≤3 g/dL).

Pregnant women taking phenytoin have increased dosage requirements, particularly during the third trimester (>26 weeks).[5,6,53–57] There are several reasons for this change including malabsorption of drug resulting in decreased bioavailability, increased metabolism of phenytoin, and decreased protein binding due to low albumin concentrations. Aggressive drug serum concentration monitoring, including the measurement of unbound phenytoin concentrations if the patient is hypoalbuminemic, is necessary to avoid seizures and subsequent harm to the unborn fetus. An additional concern when administering phenytoin to pregnant patients is the development of fetal hydantoin syndrome by the baby.

Elderly individuals over the age of 65 years have a decreased capacity to metabolize phenytoin, possibly due to age-related losses of liver parenchyma resulting in decreased amounts of CYP2C9 and CYP2C19.[42,43] Older patients also may have hypoalbuminemia with resulting decreases in plasma protein binding and increases in unbound fraction.[22,23] Many elderly patients also seem to have an increased propensity for central nervous system side effects due to phenytoin, and because of these pharmacokinetic and pharmacodynamic changes clinicians tend to prescribe lower initial phenytoin doses for older patients (~200 mg/d).

End-stage renal disease patients with creatinine clearances <10–15 mL/min have an unidentified substance in their blood that displaces phenytoin from its plasma protein binding sites.[15-19,21] This unknown compound is not removed by dialysis.[20] In addition to this, these patients tend to have hypoalbuminemia which increases the unbound fraction of phenytoin even further. Unbound phenytoin serum concentration monitoring is very helpful in determining dosage requirements for renal failure patients. Other patients are also prone to hypoalbuminemia, including patients with the nephrotic syndrome, cystic fibrosis patients, and malnourished individuals. High bilirubin concentrations can also be found in patients with biliary tract obstruction or hemolysis. Unbound phenytoin concentration monitoring should be considered in these patients especially when albumin concentrations are ≤3 g/dL or total bilirubin concentrations are ≥2 mg/dL.

Hemodialysis does not remove enough phenytoin that supplemental postdialysis doses are necessary.[58] The typical sieving coefficient during hemoperfusion for phenytoin is 0.45, so in some cases supplemental phenytoin doses could be needed.[59,60] Because of pharmacokinetic variability, check phenytoin concentrations in patients receiving hemoperfusion.

The ratio between simultaneous breast milk and plasma areas under the curve averaged 0.13.[61] The mean ratio between breast milk and plasma concentration determined at various times during a dosage interval is 0.28.[62]

DRUG INTERACTIONS

Because phenytoin is so highly liver metabolized by CYP2C9 and CYP2C19, it is prone to drug interactions that inhibit hepatic microsomal enzymes.[63] Cimetidine, valproic acid, amiodarone, choramphenicol, isoniazid, disulfiram, and omeprazole have been reported to inhibit phenytoin metabolism and increase phenytoin serum concentrations. Phenytoin is also a broad-based hepatic enzyme inducer affecting most cytochrome P450 systems. Drugs with narrow therapeutic ranges that can have their metabolism increased by concurrent phenytoin administration include carbamazepine, phenobarbital, cyclosporin, tacrolimus, and warfarin. When phenytoin therapy is added to the medication regimen for a patient, a comprehensive review for drug interactions should be conducted. Valproic acid, aspirin (>2 g/d), some highly protein bound nonsteroidal antiinflammatory drugs, and warfarin can displace phenytoin from plasma protein binding sites necessitating monitoring of unbound phenytoin concentrations.

The drug interaction between valproic acid and phenytoin deserves special examination because of its complexity and because these two agents are regularly used together for the treatment of seizures.[7–10] The drug interaction involves the plasma protein binding

displacement and intrinsic clearance inhibition of phenytoin by valproic acid. What makes this interaction so difficult to detect and understand is that these two changes do not occur simultaneously, so the impression left by the drug interaction depends on when in time it is observed in a patient. For example, a patient is stabilized on phenytoin therapy (Figure 10-2B), but because adequate control of seizures has not been attained, valproic acid is added to the regimen. As valproic acid concentrations accumulate, the first interaction observed is phenytoin plasma protein binding as the two drugs compete for binding sites on albumin. The result of this portion of the drug interaction is an increase in phenytoin unbound fraction and a decrease in phenytoin total serum concentration, but the unbound phenytoin serum concentration remains the same. As valproic acid serum concentrations achieve steady-state conditions, the higher concentrations of the drug bathe the hepatic microsomal enzyme system and inhibit the intrinsic clearance of phenytoin. This portion of the interaction decreases intrinsic clearance and hepatic clearance for phenytoin, so both unbound and total phenytoin concentrations increase. When phenytoin concentrations finally equilibrate and reach steady state under the new plasma protein binding and intrinsic clearance conditions imposed by concurrent valproic acid therapy, the total concentration of

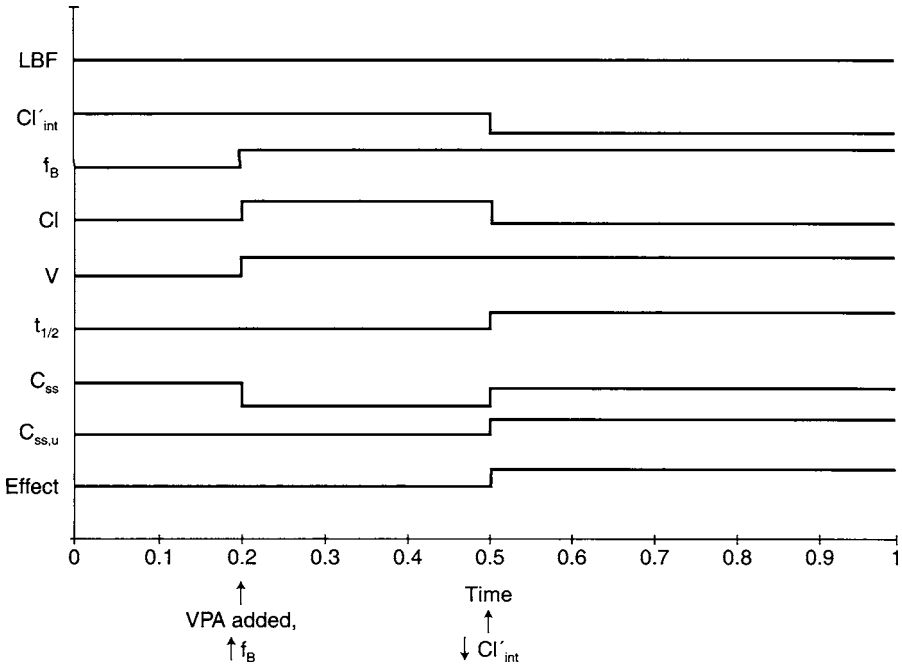

FIGURE 10-2B Schematic representation of the effect of initiating valproic acid *(VPA)* treatment in an individual stabilized on phenytoin therapy (please see Figure 10-2A legend for symbol definition). Initially, valproic acid decreases phenytoin plasma protein binding via competitive displacement for binding sites on albumin (*arrow* denotes $\uparrow f_B$). As valproic acid concentrations increase, the hepatic enzyme inhibition component of the drug interaction comes into play (*arrow* denotes $\downarrow Cl'_{int}$). The net result is total phenytoin concentrations are largely unchanged from baseline, but unbound phenytoin concentrations and pharmacologic effect increase.

phenytoin is often times at about the same level as before the drug interaction occurred, but unbound phenytoin concentrations are much higher. If only total phenytoin concentrations are measured at this point in time, clinicians will be under the impression that total concentrations did not change and no drug interaction occurred. However, if unbound phenytoin concentrations are simultaneously measured, it will be found that these concentrations have risen and that the phenytoin unbound fraction is twice or more (≥20%) of the baseline amount. In this situation, the patient may have unbound phenytoin concentrations that are toxic and a decrease in phenytoin dosage may be in order.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate phenytoin therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. Unfortunately, specific values for Michaelis-Menten pharmacokinetic variables are not known for many disease states and conditions because they are difficult to measure. Even when values are available, there is 10- to 15-fold variation for each parameter. Also, it is computationally intensive. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of phenytoin. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing with phenytoin is to compute the best dose possible for the patient given their set of disease states and conditions that influence phenytoin pharmacokinetics. The optimal way to accomplish this goal is to use average parameters measured in other patients with similar disease state and condition profiles as estimates of pharmacokinetic constants for the patient currently being treated with the drug. Unfortunately, because of the difficulty in computing Michaelis-Menten parameters, accurate estimates of V_{max} and K_m are not available for many important patient populations. Even if average population Michaelis-Menten constants are available, the l0- to 15-fold variation in these parameters means that initial doses derived from these parameters will not be successful in achieving desired goals for all patients. Phenytoin serum concentration monitoring, including unbound concentration measurement if altered plasma protein binding is suspected, is an important component of therapy for this drug. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses computed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

MICHAELIS-MENTEN PARAMETER ESTIMATES

Normal adults with normal liver and renal function as well as normal plasma protein binding have an average phenytoin V_{max} of 7 mg/kg/d and K_m of 4 μg/mL. Michaelis-Menten parameters for younger children (6 months–6 years) are V_{max} = 12 mg/kg/d and K_m = 6 μg/mL

while for older children (7–16 years) V_{max} = 9 mg/kg/d and K_m = 6 μg/mL. These are the only parameters required to estimate a maintenance dose for phenytoin.

VOLUME OF DISTRIBUTION ESTIMATE

The volume of distribution for patients with normal phenytoin plasma protein binding is estimated at 0.7 L/kg for adults. For obese individuals 30% or more above their ideal body weight, the volume of distribution can be estimated using the following equation: V = 0.7 L/kg [IBW + 1.33(TBW − IBW)], where IBW is ideal body weight in kilograms [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) or IBW_{males} (in kg) = 50 + 2.3(Ht − 60)], Ht is height in inches, and TBW is total body weight in kilograms.[64] This parameter is used to estimate the loading dose (LD in milligrams) for phenytoin, if one is indicated: LD = Css · V, where Css is the desired total phenytoin concentration in mg/L. (Note: mg/L = μg/mL and this conversion was directly made to avoid unnecessary unit conversion.) and V is volume of distribution in L. For example, the volume of distribution for a 70-kg, nonobese patient would equal 49 L (V = 0.7 L/kg · 70 kg = 49 L). The loading dose to achieve a total phenytoin concentration of 15 μg/mL is 750 mg [LD = Css · V = 15 mg/L · 49 L = 735 mg, rounded to 750 mg. (Note: mg/L = μg/mL and this conversion was directly made to avoid unnecessary unit conversion.)]. For an obese individual with a total body weight of 150 kg and an ideal body weight of 70 kg, the volume of distribution would equal 123 L: V = 0.7 L/kg [IBW + 1.33 (TBW − IBW)] = 0.7 L/kg [70 kg + 1.33(150 kg − 70 kg)] = 123 L.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by short-term intravenous infusion or orally, phenytoin follows a one-compartment pharmacokinetic model. When oral therapy is required, most clinicians utilize an extended phenytoin capsule dosage form that has good bioavailability (F = 1), supplies a continuous release of phenytoin into the gastrointestinal tract, and provides a smooth phenytoin serum concentration/time curve that emulates an intravenous infusion after once or twice daily dosing. Because of this, the Michaelis-Menten pharmacokinetic equation that computes the average phenytoin steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)}$$

Or, solved for Css:

$$Css = \frac{K_m \cdot (S \cdot MD)}{V_{max} - (S \cdot MD)}$$

where V_{max} is the maximum rate of metabolism in mg/d, S is the fraction of the phenytoin salt form that is active phenytoin (0.92 for phenytoin sodium injection and capsules; 0.92 for fosphenytoin because doses are prescribed as a phenytoin sodium equivalent or PE, 1.0 for phenytoin acid suspensions and tablets), MD is the maintenance dose of the phenytoin salt contained in the dosage form in mg/d, Css is the phenytoin concentration in mg/L (which equals μg/mL), and K_m is the substrate concentration in mg/L (which equals μg/mL) where the rate of metabolism = $V_{max}/2$.

The equation used to calculate loading doses (LD in mg) is based on a simple one-compartment model: LD = (Css · V)/S, where Css is the desired phenytoin steady-state

concentration in μg/mL which is equivalent to mg/L, V is the phenytoin volume of distribution, and S is the fraction of the phenytoin salt form that is active (0.92 for phenytoin sodium injection and capsules; 0.92 for fosphenytoin because doses are prescribed as a phenytoin sodium equivalent or PE, 1.0 for phenytoin acid suspensions and tablets). Intravenous phenytoin sodium doses should be short-term infusions given no greater than 50 mg/min, and intravenous fosphenytoin doses should be short-term infusions given no greater than 150 mg/min PE.

STEADY-STATE CONCENTRATION SELECTION

The generally accepted therapeutic ranges for total and unbound phenytoin concentrations are 10–20 μg/mL and 1–2 μg/mL, respectively, for the treatment seizures. As previously discussed, unbound concentrations represent the portion of phenytoin that is in equilibrium with the central nervous system and should most accurately reflect drug concentration at the site of action. Thus, for patients with altered phenytoin plasma protein binding it is more important to have the unbound concentration within its therapeutic range than the total concentration. To establish that the unbound fraction (f_B) is altered for a patient, phenytoin total and unbound concentrations should be simultaneously measured from the same blood sample: $f_B = C_f/C$, where C is the total phenytoin concentration in μg/mL and C_f is the unbound, or "free," phenytoin concentration in μg/mL. As long as the disease states or conditions that caused altered phenytoin plasma protein binding are stable, a previously measured unbound fraction can be used to convert newly measured total phenytoin concentrations to their unbound equivalent ($C_f = f_B C$). Phenytoin therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate Michaelis-Menten constants according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For a 75-kg patient, V_{max} = 525 mg/d: V_{max} = 7 mg/kg/d · 75 kg = 525 mg/d. For this individual, K_m = 4 mg/L.

2. *Compute dosage regimen.*

Oral extended phenytoin sodium capsules will be prescribed to this patient (F = 1, S = 0.92). The initial dosage interval (τ) will be set to 24 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$\text{MD} = \frac{V_{max} \cdot \text{Css}}{S(K_m + \text{Css})} = \frac{525 \text{ mg/d} \cdot 12 \text{ mg/L}}{0.92(4 \text{ mg/L} + 12 \text{ mg/L})} = 428 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be

measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 2 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate Michaelis-Menten constants according to disease states and conditions present in the patient.*

The V_{max} for a 7- to 16-year-old adolescent patient with normal liver and renal function is 9 mg/kg/d. For a 40-kg patient, V_{max} = 360 mg/d: V_{max} = 9 mg/kg/d · 40 kg = 360 mg/d. For this individual, K_m = 6 mg/L.

2. *Compute dosage regimen.*

Oral phenytoin suspension will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{360 \text{ mg/d} \cdot 12 \text{ mg/L}}{1.0(6 \text{ mg/L} + 12 \text{ mg/L})} = 240 \text{ mg/d, rounded to } 250 \text{ mg/d}$$

Phenytoin suspension 125 mg every 12 hours would be prescribed for the patient. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

To illustrate the differences and similarities between oral and intravenous phenytoin dosage regimen design, the same cases will be used to compute intravenous phenytoin or fosphenytoin loading and maintenance doses.

Example 3 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with intravenous phenytoin sodium. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 mg/mL.

1. *Estimate Michaelis-Menten and volume of distribution constants according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For a 75-kg patient, V_{max} = 525 mg/d: V_{max} = 7 mg/kg/d · 75 kg = 525 mg/d. For this individual, K_m = 4 mg/L. The volume of distribution for this patient would equal 53 L: V = 0.7 L/kg · 75 kg = 53 L.

2. *Compute dosage regimen.*

Intravenous phenytoin sodium will be prescribed to this patient (F = 1, S = 0.92). If a loading dose is needed it would be computed using the following equation:

LD = (V · Css) / S = (53 L · 12 mg/L) / 0.92 = 691 mg, rounded to 700 mg given at a maximal rate of 50 mg/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

For the maintenance dose, the initial dosage interval (τ) will be set to 12 hours. The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{525 \text{ mg/d} \cdot 12 \text{ mg/L}}{0.92(4 \text{ mg/L} + 12 \text{ mg/L})} = 428 \text{ mg/d, rounded to 400 mg/d}$$

The patient would be prescribed 200 mg of phenytoin sodium injection every 12 hours using an infusion rate no greater than 50 mg/min. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 4 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with intravenous fosphenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate Michaelis-Menten and volume of distribution constants according to disease states and conditions present in the patient.*

The V_{max} for a 7- to 16-year-old adolescent patient with normal liver and renal function is 9 mg/kg/d. For a 40-kg patient, V_{max} = 360 mg/d: V_{max} = 9 mg/kg/d · 40 kg = 360 mg/d. For this individual, K_m = 6 mg/L. The volume of distribution for this patient would equal 28 L: V = 0.7 L/kg · 40 kg = 28 L.

2. *Compute dosage regimen.*

Intravenous fosphenytoin will be prescribed, in phenytoin sodium equivalents or PE, to this patient (F = 1, S = 0.92). If a loading dose is needed it would be computed using the following equation: LD = (V · Css) / S = (28 L · 12 mg/L) / 0.92 = 365 mg, rounded to 350 mg given at a maximal rate of 150 mg/min PE. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{360 \text{ mg/d} \cdot 12 \text{ mg/L}}{0.92(6 \text{ mg/L} + 12 \text{ mg/L})} = 261 \text{ mg/d, rounded to 250 mg/d}$$

Intravenous fosphenytoin 125 mg PE every 12 hours given no greater than 150 mg/min PE would be prescribed for the patient. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in phenytoin pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard phenytoin doses for various situations are warranted. The original computation of these doses was based on the pharmacokinetic dosing methods described in the previous section, and subsequently modified based on clinical experience. In general, the expected phenytoin steady-state serum concentrations used to compute these doses was 10–15 μg/mL. Suggested phenytoin maintenance doses are 4–6 mg/kg/d for adults and 5–10 mg/kg/d for children (6 months–16 years old). Phenytoin loading doses are 15–20 mg/kg. For obese individuals (>30% over ideal body weight), adjusted body weight (ABW) should be used to compute loading doses: ABW (in kg) = IBW + 1.33(TBW − IBW), where IBW is ideal body weight in kilograms [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) or IBW_{males} (in kg) = 50 + 2.3(Ht − 60)], Ht is height in inches, and TBW is total body weight in kilograms.[64] Although clearance probably is increased in obese individuals, precise information regarding the best weight factor is lacking for maintenance dose computation, so most clinicians use ideal body weight to calculate this dose. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses prescribed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual. Doses of phenytoin, phenytoin sodium, or fosphenytoin (in PE or phenytoin sodium equivalents) are computed using these dosage rates since dosage amounts will be rounded to clinically acceptable amounts.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for extended phenytoin sodium capsules in an adult patient is 4–6 mg/kg/d. Using a rate of 5 mg/kg/d, the initial dose would be 400 mg/d: 5 mg/kg/d · 75 kg = 375 mg/d, rounded to 400 mg/d. Using a dosage interval of 24 hours, the prescribed dose would be 400 mg of extended phenytoin sodium capsules daily.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 2 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for phenytoin suspension in an adolescent patient is 5–10 mg/kg/d. Using a rate of 6 mg/kg/d, the initial dose would be 250 mg/d: 6 mg/kg/d · 40 kg = 240 mg/d, rounded to 250 mg/d. Using a dosage interval of 12 hours, the prescribed dose would be 125 mg of phenytoin suspension every 12 hours.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

To illustrate the differences and similarities between oral and intravenous phenytoin dosage regimen design, the same cases will be used to compute intravenous phenytoin or fosphenytoin loading and maintenance doses.

Example 3 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with intravenous phenytoin sodium. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for phenytoin sodium injection in an adult patient is 4–6 mg/kg/d. Using a rate of 5 mg/kg/d, the initial dose would be 400 mg/d: 5 mg/kg/d · 75 kg = 375 mg/d, rounded to 400 mg/d. Using a dosage interval of 12 hours, the prescribed dose would be 200 mg of phenytoin sodium injection every 12 hours. If loading dose administration was necessary, the suggested amount is 15–20 mg/kg. Using 15 mg/kg, the suggested loading dose would be 1250 mg of phenytoin sodium injection given no faster than 50 mg/min: 15 mg/kg · 75 kg = 1125 mg, rounded to 1250 mg.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 4 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with intravenous fosphenytoin. He has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for fosphenytoin injection in an adolescent patient is 5–10 mg/kg/d PE. Using a rate of 6 mg/kg/d, the initial dose would be 250 mg/d PE: 6 mg/kg/d · 40 kg = 240 mg/d, rounded to 250 mg/d. Using a dosage interval of 12 hours, the prescribed dose would be 125 mg of fosphenytoin injection every 12 hours. If loading dose administration was necessary, the suggested amount is 15–20 mg/kg PE. Using 15 mg/kg, the suggested loading dose would be 600 mg PE of fosphenytoin injection given no faster than 150 mg/min PE: 15 mg/kg · 40 kg = 600 mg.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

USE OF PHENYTOIN SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce phenytoin serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the Michaelis-Menten pharmacokinetics followed by the drug, the narrow therapeutic index of phenytoin, and the desire to avoid adverse side effects of phenytoin, measurement of phenytoin serum concentrations is conducted for almost all patients to ensure that therapeutic, nontoxic levels are present. In addition to phenytoin serum concentrations, important patient parameters (seizure frequency, potential phenytoin side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When phenytoin serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. A variety of methods are used to estimate new maintenance doses or Michaelis-Menten parameters when one steady-state phenytoin serum concentration is available. Based on typical Michaelis-Menten parameters, it is possible to adjust phenytoin doses with one or more steady-state concentrations using the *empiric dosing method*. This is a widely used technique to adjust doses by experienced clinicians. The *Graves-Cloyd method* allows adjustment of phenytoin doses using one steady-state concentration. Because it uses a power function, it is computationally intensive. The *Vozeh-Sheiner method* utilizes a specialized graph and Bayesian pharmacokinetic concepts to individualize phenytoin doses using a single steady-state concentration. Because of this, a copy of the graph paper with population orbits must be available, and plotting the data is time consuming.

Sometimes, it is useful to compute phenytoin pharmacokinetic constants for a patient and base dosage adjustments on these. If two or more steady-state phenytoin serum concentrations are available from two or more daily dosage rates, it may be possible to calculate and use *pharmacokinetic parameters* to alter the phenytoin dose. Two graphical methods allow the computation of V_{max} and K_m for patients receiving phenytoin, but they are cumbersome and time consuming. The *Mullen method* uses the same specialized graph as the Vozeh-Sheiner method, but computes the patient's own Michaelis-Menten parameters instead of Bayesian pharmacokinetic estimates. The *Ludden method* uses standard graph paper to plot the concentration-time data, and V_{max} and K_m are computed from the intercept and slope of the resulting line.

Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where serum concentrations are obtained at suboptimal times or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (V_{max}, K_m, and V) can be done with

one or more measured concentrations. So that results from the different methods can be compared, the same cases are used to compute adjusted doses for phenytoin.

Single Total Phenytoin Steady-State Serum Concentration Methods

EMPIRIC DOSING METHOD

Based on the knowledge of population Michaelis-Menten pharmacokinetic parameters, it is possible to suggest empiric dosage increases for phenytoin when one steady-state serum concentration is available (Table 10-4).[65] The lower end of the suggested dosage range for each category tends to produce more conservative increases in steady-state concentration while the upper end of the suggested dosage range tends to produce more aggressive increases. These dosage changes are based on outpatients where avoiding adverse drug reactions is paramount. For hospitalized patients or patients requiring aggressive treatment, larger empiric dosage adjustments may be needed. When dosage increases >100 mg/d are recommended, phenytoin concentrations and patient response should be carefully monitored.

Wherever possible, clinicians should avoid using more than one solid dosage form strength (i.e., mixing 30 mg and 100 mg extended phenytoin capsules, etc.) for a patient. An effective way to increase the phenytoin dose for an individual, that requires an increase in dose of 50 mg/d when using the 100 mg extended phenytoin sodium capsule dosage form, is to increase the dose by 100 mg every other day. For example, if a dosage increase of 50 mg/d is desired for an individual receiving 300 mg/d of extended phenytoin sodium capsule, a dosage increase of 300 mg/d alternating with 400 mg/d is possible if the patient is able to comply with a more complex dosage schedule. Dosage aids such as calendars, prefilled dosage cassettes, or memory aiding schemes (400 mg/d on even days, 300 mg/d on odd days) are all useful in different patient situations. Alternate daily dosages are possible because of the extended-release characteristics of extended phenytoin capsules and the long half-life of phenytoin.

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use Table 10-4 to suggest new phenytoin dose.*

TABLE 10-4 Empiric Phenytoin Dosage Increases Based on a Single Total Steady-State Concentration[65]

MEASURED PHENYTOIN TOTAL SERUM CONCENTRATION (μg/mL)	SUGGESTED DOSAGE INCREASE*
<7	100 mg/d or more
7–12	50–100 mg/d
>12	30–50 mg/d

* Higher dosage used if more aggressive therapy desired, lower dosage used if less aggressive therapy desired.

Table 10-4 suggests a dosage increase of ≥100 mg/d for this patient. The dose would be increased to 500 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 2 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the middle of the therapeutic range.

1. *Use Table 10-4 to suggest new phenytoin dose.*

Table 10-4 suggests a dosage increase of 50–100 mg/d for this patient. The dose would be increased to 300 mg/d alternating with 400 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

PSEUDOLINEAR PHARMACOKINETICS METHOD

A simple, easy way to approximate new total serum concentrations after a dosage adjustment with phenytoin is to temporarily assume linear pharmacokinetics, then add 15–33% for a dosage increase or subtract 15–33% for a dosage decrease to account for Michaelis-Menten pharmacokinetics: $Css_{new} = (D_{new} / D_{old})Css_{old}$, where Css_{new} is the expected steady-state concentration from the new phenytoin dose in μg/mL, Css_{old} is the measured steady-state concentration from the old phenytoin dose in μg/mL, D_{new} is the new phenytoin dose to be prescribed in mg/d, and D_{old} is the currently prescribed phenytoin dose in mg/d.[66] *Note:* This method is only intended to provide a rough approximation of the resulting phenytoin steady-state concentration after an appropriate dosage adjustment, such as that suggested by the Mauro dosage chart, has been made. The pseudolinear pharmacokinetics method should never be used to compute a new dose based on measured and desired phenytoin concentrations.

Example 3 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.*

Since the patient is receiving extended phenytoin sodium capsules, a convenient dosage change would be 100 mg/d and an increase to 500 mg/d is suggested. Using

pseudolinear pharmacokinetics, the resulting total steady-state phenytoin serum concentration would equal: $Css_{new} = (D_{new} / D_{old})Css_{old} = (500 \text{ mg/d} / 400 \text{ mg/d})6.2 \text{ μg/mL} = 7.8 \text{ μg/mL}$. Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to increase 15%, or 1.15 times, to 33%, or 1.33 times, greater than that predicted by linear pharmacokinetics: $Css = 7.8 \text{ μg/mL} \cdot 1.15 = 9.0 \text{ μg/mL}$ and $Css = 7.8 \text{ μg/mL} \cdot 1.33 = 10.4 \text{ μg/mL}$. Thus, a dosage increase of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 9–10 μg/mL.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 4 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the middle of the therapeutic range.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.*

Since the patient is receiving extended phenytoin sodium capsules, a convenient dosage change would be 100 mg/d and an increase to 400 mg/d is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state phenytoin serum concentration would equal: $Css_{new} = (D_{new} / D_{old})Css_{old} = (400 \text{ mg/d} / 300 \text{ mg/d})10.7 \text{ μg/mL} = 14.3 \text{ μg/mL}$. Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to increase 15%, or 1.15 times, to 33%, or 1.33 times, greater than that predicted by linear pharmacokinetics: $Css = 14.3 \text{ μg/mL} \cdot 1.15 = 16.4 \text{ μg/mL}$ and $Css = 14.3 \text{ μg/mL} \cdot 1.33 = 19.0 \text{ μg/mL}$. Thus, a dosage increase of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 16–19 μg/mL.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

GRAVES-CLOYD METHOD

This dosage adjustment method uses a steady-state phenytoin serum concentration to compute the patient's own phenytoin clearance rate (D_{old} / Css_{old}, where D_{old} is the administered phenytoin dose in mg/d and Css_{old} is the resulting measured total phenytoin steady-state concentration in μg/mL) at the dosage being given, then uses the measured concentration and desired concentration (Css_{new} in μg/mL) to estimate a new dose (D_{new} in mg/d) for the patient:[67] $D_{new} = (D_{old} / Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804}$.

Example 5 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and

the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use Graves-Cloyd method to estimate a new phenytoin dose for desired steady-state concentration.*

Phenytoin sodium 400 mg equals 368 mg of phenytoin (400 mg · 0.92 = 368 mg). A new total phenytoin steady-state serum concentration equal to 10 μg/mL is chosen for the patient: $D_{new} = (D_{old} / Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804} = (368 \text{ mg/d} / 6.2 \text{ mg/L}) \cdot (10 \text{ mg/L})^{0.199} \cdot (6.2 \text{ mg/L})^{0.804} = 407 \text{ mg/d}$. This is equivalent to 442 mg/d of phenytoin sodium (407 mg/0.92 = 442 mg) rounded to 450 mg/d, or 400 mg/d on even days alternating with 500 mg/d on odd days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 6 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration of 18 μg/mL.

1. *Use Graves-Cloyd method to estimate a new phenytoin dose for desired steady-state concentration.*

Phenytoin sodium 300 mg equals 276 mg of phenytoin (300 mg · 0.92 = 276 mg). A new total phenytoin steady-state serum concentration equal to 18 μg/mL is chosen for the patient: $D_{new} = (D_{old} / Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804} = (276 \text{ mg/d} / 10.7 \text{ mg/L}) \cdot (18 \text{ mg/L})^{0.199} \cdot (10.7 \text{ mg/L})^{0.804} = 308 \text{ mg/d}$. This is equivalent to 335 mg/d of phenytoin sodium (308 mg/0.92 = 335 mg) rounded to 350 mg/d, or 300 mg/d on odd days alternating with 400 mg/d on even days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

VOZEH-SHEINER OR ORBIT GRAPH METHOD

A graphical method that employs population Michaelis-Menten information using Bayes' theorem can also be used to adjust phenytoin doses using a single steady-state total concentration.[68] This method employs a series of orbs encompassing 50%, 75%, 85%, etc. of the population parameter combinations for V_{max} and K_m on the plot suggested by Mullen for use with multiple steady-state/dosage pairs (Figure 10-3). The use of the population's parameter orbs allows the plot to be used with one phenytoin steady-state concentration/dose pair.

The graph is divided into two sectors. On the left side of the x-axis, a steady-state total phenytoin concentration is plotted. On the y-axis, the phenytoin dosage rate (in mg/kg/d of

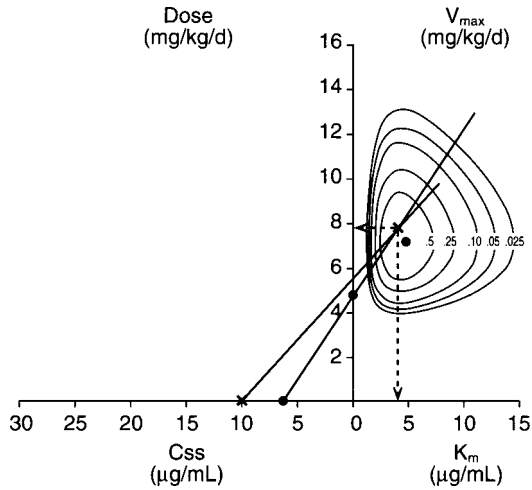

FIGURE 10-3 Vozeh-Sheiner or orbit graph employing Bayesian feedback used to estimate Michaelis-Menten parameters and phenytoin dose using one steady-state dose/concentration pair (Example 7 data shown). The orbs represent 50%, 75%, 85%, and so on, of the population parameter combinations for V_{max} and K_m. The drug dose is converted into a phenytoin amount (in mg/kg/d) and plotted on the *y*-axis (*circle,* 4.9 mg/kg/d). The concurrent steady-state phenytoin serum concentration is plotted on the left portion of the *x*-axis (*circle,* 6.2 µg/mL), and the two points are joined with a straight line across the orbs. If the line intersects more than one orb, the innermost orb is selected, and the midpoint of the line contained within that orb is found and marked (*x* mark within orbs). The new desired steady-state concentration is identified on the left portion of the x-axis (*x* mark on x-axis, 10 µg/mL), and the two *x* marks are connected by a straight line. The required phenytoin dose is identified at the intersection of the drawn line and the y-axis (5.5 mg/kg/d). If necessary, the dose would be converted to phenytoin sodium or fosphenytoin amounts. Estimates of V_{max} (7.9 mg/kg/d) and K_m (4 µg/mL) are obtained by extrapolating parallel lines to the *y*- and *x*-axes, respectively.

phenytoin; S = 0.92 for phenytoin sodium and fosphenytoin PE dosage forms) is plotted. A straight line is drawn between these two points, extended into the right sector, and through the orbs contained in the right sector. If the line intersects more than one orb, the innermost orb is selected, and the midpoint of the line contained within that orb is found and marked with a point. The midpoint within the orb and the desired steady-state phenytoin total concentration (on the left portion of the x-axis) are connected by a straight line. The intersection of this line with the y-axis is the new phenytoin dose required to achieve the new phenytoin concentration. If needed, the phenytoin dose is converted to phenytoin sodium or fosphenytoin amounts. If a line parallel to the y-axis is drawn down to the x-axis from the midpoint of the line contained within the orb, an estimate of K_m (in µg/mL) is obtained. Similarly, if a line parallel to the x-axis is drawn to the left to the y-axis from the midpoint of the line contained within the orb, an estimate of V_{max} (in mg/kg/d) is obtained.

Example 7 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 µg/mL. The patient is assessed

to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use Vozeh-Sheiner method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 10 μg/mL is chosen for the patient. Using the orbit graph, the serum concentration/dose information is plotted. (Note: phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d; 368 mg/d / 75 kg = 4.9 mg/kg/d; Figure 10-3.) According to the graph, a dose of 5.5 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 10 μg/mL. This equals an extended phenytoin sodium capsule dose of 450 mg/d, administered by alternating 400 mg/d on even days and 500 mg/d on odd days: (5.5 mg/kg/d · 75 kg) / 0.92 = 448 mg/d, rounded to 450 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 8 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration of 18 μg/mL.

1. *Use Vozeh-Sheiner method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 18 μg/mL is chosen for the patient. Using the orbit graph, the serum concentration/dose information is plotted. (Note: phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d; 276 mg/d / 55 kg = 5.0 mg/kg/d; Figure 10-4.). According to the graph, a dose of 5.7 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 18 μg/mL. This equals an extended phenytoin sodium capsule dose of 350 mg/d, administered by alternating 300 mg/d on even days and 400 mg/d on odd days: (5.7 mg/kg/d · 55 kg) / 0.92 = 341 mg/d, rounded to 350 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Two or More Phenytoin Steady-State Serum Concentrations at Two or More Dosage Levels Methods

In order to utilize each of the dosage schemes in this section, at least two phenytoin steady-state serum concentrations at different dosage rates are needed. This requirement can be difficult to achieve.

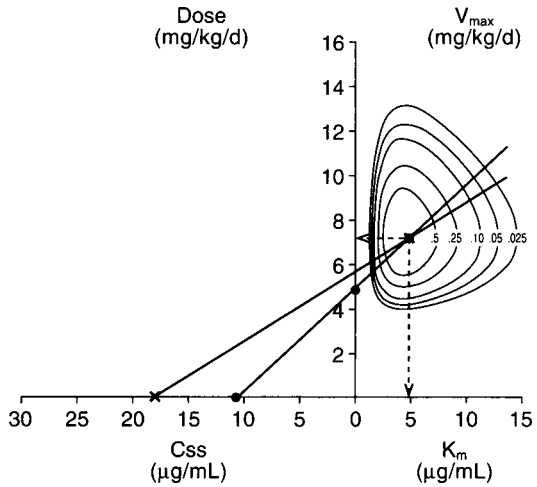

FIGURE 10-4 Vozeh-Sheiner or orbit graph employing Bayesian feedback used to estimate Michaelis-Menten parameters and phenytoin dose using one steady-state dose/concentration pair. The graph shows the solution for example 8.

EMPIRIC DOSING METHOD

Based on the knowledge of population Michaelis-Menten pharmacokinetic parameters, it is possible to suggest empiric dosage increases for phenytoin when there are two or more steady-state serum concentrations at two or more dosage levels.[66] For instance, if a patient has a steady-state phenytoin concentration equal to 11.2 μg/mL on 300 mg/d of phenytoin sodium and 25.3 μg/mL on 400 mg/d of phenytoin sodium, it is obvious that a dose of 350 mg/d of phenytoin sodium will probably produce a steady-state phenytoin serum concentration in the mid-to-upper end of the therapeutic range. Similarly, if a patient has a steady-state phenytoin concentration equal to 11.2 μg/mL on 300 mg/d of phenytoin sodium and 15.0 μg/mL on 400 mg/d of phenytoin sodium, it is apparent that a dose of 450 mg/d of phenytoin sodium will probably produce a steady-state phenytoin serum concentration in the upper end of the therapeutic range. In the latter situation, Table 10-4 can be useful to suggest dosage increases.

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 mg/mL. The dosage was increased to 500 mg/d of extended phenytoin sodium capsules for another month, the steady state phenytoin total concentration equals 22.0 mg/mL, and the patient has some lateral-gaze nystagmus. The patient is assessed to be compliant with his dosage regimen. Suggest a new phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the mid-to-upper end of the therapeutic range.

1. *Empirically suggest new phenytoin dose.*

The next logical dose to prescribe is phenytoin sodium 450 mg/d to be taken by the patient as 400 mg/d on even days and 500 mg/d on odd days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 2 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. At that time, the dose was increased to 350 mg/d of extended phenytoin sodium capsules for an additional month, and the resulting steady state concentration was 15.8 mg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a new phenytoin dosage regimen increase designed to achieve a steady-state phenytoin concentration within the upper end of the therapeutic range.

1. *Empirically suggest new phenytoin dose.*

The next logical dose to prescribe is phenytoin sodium 400 mg/d (Table 10-4).

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

MULLEN METHOD

This dosage approach uses the same dose/concentration plot as that described for the Vozeh-Sheiner or orbit graph method, but the population orbs denoting the Bayesian distribution of V_{max} and K_m parameters are omitted.[69,70] As before, the graph is divided into two sectors. On the left side of the x-axis, a steady-state total phenytoin concentration is plotted. On the y-axis, the phenytoin dosage rate (in mg/kg/d of phenytoin; S = 0.92 for phenytoin sodium and fosphenytoin PE dosage forms) is plotted. A straight line is drawn between these two points and extended into the right sector. This process is repeated for all steady-state dose/concentrations pairs that are available. The intersection of these lines in the right sector provides the Michaelis-Menten constant values for the patient. If a line parallel to the y-axis is drawn down to the x-axis from the intersection point, K_m (in μg/mL) is obtained. Similarly, if a line parallel to the x-axis is drawn to the left to the y-axis from the intersection point, an estimate of V_{max} (in mg/kg/d) is obtained. To compute the new phenytoin dose, the intersection point and the desired steady-state phenytoin total concentration (on the left portion of the x-axis) are connected by a straight line. The intersection of this line with the y-axis is the new phenytoin dose required to achieve the new phenytoin concentration. If needed, the phenytoin dose is converted to phenytoin sodium or fosphenytoin amounts.

Example 3 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The dosage was increased to 500 mg/d of extended phenytoin sodium capsules for another month, the steady state phenytoin total concentration equals 22.0 μg/mL, and the patient has some

lateral-gaze nystagmus. The patient is assessed to be compliant with his dosage regimen. Suggest a new phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use Mullen method to estimate a new phenytoin dose for desired steady-state concentration.*

Using the graph, the serum concentration/dose information is plotted. (Note: phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 75 kg = 4.9 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 500 mg/d = 460 mg/d, 460 mg/d / 75 kg = 6.1 mg/kg/d; Figure 10-5.) According to the graph, a dose of 5.5 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 11.5 μg/mL. This equals an extended phenytoin sodium capsule dose of 450 mg/d, administered by alternating 400 mg/d on even days and 500 mg/d on odd days: (5.5 mg/kg/d · 75 kg) / 0.92 = 448 mg/d, rounded to 450 mg/d. V_{max} = 6.8 mg/kg/d and K_m = 2.2 μg/mL for this patient.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be

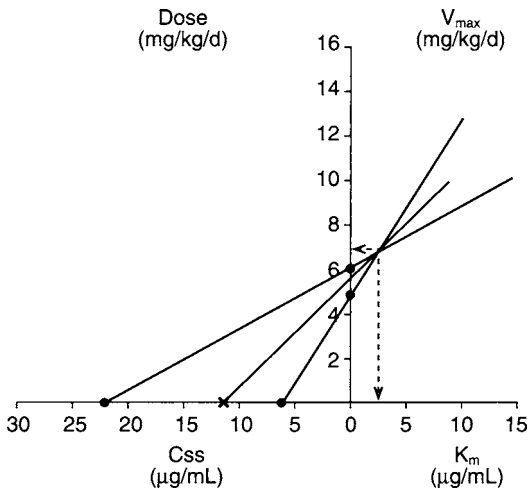

FIGURE 10-5 Mullen graph used to compute Michaelis-Menten parameters and phenytoin dose using two or more steady-state dose/concentration pairs (example 3 data shown). The first dose and concentration are plotted as circles on the *y*- (4.9 mg/kg/d) and *x*-axes (6.2 μg/mL), respectively, and joined by a straight line. This process is repeated for the second dose/concentration pair (6.1 mg/kg/d, 22 μg/mL) plus any others that are available. The intersection of the lines in the right sector of the graph is used to compute a new dose by drawing a straight line between the intersection and the new desired steady-state concentration on the left portion of the *x*-axis (*x* on *x*-axis, 11.5 μg/mL). The required dose is the intersection of this new line with the *y*-axis (5.5 mg/kg/d). Estimates of V_{max} (6.8 mg/kg/d) and K_m (2.2 μg/mL) are obtained by extrapolating parallel lines to the *y*- and *x*-axes, respectively.

measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 4 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. At that time, the dose was increased to 350 mg/d of extended phenytoin sodium capsules for an additional month, and the resulting steady state concentration was 15.8 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a new phenytoin dosage regimen increase designed to achieve a steady-state phenytoin concentration within the upper end of the therapeutic range.

1. *Use Mullen method to estimate a new phenytoin dose for desired steady-state concentration.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d, 276 mg/d / 55 kg = 5 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 350 mg/d = 322 mg/d, 322 mg/d / 55 kg = 5.9 mg/kg/d; Figure 10-6.) According to the graph, a dose of 6.7 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 22 μg/mL. This equals an extended phenytoin sodium capsule dose of 400 mg/d: (6.7 mg/kg/d · 55 kg) / 0.92 = 401 mg/d, rounded to 400 mg/d. V_{max} = 9.4 mg/kg/d and K_m = 9.5 μg/mL for this patient.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

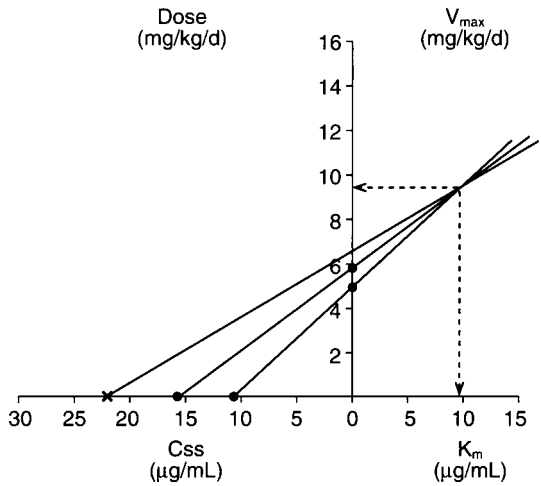

FIGURE 10-6 Mullen graph used to estimate Michaelis-Menten parameters and phenytoin dose using two or more steady-state dose/concentration pairs. The graph shows the solution for example 4.

LUDDEN METHOD

This method involves the arrangement of the Michaelis-Menten equation so that two or more maintenance doses (MD, in mg/d of phenytoin) and steady-state concentrations (Css in mg/L = μg/mL) can be used to obtain graphical solutions for V_{max} and K_m: $MD = -K_m(MD / Css) + V_{max}$.[31] When maintenance dose is plotted on the y-axis and MD/Css is plotted on the x-axis of Cartesian graph paper, a straight line with a y-intercept of V_{max} and a slope equal to $-K_m$ is found. If three or more dose/concentration pairs are available, it is best to actually plot the data so the best straight line can be drawn through the points. However, if only two dose/concentration pairs are available, a direct mathematical solution can be used. The slope for a simple linear equation is the quotient of the change in the y-axis values (Δy) and the change in the x-axis values (Δx): slope = Δy/Δx. Applying this to the above rearrangement of the Michaels-Menten equation, $-K_m = (MD_1 - MD_2) / [(MD_1/Css_1) - (MD_2 / Css_2)]$, where the subscript 1 indicates the higher dose and 2 indicates the lower dose. Once this has been accomplished, V_{max} can be solved for in the rearranged Michaelis-Menten equation: $V_{max} = MD + K_m(MD / Css)$. The Michaels-Menten equation can be used to compute steady-state concentrations for a given dose or vica versa.

Example 5 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The dosage was increased to 500 mg/d of extended phenytoin sodium capsules for another month, the steady state phenytoin total concentration equals 22.0 μg/mL, and the patient has some lateral-gaze nystagmus. The patient is assessed to be compliant with his dosage regimen. Suggest a new phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Use Ludden method to estimate V_{max} and K_m.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 75 kg = 4.9 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 500 mg/d = 460 mg/d, 460 mg/d / 75 kg = 6.1 mg/kg/d; Figure 10-7.) According to the graph, V_{max} = 510 mg/d and K_m = 2.4 mg/L.

Because only two dose/steady-state concentrations pairs are available, a direct mathematical solution can also be conducted: $-K_m = (MD_1 - MD_2) / [(MD_1/Css_1) - (MD_2/Css_2)]$ = (460 mg/d – 368 mg/d) / [(460 mg/d / 22 mg/L) – (368 mg/d / 6.2 mg/L)] = –2.4 mg/L, K_m = 2.4 mg/L; $V_{max} = MD + K_m(MD/Css)$ = 368 mg/d + 2.4(368 mg/d / 6.2 mg/L) = 510 mg/d.

2. *Use Michaelis-Menten equation to compute a new phenytoin dose for desired steady-state concentration.*

According to the Michaelis-Menten equation, a dose equal to 450 mg of phenytoin sodium is required to achieve a steady-state concentration equal to 10.4 μg/mL:

$$Css = \frac{K_m \cdot (S \cdot MD)}{V_{max} - (S \cdot MD)} = \frac{2.4 \text{ mg/L} \cdot (0.92 \cdot 450 \text{ mg/d})}{510 \text{ mg/d} - (0.92 \cdot 450 \text{ mg/d})} = 10.4 \text{ mg/L}$$

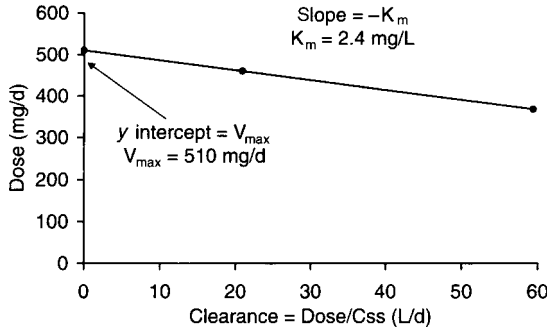

FIGURE 10-7 Ludden graph used to compute Michaelis-Menten parameters and phenytoin dose using two or more steady-state dose/concentration pairs (example 5 data shown). Dose is plotted on the y-axis while clearance (Dose/Css) is plotted on the x-axis for each data pair. The best straight line is drawn through the points. Slope equals $-K_m$, and V_{max} is the y-intercept. These values are then used to compute the required maintenance dose (MD) for any desired steady-state serum concentration: $MD = (V_{max} \cdot Css) / [S(K_m + Css)]$.

This dose would administered by alternating 400 mg/d on even days and 500 mg/d on odd days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 6 GF is a 35-year-old, 55-kg female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function. The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. At that time, the dose was increased to 350 mg/d of extended phenytoin sodium capsules for an additional month, and the resulting steady state concentration was 15.8 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a new phenytoin dosage regimen increase designed to achieve a steady-state phenytoin concentration within the upper end of the therapeutic range.

1. *Use Ludden method to estimate V_{max} and K_m.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d, phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 350 mg/d = 322 mg/d; Figure 10-8.) According to the graph, V_{max} = 495 mg/d and K_m = 8.5 mg/L.

Because only two dose/steady-state concentrations pairs are available, a direct mathematical solution can also be conducted: $-K_m = (MD_1 - MD_2) / [(MD_1/Css_1) - (MD_2/Css_2)]$ = (322 mg/d – 276 mg/d) / [(322 mg/d / 15.8 mg/L) – (276 mg/d / 10.7 mg/L)] = – 8.5 mg/L, K_m = 8.5 mg/L; $V_{max} = MD + K_m(MD/Css)$ = 322 mg/d + 8.5 mg/L(322 mg/d / 15.8 mg/L) = 495 mg/d.

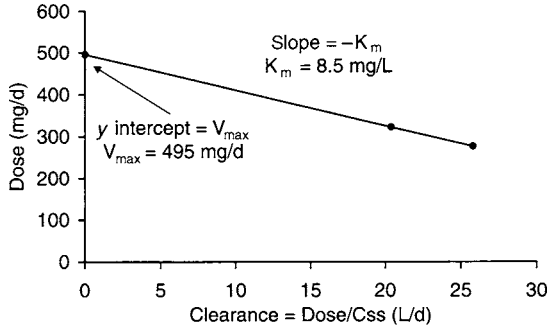

FIGURE 10-8 Ludden graph used to compute Michaelis-Menten parameters and phenytoin dose using two or more steady-state dose/concentration pairs. The graph shows the solution for example 6.

2. *Use Michaelis-Menten equation to compute a new phenytoin dose for desired steady-state concentration.*

According to the Michaelis-Menten equation, a dose equal to 400 mg of phenytoin sodium is required to achieve a steady-state concentration equal to 24.6 μg/mL:

$$\text{Css} = \frac{K_m \cdot (S \cdot MD)}{V_{max} - (S \cdot MD)} = \frac{8.5 \text{ mg/L} \cdot (0.92 \cdot 400 \text{ mg/d})}{495 \text{ mg/d} - (0.92 \cdot 400 \text{ mg/d})} = 24.6 \text{ mg/L}$$

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by

the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. When only a limited number of phenytoin concentrations are available, Bayesian pharmacokinetic computer programs can be used to compute a complete patient pharmacokinetic profile that includes V_{max}, K_m, and volume of distribution. These are distinct advantages compared to the other methods used to adjust phenytoin dose based on one steady-state serum concentration. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[71]

Example 1 TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function (total bilirubin = 0.5 mg/dL, albumin = 4.0 g/dL, serum creatinine = 0.9 mg/dL). The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. A 400 mg dose of phenytoin sodium is equal to 368 mg of phenytoin (400 mg phenytoin sodium · 0.92 = 368 mg phenytoin). Extended phenytoin sodium capsules are input as a slow release dosage form.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 53 L, a V_{max} equal to 506 mg/d, and a K_m equal to 4.3 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 414 mg/d of phenytoin will produce a total steady-state concentration of 12.1 μg/mL. This is equivalent to 450 mg/d of phenytoin sodium (414 mg/d phenytoin / 0.92 = 450 mg/d phenytoin sodium). Extended phenytoin sodium capsules would be prescribed as 400 mg/d on even days alternating with 500 mg/d on odd days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 2 GF is a 35-year-old, 55-kg (5 ft 4 in) female with tonic-clonic seizures who requires therapy with oral phenytoin. She has normal liver and renal function (total bilirubin = 0.6 mg/dL, albumin = 4.6 g/dL, serum creatinine = 0.6 mg/dL). The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 10.7 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration of 18 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. A 300 mg dose of phenytoin sodium is equal to 276 mg of phenytoin (300 mg phenytoin sodium · 0.92 = 276 mg phenytoin). Extended phenytoin sodium capsules are input as a slow release dosage form.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 34 L, a V_{max} equal to 354 mg/d, and a K_m equal to 5.8 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 304 mg/d of phenytoin will produce a total steady-state concentration of 19.6 μg/mL. This is equivalent to 330 mg/d of phenytoin sodium (304 mg/d phenytoin / 0.92 = 330 mg/d phenytoin sodium). Extended phenytoin sodium capsules would be prescribed as 330 mg/d (three 100 mg capsules + one 30 mg capsule).

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Example 3 TY is a 27-year-old, 60-kg (5 ft 6 in) female with complex partial seizures who requires therapy with oral phenytoin. She has normal liver and renal function (total bilirubin = 0.8 mg/dL, albumin = 5.1 g/dL, serum creatinine = 0.4 mg/dL). The patient was prescribed 300 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 8.7 μg/mL. At that time, the dose

was increased to 400 mg/d of extended phenytoin sodium capsules for an additional month, and the resulting steady-state concentration was 13.2 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a new phenytoin dosage regimen increase designed to achieve a steady-state phenytoin concentration within the upper end of the therapeutic range.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. A 300 mg dose of phenytoin sodium is equal to 276 mg of phenytoin (300 mg phenytoin sodium · 0.92 = 276 mg phenytoin) while a 400 mg dose of phenytoin sodium equals 368 mg of phenytoin (400 mg phenytoin sodium · 0.92 = 368 mg phenytoin). Extended phenytoin sodium capsules are input as a slow release dosage form.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 43 L, a V_{max} equal to 586 mg/d, and a K_m equal to 13.2 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 396 mg/d of phenytoin will produce a total steady-state concentration of 20.4 μg/mL. This is equivalent to 430 mg/d of phenytoin sodium (396 mg/d phenytoin / 0.92 = 430 mg/d phenytoin sodium). Extended phenytoin sodium capsules would be prescribed as 430 mg/d (four 100 mg capsules + one 30 mg capsule).

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 10-5.

USE OF PHENYTOIN BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

If a patient has a subtherapeutic phenytoin serum concentration in an acute situation, it may be desirable to increase the phenytoin concentration as quickly as possible. In this setting, it would not be acceptable to simply increase the maintenance dose and wait for therapeutic steady-state serum concentrations to be established in the patient. A rational way to increase

TABLE 10-5 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Vozeh-Sheiner method (1 concentration/dose pair) or Mullen method (≥2 concentration/ dose pairs) or Ludden method (≥2 concentration/ dose pairs)
Literature-based/concept	Literature-based recommended dosing	Empiric dosing method
Mathematical	———*	Graves-Cloyd method (1 concentration/dose pair)
Computerized	Bayesian computer program	Bayesian computer program

* Any initial dosing method appropriate for patient.

the serum concentrations rapidly is to administer a booster dose of phenytoin, a process also known as "reloading" the patient with phenytoin, computed using pharmacokinetic techniques. A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current phenytoin concentration present in the patient: $BD = [(C_{desired} - C_{actual})V] / S$, where $C_{desired}$ is the desired phenytoin concentration, C_{actual} is the actual current phenytoin concentration for the patient, S is the fraction of the phenytoin salt form that is active phenytoin (0.92 for phenytoin sodium injection and capsules; 0.92 for fosphenytoin because doses are prescribed as a phenytoin sodium equivalent or PE, 1.0 for phenytoin acid suspensions and tablets), and V is the volume of distribution for phenytoin. If the volume of distribution for phenytoin is known for the patient, it can be used in the calculation. However, this value is not usually known and is assumed to equal the population average of 0.7 L/kg. For obese individuals 30% or more above their ideal body weight, the volume of distribution can be estimated using the following equation: V = 0.7 L/kg [IBW + 1.33(TBW − IBW)], where IBW is ideal body weight in kilograms [$IBW_{females}$ (in kg) = 45 + 2.3(Ht − 60) or IBW_{males} (in kg) = 50 + 2.3(Ht − 60)], Ht is height in inches, and TBW is total body weight in kilograms.

Concurrent with the administration of the booster dose, the maintenance dose of phenytoin is usually increased. Clinicians need to recognize that the administration of a booster dose does not alter the time required to achieve steady-state conditions when a new phenytoin dosage rate is prescribed. It still requires a sufficient time period to attain steady state when the dosage rate is changed. However, usually the difference between the postbooster dose phenytoin concentration and the ultimate steady-state concentration has been reduced by giving the extra dose of drug.

Example 1 BN is a 22-year-old, 85-kg (6 ft 2 in) male with complex partial seizures who is receiving therapy with intravenous phenytoin sodium. He has normal liver and

renal function. After receiving an initial loading dose of phenytoin sodium (1000 mg) and a maintenance dose of 300 mg/d of phenytoin sodium for 5 days, his phenytoin concentration is measured at 5.6 μg/mL immediately after seizure activity was observed. Compute a booster dose of phenytoin to achieve a phenytoin concentration equal to 15 μg/mL.

1. *Estimate volume of distribution according to disease states and conditions present in the patient.*

In the case of phenytoin, the population average volume of distribution equals 0.7 L/kg and this will be used to estimate the parameter for the patient. The patient is nonobese, so his actual body weight will be used in the computation: V = 0.7 L/kg · 85 kg = 60 L.

2. Compute booster dose.

The booster dose is computed using the following equation: $BD = [(C_{desired} - C_{actual})V] / S = [(15 \text{ mg/L} - 5.6 \text{ mg/L})60 \text{ L}] / 0.92 = 613$ mg, rounded to 600 mg of phenytoin sodium infused no faster than 50 mg/min. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take additional time for new steady-state conditions to be achieved. Phenytoin serum concentrations should be measured at this time.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current anticonvulsant therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with phenytoin exists.

1. DF is a 23-year-old, 85-kg (6 ft 1 in) male with tonic-clonic seizures who requires therapy with oral phenytoin. He has normal liver and renal function (bilirubin = 1.0 mg/dL, albumin = 4.9 g/dL, serum creatinine = 0.7 mg/dL). Suggest an initial extended phenytoin sodium capsule dosage regimen designed to achieve a steady-state phenytoin concentration equal to 10 μg/mL.

2. Patient DF (please see problem 1) was prescribed extended phenytoin sodium capsules 500 mg/d orally. The current steady-state phenytoin concentration equals 23.5 μg/mL. Compute a new oral phenytoin dose that will provide a steady-state concentration of 15 μg/mL.

3. TR is a 56-year-old, 70-kg (5 ft 9 in) male with complex partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function (bilirubin = 0.8 mg/dL, albumin = 4.4 g/dL, serum creatinine = 0.9 mg/dL). Suggest an initial phenytoin suspension dosage regimen designed to achieve a steady-state phenytoin concentration equal to 15 μg/mL.

4. Patient TR (please see problem 3) was prescribed phenytoin suspension 200 mg orally every 12 hours. The current steady-state phenytoin concentration equals 8 μg/mL.

Compute a new oral phenytoin dose that will provide a steady-state concentration of 15 μg/mL.

5. PL is a 64-year-old, 60-kg (5 ft 2 in) female with simple partial seizures who requires therapy with intravenous fosphenytoin. She has normal liver and renal function (bilirubin = 0.8 mg/dL, albumin = 3.6 g/dL, serum creatinine = 1.2 mg/dL). Suggest an initial intravenous fosphenytoin regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

6. Patient PL (please see problem 5) was prescribed intravenous fosphenytoin injection 200 mg/d PE. A phenytoin serum concentration was obtained just before the fourth dose of this regimen and equaled 4.1 μg/mL. Assuming the phenytoin concentration was zero before the first dose, compute a new intravenous fosphenytoin injection that will provide a steady-state concentration of 12 μg/mL.

7. MN is a 24-year-old, 55-kg (5 ft 5 in) female with complex partial seizures who requires therapy with intravenous phenytoin sodium. She has normal liver and renal function (bilirubin = 0.8 mg/dL, albumin = 3.6 g/dL, serum creatinine = 1.2 mg/dL). Suggest an initial intravenous phenytoin sodium dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

8. Patient MN (please see problem 7) was prescribed intravenous phenytoin sodium injection 300 mg/d. A phenytoin serum concentration was obtained at steady state and equaled 6.4 μg/mL. The dose was increased to intravenous phenytoin sodium injection 400 mg/d and the measured steady state concentration equaled 10.7 μg/mL. Compute a new intravenous phenytoin sodium injection dose that will provide a steady-state concentration of 15 μg/mL.

9. SA is a 62-year-old, 130-kg (5 ft 11 in) male with complex partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function (bilirubin = 0.6 mg/dL, albumin = 3.9 g/dL, serum creatinine = 1.0 mg/dL). Suggest an initial extended phenytoin sodium capsule dosage regimen designed to achieve a steady-state concentration equal to 10 μg/mL.

10. Patient SA (please see problem 9) was prescribed extended phenytoin sodium capsules 200 mg orally every 12 hours. A phenytoin serum concentration was obtained at steady state equaled 6.2 μg/mL. The dose was increased to extended phenytoin sodium capsules 300 mg orally every 12 hours, and the measured steady-state concentration equaled 25.7 μg/mL. Compute a new oral phenytoin dose that will provide a steady-state concentration of 15 μg/mL.

11. VG is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.4 g/dL) and normal renal function (creatinine clearance = 90 mL/min). His total phenytoin concentration is 8.9 μg/mL. Assuming that any unbound concentrations performed by the clinical laboratory will be conducted at 25°C, compute an estimated normalized phenytoin concentration for this patient.

12. DE is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.0 g/dL) and poor renal function (creatinine clearance = 10 mL/min). His total phenytoin concentration is 8.1 μg/mL. Compute an estimated normalized phenytoin concentration for this patient.

13. KL is an epileptic patient being treated with phenytoin and valproic acid. He has a normal albumin concentration (albumin = 4.0 g/dL) and normal renal function (creatinine clearance = 95 mL/min). His steady-state total phenytoin and valproic acid concentrations are 6 μg/mL and 90 μg/mL, respectively. Compute an estimated unbound phenytoin concentration for this patient.

14. YS is a 9-year-old, 35-kg female with complex partial seizures who requires therapy with oral phenytoin. She has normal liver and renal function. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 μg/mL.

15. Patient YS (please see problem 14) was prescribed phenytoin suspension 150 mg orally every 12 hours. The current steady-state phenytoin concentration equals 23 μg/mL. Compute a new oral phenytoin dose that will provide a steady-state concentration of 15 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1* The initial phenytoin dose for patient DF would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For an 85-kg patient, V_{max} = 595 mg/d: V_{max} = 7 mg/kg/d · 85 kg = 595 mg/d. For this individual, K_m = 4 mg/L.

2. *Compute dosage regimen.*

Oral phenytoin sodium capsules will be prescribed to this patient (F = 1, S = 0.92). The initial dosage interval (τ) will be set to 24 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{595 \text{ mg/d} \cdot 10 \text{ mg/L}}{0.92\ (4 \text{ mg/L} + 10 \text{ mg/L})} = 462 \text{ mg/d, rounded to } 500 \text{ mg/d}$$

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Dosing Method

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for extended phenytoin sodium capsules in an adult patient is 4–6 mg/kg/d. Using a rate of 5 mg/kg/d, the initial dose would be 400 mg/d: 5 mg/kg/d · 85 kg = 425 mg/d, rounded to 400 mg/d. Using a dosage interval of 24 hours, the prescribed dose would be 400 mg of extended phenytoin sodium capsules daily.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

2. *Solution to problem 2* The revised phenytoin dose of patient DF would be calculated as follows:

Empiric Dosing Method

1. *Suggest new phenytoin dose.*

Since the patient is receiving extended phenytoin sodium capsules, a convenient dosage change would be 100 mg/d and a decrease to 400 mg/d is suggested.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage decrease, then compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.*

Since the patient is receiving extended phenytoin sodium capsules, a convenient dosage change would be 100 mg/d and a decrease to 400 mg/d is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state phenytoin serum concentration would equal: $Css_{new} = (D_{new}/D_{old})Css_{old}$ = (400 mg/d / 500 mg/d) 23.5 μg/mL = 18.8 μg/mL. Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to decrease 15%, or 0.85 times, to 33%, or 0.67 times, greater than that predicted by linear pharmacokinetics: Css = 18.8 μg/mL · 0.85 = 16 μg/mL and Css = 18.8 μg/mL · 0.67 = 12.6 μg/mL. Thus, a dosage decrease of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 12–16 μg/mL.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Graves-Cloyd Method

1. *Use Graves-Cloyd method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 15 µg/mL is chosen for the patient (460 mg phenytoin = 500 mg phenytoin sodium · 0.92): $D_{new} = (D_{old}/Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804} = (460 \text{ mg/d} / 23.5 \text{ mg/L}) \cdot (15 \text{ mg/L})^{0.199} \cdot (23.5 \text{ mg/L})^{0.804} = 425$ mg/d of phenytoin acid, which equals 462 mg of phenytoin sodium (462 mg phenytoin sodium = 425 mg phenytoin/0.92). This dose would be rounded to 450 mg/d, or 400 mg/d on even days alternating with 500 mg/d on odd days.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Vozeh-Sheiner Method

1. *Use Vozeh-Sheiner method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 15 µg/mL is chosen for the patient. Using the orbit graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 500 mg/d = 460 mg/d; 460 mg/d / 85 kg = 5.4 mg/kg/d; Figure 10-9.) According to the graph, a dose of 4.9 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 15 µg/mL. This equals an extended phenytoin sodium capsule dose of 450 mg/d, administered by alternating 400 mg/d on even days and 500 mg/d on odd days: (4.9 mg/kg/d · 85 kg)/0.92 = 453 mg/d, rounded to 450 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

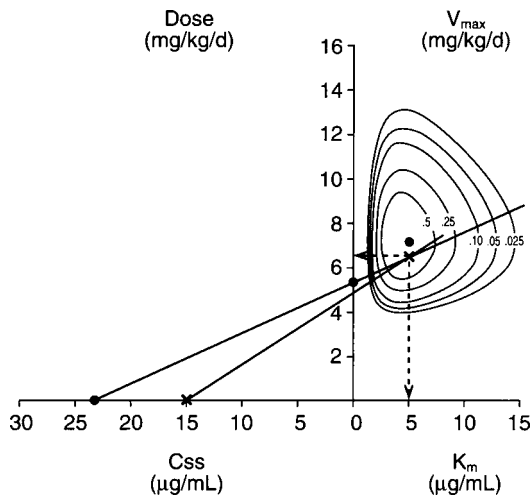

FIGURE 10-9 Solution to problem 2 using Vozeh-Sheiner or orbit graph.

3. *Solution to problem 3* The initial phenytoin dose for patient TR would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For a 70-kg patient, V_{max} = 490 mg/d: V_{max} = 7 mg/kg/d · 70 kg = 490 mg/d. For this individual, K_m = 4 mg/L.

2. *Compute dosage regimen.*

Oral phenytoin suspension will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{490 \text{ mg/d} \cdot 15 \text{ mg/L}}{1\ (4 \text{ mg/L} + 15 \text{ mg/L})} = 387 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

A dose of phenytoin suspension 200 mg every 12 hours would be prescribed. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Dosing Method

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for extended phenytoin sodium capsules in an adult patient is 4–6 mg/kg/d. Using a rate of 5 mg/kg/d, the initial dose would be 400 mg/d: 5 mg/kg/d · 70 kg = 350 mg/d, rounded to 400 mg/d. Using a dosage interval of 12 hours, the prescribed dose would be 200 mg of phenytoin suspension every 12 hours.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

4. *Solution to problem 4* The revised phenytoin dose of patient TR would be calculated as follows:

Empiric Dosing Method

1. *Suggest new phenytoin dose.*

Since the patient is receiving phenytoin suspension, a convenient dosage change would be 100 mg/d and an increase to 500 mg/d or 250 mg every 12 hours is suggested (Table 10-4).

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.*

Since the patient is receiving phenytoin suspension, a convenient dosage change would be 100 mg/d and a increase to 500 mg/d is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state phenytoin serum concentration would equal: $Css_{new} = (D_{new}/D_{old})Css_{old}$ = (500 mg/d / 400 mg/d) 8 μg/mL = 10 μg/mL. Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to increase 15%, or 1.15 times, to 33%, or 1.33 times, greater than that predicted by linear pharmacokinetics: Css = 10 μg/mL · 1.15 = 11.5 μg/mL and Css = 10 μg/mL · 1.33 = 13.3 μg/mL. Thus, a dosage increase of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 11–13 μg/mL.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Graves-Cloyd Method

1. *Use Graves-Cloyd method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 15 μg/mL is chosen for the patient: $D_{new} = (D_{old}/Css_{old}) \cdot Css_{new}^{0.199} \cdot Css_{old}^{0.804}$ = (400 mg/d / 8 mg/L) · $(15 \text{ mg/L})^{0.199} \cdot (8 \text{ mg/L})^{0.804}$ = 456 mg/d, rounded to 450 mg/d, or 225 mg every 12 hours.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Vozeh-Sheiner Method

1. *Use Vozeh-Sheiner method to estimate a new phenytoin dose for desired steady-state concentration.*

A new total phenytoin steady-state serum concentration equal to 15 μg/mL is chosen for the patient. Using the orbit graph, the serum concentration/dose information is plotted. (Note: 400 mg/d / 70 kg = 5.7 mg/kg/d; Figure 10-10.) According to the graph, a dose of 6.6 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 15 μg/mL. This equals a phenytoin suspension dose of 450 mg/d, administered as 225 mg every 12 hours: 6.6 mg/kg/d · 70 kg = 462 mg/d, rounded to 450 mg/d.

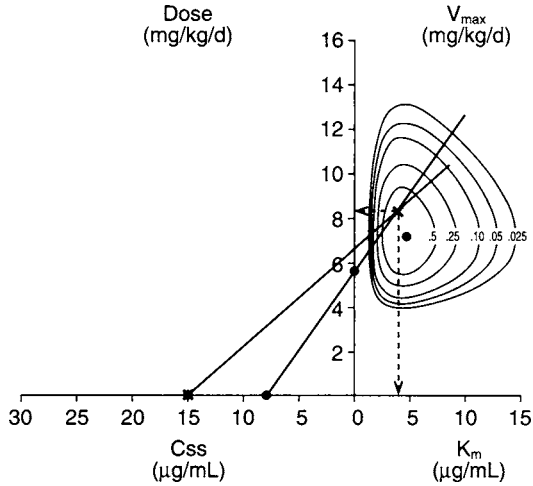

FIGURE 10-10 Solution to problem 4 using Vozeh-Sheiner or orbit graph.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

5. *Solution to problem 5* The initial phenytoin dose for patient PL would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants and volume of distribution according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For a 60-kg patient, V_{max} = 420 mg/d: V_{max} = 7 mg/kg/d · 60 kg = 420 mg/d. For this individual, K_m = 4 mg/L. The volume of distribution for this patient would equal 42 L: V = 0.7 L/kg · 60 kg = 42 L.

2. *Compute dosage regimen.*

Fosphenytoin will be given to this patient, which is prescribed in phenytoin sodium equivalents or PE (F = 1, S = 0.92). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{420 \text{ mg/d} \cdot 12 \text{ mg/L}}{0.92\ (4 \text{ mg/L} + 12 \text{ mg/L})} = 342 \text{ mg/d, rounded to } 350 \text{ mg}$$

$$LD = (V \cdot Css) / S = (42 \text{ L} \cdot 12 \text{ mg/L}) / 0.92 = 548 \text{ mg, rounded to } 550 \text{ mg}$$

The maintenance dose would be given as 175 mg every 12 hours. Maintenance and loading dose infusion rates should not exceed 150 mg/min PE. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Dosing Method

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for fosphenytoin injection in an adult patient is 4–6 mg/kg/d PE. Using a rate of 5 mg/kg/d, the initial dose would be 300 mg/d or 150 mg every 12 hours: 5 mg/kg/d · 60 kg = 300 mg/d. Suggested loading doses for fosphenytoin is 15–20 mg/kg PE. Using a dose of 18 mg/kg PE, the loading dose would be 1000 mg PE: 18 mg/kg PE · 60 kg = 1080 mg PE, rounded to 1000 mg PE. Maintenance and loading dose infusion rates should not exceed 150 mg/min PE.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

6. *Solution to problem 6* The revised phenytoin dose of patient PL would be calculated as follows:

Bayesian Pharmacokinetic Computer Method

Because the patient has only received three doses of fosphenytoin, it is very unlikely the measured serum concentration is a steady-state concentration. Thus, methods that require a single steady-state serum concentration should not be used.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. A 200 mg/d PE dose of fosphenytoin is equal to 184 mg of phenytoin (200 mg PE fosphenytoin · 0.92 = 184 mg phenytoin). This dose was entered into the program along with a dose length time of 1.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 47 L, a V_{max} equal to 299 mg/d, and a K_m equal to 6.0 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 200 mg/d of phenytoin will produce a total steady-state concentration of 12 μg/mL. This is equivalent to 217 mg/d of phenytoin sodium (200 mg/d phenytoin / 0.92 = 217 mg/d PE fosphenytoin), and this dose

would be rounded to 200 mg/d PE. Fosphenytoin would be prescribed as 200 mg/d PE at an infusion rate no greater than 150 mg/min PE.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

7. *Solution to problem 7* The initial phenytoin dose for patient MN would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants and volume of distribution according to disease states and conditions present in the patient.*

The V_{max} for a nonobese adult patient with normal liver and renal function is 7 mg/kg/d. For a 55-kg patient, V_{max} = 385 mg/d: V_{max} = 7 mg/kg/d · 55 kg = 385 mg/d. For this individual, K_m = 4 mg/L. The volume of distribution for this patient would equal 39 L: V = 0.7 L/kg · 55 kg = 39 L.

2. *Compute dosage regimen.*

Phenytoin sodium injection will be given to this patient (F = 1, S = 0.92). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{385 \text{ mg/d} \cdot 12 \text{ mg/L}}{0.92\ (4 \text{ mg/L} + 12 \text{ mg/L})} = 314 \text{ mg/d, rounded to 300 mg/d}$$

$$LD = (V \cdot Css) / S = (39 \text{ L} \cdot 12 \text{ mg / L}) / 0.92 = 509 \text{ mg, rounded to 500 mg}$$

The maintenance dose would be given as 150 mg every 12 hours. Maintenance and loading dose infusion rates should not exceed 50 mg/min. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Dosing Method

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for fosphenytoin injection in an adult patient is 4–6 mg/kg/d PE. Using a rate of 5 mg/kg/d, the initial dose would be 300 mg/d or 150 mg every 12 hours: 5 mg/kg/d · 55 kg = 275 mg/d, rounded to 300 mg/d. The suggested loading dose for phenytoin sodium injection is 15–20 mg/kg. Using a dose of 18 mg/kg, the loading dose would be 1000 mg: 18 mg/kg · 55 kg = 990 mg PE,

rounded to 1000 mg PE. Maintenance and loading dose infusion rates should not exceed 50 mg/min.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

8. *Solution to problem 8* The revised phenytoin dose of patient MN would be calculated as follows:

Empiric Dosing Method

1. *Empirically suggest new phenytoin dose.*

The next logical dose to prescribe is phenytoin sodium 500 mg/d (Table 10-4).

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Mullen Method

1. *Use Mullen method to estimate a new phenytoin dose for desired steady-state concentration.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d, 276 mg/d / 55 kg = 5 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 55 kg = 6.7 mg/kg/d; Figure 10-11). According to

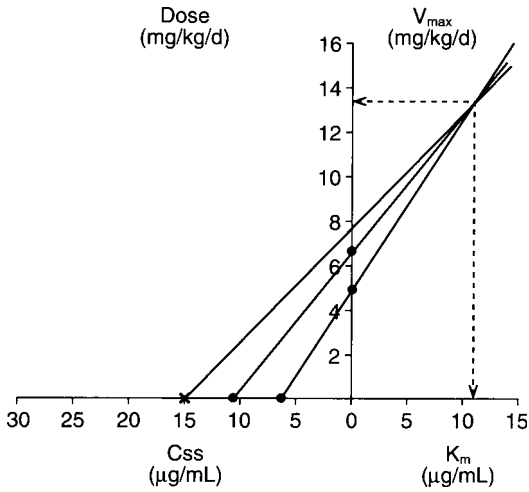

FIGURE 10-11 Solution to problem 8 using Mullen graph.

the graph, a dose of 7.7 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 15 μg/mL. This equals a phenytoin sodium injection dose of 450 mg/d or 225 mg every 12 hours: (7.7 mg/kg/d · 55 kg) / 0.92 = 460 mg/d, rounded to 450 mg/d. The dose would be given as 225 mg every 12 hours. V_{max} = 13.4 mg/kg/d and K_m = 10.6 μg/mL for this patient.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Ludden Method

1. *Use Ludden method to estimate V_{max} and K_m.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d, 276 mg/d / 55 kg = 5 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 55 kg = 6.7 mg/kg/d; Figure 10-12.) According to the graph, V_{max} = 729 mg/d and K_m = 10.5 mg/L.

Because only two dose/steady-state concentration pairs are available, a direct mathematical solution can also be conducted: $-K_m = (MD_1 - MD_2) / [(MD_1/Css_1) - (MD_2/Css_2)]$ = (368 mg/d − 276 mg/d) / [(368 mg/d / 10.7 mg/L) − (276 mg/d / 6.4 mg/L)] = −10.5 mg/L, K_m = 10.5 mg/L; $V_{max} = MD + K_m(MD/Css)$ = 368 mg/d + 10.5 mg/L (368 mg/d / 10.7 mg/L) = 729 mg/d.

2. *Use Michaelis-Menten equation to compute a new phenytoin dose for desired steady-state concentration.*

According to the Michaelis-Menten equation, a dose equal to 450 mg of phenytoin sodium is required to achieve a steady-state concentration equal to 10.4 μg/mL:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{729 \text{ mg/d} \cdot 15 \text{ mg/L}}{0.92\,(10.5 \text{ mg/L} + 15 \text{ mg/L})} = 466 \text{ mg/d, rounded to } 450 \text{ mg/d}$$

This dose would be administered by giving 225 mg every 12 hours.

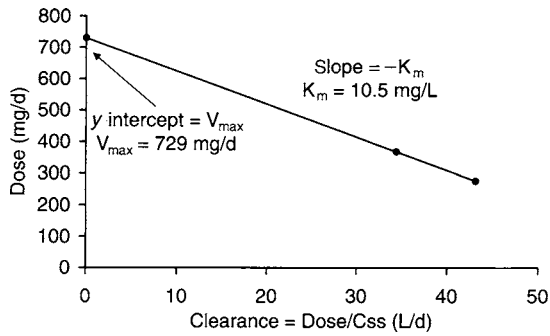

FIGURE 10-12 Solution to problem 8 using Ludden graph.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Bayesian Pharmacokinetic Computer Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 300 mg/d = 276 mg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d.) These doses were entered into the program along with a dose length time of 1.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 49 L, a V_{max} equal to 633 mg/d, and a K_m equal to 10.8 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 414 mg/d of phenytoin will produce a total steady-state concentration of 20.3 μg/mL. This is equivalent to 450 mg/d of phenytoin sodium (414 mg/d phenytoin / 0.92 = 450 mg/d phenytoin sodium), and this dose would be given as 225 mg every 12 hours.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

9. *Solution to problem 9* The initial phenytoin dose for patient SA would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants and volume of distribution according to disease states and conditions present in the patient.*

The V_{max} for an adult patient with normal liver and renal function is 7 mg/kg/d. In obese individuals, it is unclear whether to use ideal body weight (IBW) or total body weight (TBW) for maintenance dose calculation. Currently, most clinicians use ideal body weight since it produces the most conservative dosage recommendation: IBW_{males} = 50 + 2.3(Ht − 60) = 50 + 2.3(71 in − 60) = 75 kg. For a 75-kg patient, V_{max} = 525 mg/d: V_{max} = 7 mg/kg/d · 75 kg = 525 mg/d. For this individual, K_m = 4 mg/L.

2. *Compute dosage regimen.*

Extended phenytoin sodium capsules will be given to this patient (F = 1, S = 0.92). The initial dosage interval (τ) will be set to 24 hours. (Note: μg/mL = mg/L and this

concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{525 \text{ mg/d} \cdot 10 \text{ mg/L}}{0.92\ (4 \text{ mg/L} + 10 \text{ mg/L})} = 408 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

The maintenance dose would be given as 400 mg/d. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Dosing Method

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for phenytoin sodium injection in an adult patient is 4–6 mg/kg/d. In obese individuals, it is unclear whether to use ideal body weight (IBW) or total body weight (TBW) for dose calculation. Currently, most clinicians use ideal body weight since it produces the most conservative dosage recommendation: $IBW_{males} = 50 + 2.3(Ht - 60) = 50 + 2.3(71 \text{ in} - 60) = 75$ kg. Using a rate of 5 mg/kg/d, the initial dose would be 400 mg/d or 200 mg every 12 hours: 5 mg/kg/d · 75 kg = 375 mg/d, rounded to 400 mg/d.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

10. *Solution to problem 10* The revised phenytoin dose of patient SA would be calculated as follows:

Empiric Dosing Method

1. *Empirically suggest new phenytoin dose.*

The next logical dose to prescribe is phenytoin sodium 200 mg every morning plus 300 mg every evening.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Mullen Method

1. *Use Mullen method to estimate a new phenytoin dose for desired steady-state concentration.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 600 mg/d = 552 mg/d,

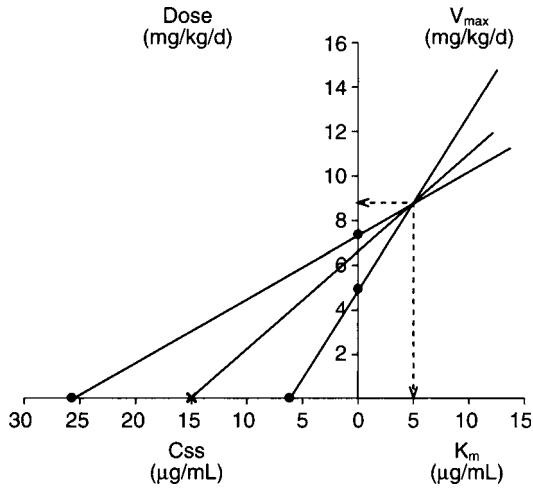

FIGURE 10-13 Solution to problem 10 using Mullen graph.

552 mg/d / 75 kg IBW = 7.4 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 75 kg IBW = 4.9 mg/kg/d; Figure 10-13.) According to the graph, a dose of 6.7 mg/kg/d of phenytoin is required to achieve a steady-state concentration equal to 15 μg/mL. This equals an extended phenytoin sodium capsule dose of 500 mg/d or 200 mg every morning plus 300 mg every evening: (6.7 mg/kg/d · 75 kg)/0.92 = 546 mg/d, rounded to 500 mg/d. V_{max} = 8.8 mg/kg/d and K_m = 5 μg/mL for this patient.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Ludden Method

1. *Use Ludden method to estimate V_{max} and K_m.*

Using the graph, the serum concentration/dose information is plotted. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 600 mg/d = 552 mg/d, 552 mg/d / 75 kg IBW = 7.4 mg/kg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d, 368 mg/d / 75 kg IBW = 4.9 mg/kg/d; Figure 10-14.) According to the graph, V_{max} = 659 mg/d and K_m = 4.9 mg/L.

Because only two dose/steady-state concentrations pairs are available, a direct mathematical solution can also be conducted: $-K_m = (MD_1 - MD_2) / [(MD_1/Css_1) - (MD_2 / Css_2)]$ = (552 mg/d − 368 mg/d) / [(552 mg/d / 25.7 mg/L) − (368 mg/d / 6.2 mg/L)] = − 4.9 mg/L, K_m = 4.9 mg/L; $V_{max} = MD + K_m(MD/Css)$ = 368 mg/d + 4.9 mg/L (368 mg/d / 6.2 mg/L) = 659 mg/d.

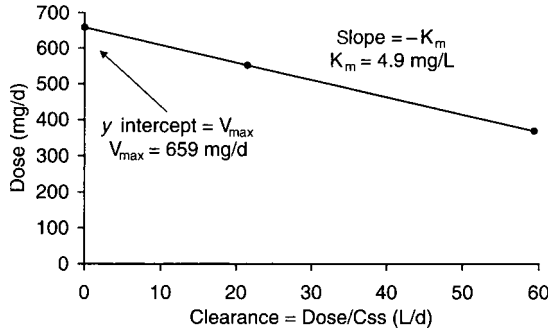

FIGURE 10-14 Solution to problem 10 using Ludden graph.

2. *Use Michaelis-Menten equation to compute a new phenytoin dose for desired steady-state concentration.*

According to the Michaelis-Menten equation, a dose equal to 500 mg of phenytoin sodium is required to achieve a steady-state concentration equal to 15 μg/mL:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{659 \text{ mg/d} \cdot 15 \text{ mg/L}}{0.92\ (4.9 \text{ mg/L} + 15 \text{ mg/L})} = 540 \text{ mg/d, rounded to } 500 \text{ mg/d}$$

This dose would administered by giving 200 mg every morning plus 300 mg every evening.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Bayesian Pharmacokinetic Computer Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

DrugCalc requires doses to be entered in terms of phenytoin. (Note: Phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 600 mg/d = 552 mg/d; phenytoin dose = 0.92 · phenytoin sodium dose = 0.92 · 400 mg/d = 368 mg/d.)

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 90 L, a V_{max} equal to 510 mg/d, and a K_m equal to 4.3 mg/L.

3. *Compute dose required to achieve desired phenytoin serum concentrations.*

The one-compartment model Michaelis-Menten equations used by the program to compute doses indicates that a dose of 440 mg/d of phenytoin will produce a total steady-state concentration of 15 μg/mL. This is equivalent to 478 mg/d of phenytoin

sodium (440 mg/d phenytoin / 0.92 = 478 mg/d phenytoin sodium), and this dose would be rounded to 500 mg/d given as 200 mg in the morning plus 300 mg in the evening.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

11. *Solution to problem 11* For patient VG:

1. *Choose appropriate equation to estimate normalized total phenytoin concentration at the appropriate temperature*

$$C_{\text{Normal Binding}} = C / (0.25 \cdot \text{Alb} + 0.1) = (8.9\ \mu\text{g/mL}) / (0.25 \cdot 2.4\ \text{g/dL} + 0.1)$$
$$= 12.7\ \mu\text{g/mL}$$
$$(C_{f_{EST}}) = 0.1\ C_{\text{Normal Binding}} = 0.1 \cdot 12.7\ \mu\text{g/mL} = 1.3\ \mu\text{g/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 12.7 μg/mL for a patient with normal drug protein binding ($C_{f_{EST}}$ = 1.3 μg/mL). Because the estimated total value is within the therapeutic range of 10–20 μg/mL, it is likely that the patient has an unbound phenytoin concentration within the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

12. *Solution to problem 12* For patient DE:

1. *Choose appropriate equation to estimate normalized total phenytoin concentration.*

$$C_{\text{Normal Binding}} = C/(0.1 \cdot \text{Alb} + 0.1) = (8.1\ \mu\text{g/mL})/(0.1 \cdot 2.0\ \text{g/dL} + 0.1) = 27\ \mu\text{g/mL}$$
$$(C_{f_{EST}}) = 0.1\ C_{\text{Normal Binding}} = 0.1 \cdot 27\ \mu\text{g/mL} = 2.7\ \mu\text{g/mL}$$

This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 27 μg/mL for a patient with normal drug protein binding ($C_{f_{EST}}$ = 2.7 μg/mL). Because the estimated total value is above the therapeutic range of 10–20 μg/mL, it is likely that the patient has an unbound phenytoin concentration above the therapeutic range. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

13. *Solution to problem 13* For patient KL:

1. *Choose appropriate equation to estimate unbound phenytoin concentration.*

$$C_{f_{EST}} = (0.095 + 0.001 \cdot \text{VPA})\text{PHT}$$
$$= (0.095 + 0.001 \cdot 90\ \mu\text{g/mL})6\ \mu\text{g/mL} = 1.1\ \mu\text{g/mL}$$

This patient's estimated unbound phenytoin concentration is expected to be within the therapeutic range for unbound concentrations. If possible, this should be confirmed by obtaining an actual, measured unbound phenytoin concentration.

14. *Solution to problem 14* For patient YS:

Pharmacokinetic Dosing Method

1. *Estimate Michaelis-Menten constants according to disease states and conditions present in the patient.*

The V_{max} for a 7- to 16-year-old adolescent patient with normal liver and renal function is 9 mg/kg/d. For a 35-kg patient, V_{max} = 315 mg/d: V_{max} = 9 mg/kg/d · 35 kg = 315 mg/d. For this individual, K_m = 6 mg/L.

2. *Compute dosage regimen.*

Oral phenytoin suspension will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for phenytoin is:

$$MD = \frac{V_{max} \cdot Css}{S(K_m + Css)} = \frac{315 \text{ mg/d} \cdot 12 \text{ mg/L}}{1.0(6 \text{ mg/L} + 12 \text{ mg/L})} = 210 \text{ mg/d, rounded to } 200 \text{ mg/d}$$

Phenytoin suspension 100 mg every 12 hours would be prescribed for the patient. A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Literature-Based Recommended Dosing

1. *Estimate phenytoin dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for phenytoin suspension in an adolescent patient is 5–10 mg/kg/d. Using a rate of 6 mg/kg/d, the initial dose would be 200 mg/d: 6 mg/kg/d · 35 kg = 210 mg/d, rounded to 200 mg/d. Using a dosage interval of 12 hours, the prescribed dose would be 100 mg of phenytoin suspension every 12 hours.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

15. *Solution to problem 15* The revised phenytoin dose of patient YS would be calculated as follows:

Empiric Dosing Method

1. *Suggest new phenytoin dose.*

Since the patient is receiving phenytoin suspension, a convenient dosage change would be 50 mg/d and a decrease to 250 mg/d or 125 mg every 12 hours is empirically suggested.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage decrease, then compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.*

Since the patient is receiving phenytoin suspension, a convenient dosage change would be 50 mg/d and a decrease to 250 mg/d is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state phenytoin serum concentration would equal: $Css_{new} = (D_{new}/D_{old})Css_{old}$ = (250 mg/d / 300 mg/d) 23 μg/mL = 19 μg/mL. Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to decrease 15%, or 0.85 times, to 33%, or 0.67 times, more than that predicted by linear pharmacokinetics: Css = 19 μg/mL · 0.85 = 16.2 μg/mL and Css = 19 μg/mL · 0.67 = 12.7 μg/mL. Thus, a dosage decrease of 50 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 13–16 μg/mL.

A steady-state trough total phenytoin serum concentration should be measured after steady state is attained in 7–14 days. Phenytoin serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenytoin toxicity.

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11

CARBAMAZEPINE

INTRODUCTION

Carbamazepine is an iminostilbene derivative related to the tricyclic antidepressants that is used in the treatment of tonic-clonic (grand mal), partial or secondarily generalized seizures (Table 11-1).[1,2] Although methods have been suggested to treat acute seizures with carbamazepine, lack of an intravenous dosage form has limited its use in this area. Thus, the drug is used primarily as a prophylactic agent in the chronic therapy of epilepsy. Carbamazepine is also a useful agent to treat trigeminal neuralgia and bipolar affective disorders.[2,3]

The antiseizure activity of carbamazepine is related to its ability to decrease transmission in the nucleus ventralis anterior section of the thalamus, an area of the brain thought to be involved with the generalization and propagation of epileptic discharges.[1,2] Although the exact cellular mechanism of action is unclear, inhibition of voltage-gated sodium channels appears to be involved. Additionally, carbamazepine depresses posttetanic potentiation and may prevent increases in cyclic adenosine monophosphate (cAMP).

THERAPEUTIC AND TOXIC CONCENTRATIONS

The accepted therapeutic range for carbamazepine is 4–12 μg/mL when the drug is used for the treatment of seizures. Carbamazepine plasma protein binding is quite variable among individuals because it is bound to both albumin and α_1-acid glycoprotein (AGP). In patients with normal concentrations of these proteins, plasma protein binding is 75–80% resulting in a free fraction of drug of 20–25%.[4–6] AGP is classified as an acute phase reactant protein that is present in lower amounts in all individuals but is secreted in large amounts in response to certain stresses and disease states such as trauma, heart failure, and myocardial infarction. In patients with these disease states, carbamazepine binding to AGP can be even larger resulting in an unbound fraction as low as 10–15%.

Little prospective work has been done to establish the therapeutic range for unbound carbamazepine serum concentrations or the clinical situations where unbound carbamazepine

TABLE 11-1 International Classification of Epileptic Seizures with Treatment Recommendations[39,40]

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	*Drugs of choice* Carbamazepine Phenytoin Lamotrigine Oxcarbazepine *Alternatives* Valproic acid Gabapentin Topiramate Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)	*Drugs of choice* Ethosuximide Valproic acid *Alternatives* Lamotrigine Clonazepam Zonisamide Levetiracetam
	2. Tonic-clonic seizures (also known as grand mal seizures)	*Drugs of choice* Valproic acid Phenytoin Carbamazepine *Alternatives* Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

serum concentration measurement is useful. As an initial guide, 25% of the total carbamazepine therapeutic range has been used to establish a preliminary desirable range for unbound carbamazepine serum concentrations of 1–3 μg/mL. Although carbamazepine is highly plasma protein bound, it is harder to displace this agent to the extent that a clinically important change in protein binding takes place. Generally speaking, a doubling in unbound fraction in the plasma is required to produce such an alteration. In comparison, phenytoin is 90% protein bound under usual circumstances resulting in an unbound fraction in the plasma of 10%. It is relatively easy to change the protein binding of phenytoin from 90–80%, under a variety of disease states or conditions, which increases the unbound fraction in the plasma from 10% to 20%. However, it is very difficult to change the protein binding of carbamazepine from 80% to 60% to achieve the same doubling of unbound fraction in the plasma (20–40%). As a result of this, the use of unbound carbamazepine serum concentrations are currently limited to those patients that have total concentrations within the therapeutic range but experience adverse effects usually seen at higher concentrations, or those patients that have total concentrations below the therapeutic range but have a therapeutic response usually observed at higher concentrations.

Carbamazepine-10, 11-epoxide is an active metabolite of carbamazepine that contributes to both the therapeutic and toxic effects of the drug, and can be measured in serum samples at a limited number of epilepsy centers.[7–13] The concentration of the epoxide is often related to the presence or absence of other inhibitors or inducers of hepatic drug metabolizing enzymes. Epoxide concentrations tend to be higher in patients taking enzyme inducers and lower in patients taking enzyme inhibitors. The percent of epoxide to parent drug in chronically treated patients averages about 12% for carbamazepine monotherapy, 14% when carbamazepine is taken with phenobarbital, 18% when carbamazepine is taken with phenytoin, and about 25% when carbamazepine is taken with both phenytoin and phenobarbital. Currently, the therapeutic range of carbamazepine-10, 11-epoxide is not known although a suggested range of 0.4–4 μg/mL is used by several research centers.

In the upper end of the therapeutic range (>8 μg/mL) some patients will begin to experience the concentration-related adverse effects of carbamazepine treatment: nausea, vomiting, lethargy, dizziness, drowsiness, headache, blurred vision, diplopia, unsteadiness, ataxia, incoordination. Because carbamazepine induces its own hepatic metabolism, these adverse effects can also be seen early during dosage titration periods soon after dosage increases are made. To improve patient acceptance, it is important to initiate and titrate carbamazepine doses at a slow rate to minimize side effects. Clinicians should understand that all patients with "toxic" carbamazepine serum concentrations in the listed ranges will not exhibit signs or symptoms of carbamazepine toxicity. Rather, carbamazepine concentrations in the ranges given increase the likelihood that an adverse drug effect will occur.

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects. While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (nausea, vomiting, lethargy, dizziness, drowsiness, headache, blurred vision, diplopia, unsteadiness, ataxia, incoordination).

Because carbamazepine has antidiuretic effects associated with reduced levels of antidiuretic hormone, some patients may develop hyponatremia during chronic therapy with carbamazepine, and serum sodium concentrations can be periodically measured.

Hematologic adverse effects can be divided into two types. The first is a leukopenia that occurs in many patients and requires no therapeutic intervention. The typical clinical picture is an individual with a normal white blood cell count who develops a transient decrease in this index. In a few patients, a decreased, stable white blood cell count of 3000 cells/mm^2 or less may persist and does not appear to cause any deleterious effects. The second hematologic effect is severe and usually requires discontinuation of the drug. Thrombocytopenia, leukopenia (trend downward in white blood cell count with <2500 cells/mm^2 or absolute neutrophil count <1000 cells/mm^2), or anemia are in this category. Rarely, aplastic anemia and agranulocytosis has been reported during carbamazepine treatment. Drug induced hepatitis due to carbamazepine therapy has also been reported. The severe hematologic and hepatic adverse effects tend to occur early in treatment. Because of this, many clinicians measure a complete blood cell count and liver function tests monthly for the first 3–6 months after a patient first begins carbamazepine treatment, and repeat these tests every 3–6 months for the first year. Other idiosyncratic side effects include skin rash, Stevens-Johnson syndrome, and systemic lupus-like reactions.

Carbamazepine serum concentrations should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Carbamazepine serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum. Because carbamazepine induces its own hepatic metabolism, it is fairly easy to attain toxic concentrations with modest increases in drug dose before maximal enzyme induction has occurred.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Carbamazepine is primarily eliminated by hepatic metabolism (>99%) mainly via the CYP3A4 enzyme system.[14,15] Altogether 33 metabolites have been identified with carbamazepine-10, 11-epoxide being the major species. The epoxide metabolite is active and probably contributes to both the therapeutic and toxic side effects observed during therapy. Carbamazepine is a potent inducer of hepatic drug metabolizing enzymes, and induces its own metabolism, a process known as autoinduction (Figure 11-1).[16–20] As a result, patients cannot initially be placed on the dose of carbamazepine that will ultimately result in a safe and effective outcome. At first, patients are started on $^1/_4$–$^1/_3$ of the desired maintenance dose. This exposes hepatic drug metabolizing enzymes to carbamazepine and begins the induction process. The dose is increased by a similar amount every 2–3 weeks until the total desired daily dose is ultimately given. This gradual exposure of carbamazepine allows liver enzyme induction and carbamazepine clearance increases to occur over a 6- to 12-week time period. Therapeutic effect and steady-state carbamazepine serum concentrations can be assessed 2–3 weeks after the final dosage increase. Autoinduction continues to occur in patients who are stabilized on a carbamazepine dose but require a dosage increase. It

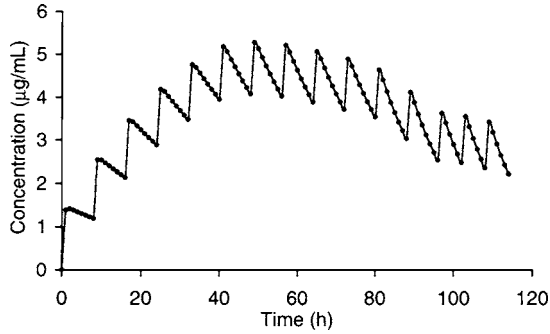

FIGURE 11-1 Carbamazepine induces its own metabolism via the hepatic microsomal enzyme system CYP3A4 system. This process is known as *autoinduction.* When dosing is initiated, serum concentrations increase according to the baseline clearance and half-life. After a few doses of carbamazepine, enough autoinduction has occurred that clearance increases, half-life decreases, and drug accumulation slows down. With additional exposure of liver tissue to carbamazepine, clearance continues to increase and half-life continues to shorten. As a result of these pharmacokinetic changes, carbamazepine concentrations decline and ultimately stabilize in accord with the new clearance and half-life values. Maximal autoinduction usually occurs 2–3 weeks after dosing commenced. Because of the autoinduction phenomenon, the ultimate desired maintenance dose cannot be started with the first dose. Additional autoinduction occurs with subsequent increases in dose.

appears that a 2- to 3-week time period is also needed under chronic dosing conditions for maximal autoinduction to occur after a dosage increase. The effects of autoinduction are reversible even when doses are held for as few as 6 days.[21]

An injectable form of carbamazepine is not available. For oral use, the drug is available as immediate-release tablets (chewable: 100 mg, regular: 100 mg, 200 mg, 300 mg), sustained-release tablets (100 mg, 200 mg, 400 mg), sustained-release capsules (100, 200, 300 mg), and suspension (100 mg/5 mL). The rapid release dosage forms are erratically absorbed from the gastrointestinal tract resulting in peak concentrations between 2–24 hours after a single dose of tablets (average 6 hours). During multiple dose studies after maximal autoinduction has taken place, peak concentrations occur about 3 hours after tablet administration. Peak concentrations after multiple doses of the sustained-release dosage forms are observed 3–12 hours after administration. Rectal administration of an extemporaneously compounded carbamazepine retention enema results in similar serum concentrations as that produced by a comparable immediate-release tablet.[22,23]

The absolute oral bioavailability of carbamazepine is not known because no intravenous form of the drug is available for comparison. Based on the best estimates available, carbamazepine bioavailability is good and averages about 85–90%. The relative bioavailability of other dosage forms (chewable tablet, suspension, sustained-release tablets and sustained-release capsules) compared to the immediate-release tablet approaches 100%. If a patient is receiving a stable dose of carbamazepine on one dosage form, the same total daily dose of another dosage form can typically be substituted without adjustment. However, some bioequivalence problems have been reported for generic carbamazepine products.[24–26]

Usual initial maintenance doses are 10–20 mg/kg/d for children under 6 years of age, 200 mg/d for children 6–12 years old and 400 mg/d for adults. Twice daily dosing is initially used until autoinduction takes place. Dosage increases to allow for autoinduction

are made every 2–3 weeks depending on response and adverse effects. Most adults will require 800–1200 mg/d of carbamazepine while older children will require 400–800 mg/d. Although some minor side effects occur, single loading doses of 8 mg/kg have been given to adults as suspension or immediate-release tablets in order to achieve therapeutic concentrations within 2–4 hours after administration.[27]

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

After single doses of carbamazepine, the oral clearance (Cl/F) is 11–26 mL/h/kg and half-life is 35 hours for adults.[28–30] During multiple dosing after maximal autoinduction has taken place, oral clearance equals 50–100 mg/h/kg and half-life equals 5–27 hours. In children 6–12 years old, oral clearance and half-life equal 50–200 mL/h/kg and 3–15 hours, respectively, during chronic dosing. Clearance rates can be higher and half-lives shorter in patients receiving other hepatic drug metabolizing enzyme inducers (phenytoin, phenobarbital, rifampin).[31–33] Carbamazepine volume of distribution using immediate-release tablets (V/F) is 1–2 L/kg.

Patients with liver cirrhosis or acute hepatitis have reduced carbamazepine clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of CYP3A4 available to metabolize the drug and decreases clearance. The volume of distribution may be larger because of reduced plasma protein binding. Protein binding may be reduced and unbound fraction maybe increased due to hypoalbuminemia and/or hyperbilirubinemia (especially albumin ≤3 g/dL and/or total bilirubin ≥2 mg/dL). However, the effects that liver disease has on carbamazepine pharmacokinetics are highly variable and difficult to accurately predict. It is possible for a patient with liver disease to have relatively normal or grossly abnormal carbamazepine clearance and volume of distribution. For example, a liver disease patient who has relatively normal albumin and bilirubin concentrations can have a normal volume of distribution for carbamazepine. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 11-2).[34] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 11-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for carbamazepine. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Carbamazepine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Elderly patients have lower carbamazepine oral clearance rates than younger adults so lower initial doses (100 mg/d) may be used in older individuals. During the third trimester of pregnancy, oral clearance of carbamazepine may decrease and require dosage

TABLE 11-2 Child-Pugh Scores for Patients with Liver Disease[34]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

adjustment. Doses of carbamazepine do not require adjustment for patients with renal failure, and the drug is not removed by dialysis.[35,36] Breast milk concentrations of carbamazepine are about 60% of concurrent serum concentrations.

DRUG INTERACTIONS

Carbamazepine is a potent inducer of hepatic drug metabolizing enzyme systems and P-glycoprotein.[37] The CYP1A2, CYP2C9, and CYP3A4 enzyme systems are all induced by carbamazepine, and drug substrates for other enzyme systems also have known drug interactions with carbamazepine. Other antiepileptic drugs that have their clearance rates increased and steady-state concentrations decreased by carbamazepine-related enzyme induction include felbamate, lamotrigine, phenytoin, primidone, tiagabine, topiramate, and valproic acid. Carbamazepine therapy also increases the clearance and decreases steady-state concentrations of many other drugs including oral contraceptives, calcium channel blockers, tricyclic antidepressants, cyclosporin, tacrolimus, theophylline, and warfarin. As a general rule, when carbamazepine is added to a patient's drug regimen, loss of therapeutic effect of one of the other drugs the patient is taking must be considered as a possible drug interaction with carbamazepine.

Carbamazepine is a substrate for CYP3A4, and other drugs can affect carbamazepine clearance and steady-state serum concentrations.[37] Phenytoin and phenobarbital can increase carbamazepine clearance and decrease carbamazepine steady-state serum concentrations. Cimetidine, macrolide antibiotics, azole antifungals, fluoxetine, fluvoxamine, nefazodone, cyclosporine, diltiazem, verapamil, indinavir, and ritonavir are examples of drugs that decrease carbamazepine clearance and increase carbamazepine steady-state concentrations. Administration of single doses of carbamazepine with grapefruit juice increases both the area under the serum concentration versus time curve (AUC) and maximal serum concentration (C_{max}) of carbamazepine by about 40%.

INITIAL DOSAGE DETERMINATION METHODS

Because of the large amount of variability in carbamazepine pharmacokinetics, even when concurrent disease states and conditions are identified, most clinicians believe that the use of standard carbamazepine doses for various situations are warranted. The original

computation of these doses were based on the pharmacokinetic dosing methods, and subsequently modified based on clinical experience. In general, the expected carbamazepine steady-state serum concentrations used to compute these doses was 6–8 μg/mL. Usual initial maintenance doses are 10–20 mg/kg/d for children under 6 years of age, 200 mg/d for children 6–12 years old and 400 mg/d for adults. Twice daily dosing is initially used until autoinduction takes place. Dosage increases to allow for autoinduction are made every 2–3 weeks depending on response and adverse effects. Most adults will require 800–1200 mg/d of carbamazepine while older children will require 400–800 mg/d. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses prescribed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

Example 1 KL is a 51-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 μg/mL.

1. *Estimate carbamazepine dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for immediate-release carbamazepine tablets in an adult patient is 200 mg twice daily (400 mg/d). This dose would be titrated upward in 200-mg increments every 2–3 weeks while monitoring for adverse and therapeutic effects. The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 800–1200 mg/d.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

Example 2 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 μg/mL.

1. *Estimate carbamazepine dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for immediate-release carbamazepine tablets for a child in this age range is 100 mg twice daily (200 mg/d). This dose would be titrated upward in 100-mg increments every 2–3 weeks while monitoring for adverse and therapeutic effects. The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 400–800 mg/d.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

USE OF CARBAMAZEPINE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce carbamazepine serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the autoinduction pharmacokinetics followed by the drug, the narrow therapeutic index of carbamazepine and the desire to avoid adverse side effects of carbamazepine, measurement of carbamazepine serum concentrations is conducted for almost all patients to ensure that therapeutic, nontoxic levels are present. In addition to carbamazepine serum concentrations, important patient parameters (seizure frequency, potential carbamazepine side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions. When carbamazepine serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment.

Pseudolinear Pharmacokinetics Method

A simple, easy way to approximate new total serum concentrations after a dosage adjustment with carbamazepine is to temporarily assume linear pharmacokinetics, then subtract 10–20% for a dosage increase or add 10–20% for a dosage decrease to account for autoinduction pharmacokinetics: $Css_{new} = (D_{new} / D_{old})Css_{old}$, where Css_{new} is the expected steady-state concentration from the new carbamazepine dose in μg/mL, Css_{old} is the measured steady-state concentration from the old carbamazepine dose in μg/mL, D_{new} is the new carbamazepine dose to be prescribed in mg/d, and D_{old} is the currently prescribed carbamazepine dose in mg/d. *Note:* This method is only intended to provide a rough approximation of the resulting carbamazepine steady-state concentration after an appropriate dosage adjustment, such as 100–200 mg/d, has been made. The pseudolinear pharmacokinetics method should never be used to compute a new dose based on measured and desired carbamazepine concentrations.

Example 1 KL is a 51-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. After dosage titration, the patient was prescribed 200 mg in the morning, 200 mg in the afternoon, and 400 mg at bedtime (800 mg/d) of carbamazepine tablets for 1 month, and the steady-state carbamazepine total concentration equals 3.8 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the therapeutic range.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for autoinduction pharmacokinetics.*

Since the patient is receiving carbamazepine tablets, a convenient dosage change would be 200 mg/d and an increase to 1000 mg/d (400 mg in the morning and bedtime, 200 mg in the afternoon) is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state carbamazepine serum concentration would equal $Css_{new} = (D_{new} / D_{old})Css_{old} =$

(1000 mg/d / 800 mg/d) 3.8 μg/mL = 4.8 μg/mL. Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics: Css = 4.8 μg/mL · 0.90 = 4.3 μg/mL and Css = 4.8 μg/mL · 0.80 = 3.8 μg/mL. Thus, a dosage increase of 200 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 3.8 and 4.3 μg/mL.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is attained in 2–3 weeks. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

Example 2 UO is a 10-year-old, 40-kg male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. After dosage titration, the patient was prescribed 200 mg three times daily (600 mg/d) of carbamazepine tablets for 1 month, and the steady-state carbamazepine total concentration equals 5.1 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the middle of the therapeutic range.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for autoinduction pharmacokinetics.*

Since the patient is receiving carbamazepine tablets, a convenient dosage change would be 200 mg/d and an increase to 800 mg/d (300 mg in the morning and bedtime, 200 mg in the afternoon) is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state carbamazepine serum concentration would equal $Css_{new} = (D_{new} / D_{old})Css_{old}$ = (800 mg/d / 600 mg/d) 5.1 μg/mL = 6.8 μg/mL. Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics: Css = 6.8 μg/mL · 0.90 = 6.1 μg/mL and Css = 6.8 μg/mL · 0.80 = 5.4 μg/mL. Thus, a dosage increase of 200 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 5.4 μg/mL and 6.1 μg/mL.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is attained in 2–3 weeks. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[38] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Unfortunately, these types of computer programs have not been able to give acceptable solutions unless four or more carbamazepine

concentrations are available. This is due to the complexity of the autoinduction pharmacokinetics that carbamazepine follows under chronic dosing conditions. Because of the large number of concentrations needed, this dosage adjustment approach cannot be recommended at this time.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current anticonvulsant therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with carbamazepine exists.

1. TY is a 47-year-old, 85-kg (6 ft 1 in) male with tonic-clonic seizures who requires therapy with oral carbamazepine. He has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 μg/mL.

2. Patient TY (please see problem 1) was prescribed 400 mg every 12 hours of sustained-release carbamazepine tablets for 1 month after dosage titration, and the steady-state carbamazepine total concentration equals 4.5 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the middle portion of the therapeutic range.

3. IU is a 9-year-old, 35-kg female with simple partial seizures who requires therapy with oral carbamazepine. She has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 μg/mL.

4. Patient IU (please see problem 3) was prescribed 150 mg three times daily (450 mg/d) of carbamazepine suspension for 1 month after dosage titration, and the steady-state carbamazepine total concentration equals 4.9 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the middle of the therapeutic range.

5. LK is a 4-year-old, 22-kg male with complex partial seizures who requires therapy with carbamazepine suspension. He has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 μg/mL.

6. Patient LK (please see problem 5) was prescribed 100 mg three times daily (300 mg/d) of carbamazepine suspension for 1 month after dosage titration, and the steady-state carbamazepine total concentration equals 6.1 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the upper end of the therapeutic range.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

1. *Estimate carbamazepine dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for immediate-release carbamazepine tablets in an adult patient is 200 mg twice daily (400 mg/d). This dose would be titrated upward in 200-mg increments every 2–3 weeks while monitoring for adverse and therapeutic effects. The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 800–1200 mg/d.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

2. *Solution to problem 2.*

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for autoinduction pharmacokinetics.*

Since the patient is receiving sustained-release carbamazepine tablets, a convenient dosage change would be 400 mg/d and an increase to 1200 mg/d (600 mg every 12 hours) is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state carbamazepine serum concentration would equal $Css_{new} = (D_{new} / D_{old})Css_{old}$ = (1200 mg/d / 800 mg/d) 4.5 μg/mL = 6.8 μg/mL. Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics: Css = 6.8 μg/mL · 0.90 = 6.1 μg/mL and Css = 6.8 μg/mL · 0.80 = 5.4 μg/mL. Thus, a dosage increase of 400 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 5.4–6.1 μg/mL.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is attained in 2–3 weeks. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

3. *Solution to problem 3.*

1. *Estimate carbamazepine dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for carbamazepine suspension in a child in this age range is 100 mg twice daily (200 mg/d). This dose would be titrated upward in 100-mg increments every 2–3 weeks while monitoring for adverse and therapeutic effects. The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 400–800 mg/d.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained. Carbamazepine

serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

4. *Solution to problem 4.*

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for autoinduction pharmacokinetics.*

Since the patient is receiving carbamazepine suspension, a convenient dosage change would be 150 mg/d and an increase to 600 mg/d (200 mg three times daily) is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state carbamazepine serum concentration would equal $Css_{new} = (D_{new}/D_{old})Css_{old}$ = (600 mg/d / 450 mg/d) 4.9 μg/mL = 6.5 μg/mL. Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics: Css = 6.5 μg/mL · 0.90 = 5.9 μg/mL and Css = 6.5 μg/mL · 0.80 = 5.2 μg/mL. Thus, a dosage increase of 150 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 5.2 μg/mL and 5.9 μg/mL.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is attained in 2–3 weeks. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

5. *Solution to problem 5.*

1. *Estimate carbamazepine dose according to disease states and conditions present in the patient.*

The suggested initial dosage rate for carbamazepine suspension in a child in this age range is 10–20 mg/kg/d. Using a dose of 15 mg/kg/d, the target maintenance dose equals 300 mg/d (15 mg/kg/d · 22 kg = 330 mg/d, rounded to 300 mg/d). The starting dose would be $^1/_4$–$^1/_3$ of the target maintenance dose or 100 mg/d given as 50 mg twice daily. This dose would be titrated upward in 100 mg/d increments every 2–3 weeks while monitoring for adverse and therapeutic effects. The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 300 mg/d given as 100 mg three times daily.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

6. *Solution to problem 6.*

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for autoinduction pharmacokinetics.*

Since the patient is receiving carbamazepine suspension, a convenient dosage change would be 150 mg/d and an increase to 450 mg/d (150 mg three times daily) is suggested. Using pseudolinear pharmacokinetics, the resulting total steady-state carbamazepine

serum concentration would equal $Css_{new} = (D_{new} / D_{old})Css_{old}$ = (450 mg/d / 300 mg/d) 6.1 μg/mL = 9.2 μg/mL. Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics: Css = 9.2 μg/mL · 0.90 = 8.3 μg/mL and Css = 9.2 μg/mL · 0.80 = 7.4 μg/mL. Thus, a dosage increase of 150 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 7.4–8.3 μg/mL.

A steady-state trough total carbamazepine serum concentration should be measured after steady state is attained in 2–3 weeks. Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

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12

VALPROIC ACID

INTRODUCTION

Valproic acid is an agent that is chemically related to free fatty acids and is used in the treatment of generalized, partial, and absence (petit mal) seizures. As such, it has the widest spectrum of activity compared to the other currently available antiepileptic drugs (Table 12-1).[1,2] Now available in intravenous, as well as oral, form, valproic acid can be used for the acute treatment and chronic prophylaxis of seizures.[3,4] Valproic acid is also a useful agent for the treatment of bipolar affective disorders and the prevention of migraine headaches.[5]

Although the precise mechanism of action for valproic acid is unknown, its antiepileptic effect is thought to result from its ability to increase concentrations of the neuroinhibitor γ-aminobutyric acid (GABA), to potentiate the postsynaptic response to GABA, or to exert a direct effect on cellular membranes.[6]

THERAPEUTIC AND TOXIC CONCENTRATIONS

The generally accepted therapeutic range for total valproic acid steady-state concentrations is 50–100 μg/mL, although some clinicians suggest drug concentrations as high as 175 μg/mL with appropriate monitoring of serum concentrations and possible adverse effects. Valproic acid is highly protein bound to albumin with typical values of 90–95%.[7,8] Plasma protein binding of valproic acid is saturable within the therapeutic range, which results in less protein binding and higher unbound fraction of drug at higher concentrations. The concentration-dependent protein binding of valproic acid causes the drug to follow nonlinear pharmacokinetics (Figure 12-1). This type of nonlinear pharmacokinetics is fundamentally different than that observed during phenytoin administration. Phenytoin hepatic metabolism becomes saturated, which causes Michaelis-Menten pharmacokinetics to take place. As a result, when phenytoin doses are increased, total and unbound steady-state concentrations increase more than a proportional amount (e.g., when the dose

TABLE 12-1 International Classification of Epileptic Seizures with Treatment Recommendations

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	*Drugs of choice* Carbamazepine Phenytoin Lamotrigine Oxcarbazepine *Alternatives* Valproic acid Gabapentin Topiramate Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)	*Drugs of choice* Ethosuximide Valproic acid *Alternatives* Lamotrigine Clonazepam Zonisamide Levetiracetam
	2. Tonic-clonic seizures (also known as grand mal seizures)	*Drugs of choice* Valproic acid Phenytoin Carbamazepine *Alternatives* Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

is doubled, serum concentrations may increase three- to five-fold or more). In the case of valproic acid, when the dose is increased total drug steady-state concentration increases less than expected, but unbound steady-state drug concentration increases in a proportional fashion (e.g., when the dose is doubled, total serum concentration increases 1.6–1.9 times but unbound steady-state serum concentration doubles; Figure 12-2). The pharmacokinetic rationale for these changes is explained fully in the Basic Clinical Pharmacokinetic Parameters section later in this chapter.

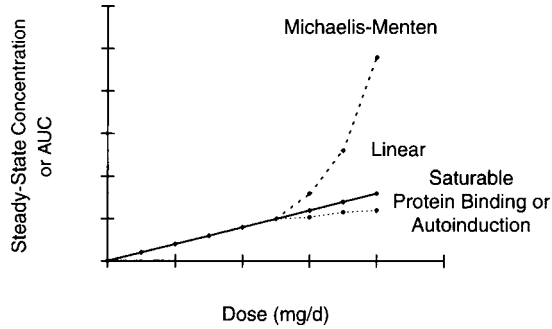

FIGURE 12-1 If a drug follows linear pharmacokinetics, Css or AUC increases proportionally with dose resulting in a straight line on the plot. Nonlinear pharmacokinetics occurs when the Css or AUC versus dose plot results in something other than a straight line. If a drug follows Michaelis-Menten pharmacokinetics (e.g., phenytoin, aspirin), as steady-state drug concentrations approach Km serum concentrations increase more than expected due to dose increases. If a drug follows nonlinear protein binding (e.g., valproic acid, disopyramide), total steady-state drug concentrations increase less than expected as dose increases.

Insufficient prospective work has been done to establish the therapeutic range for unbound valproic acid steady-state serum concentrations. As an initial guide, 5% of the lower end and 10% of the upper end of the total concentration therapeutic range is used to construct the preliminary unbound steady-state concentration therapeutic range for valproic acid of 2.5–10 μg/mL. The percent used for each case is the average unbound fraction of drug at the appropriate concentration.

More information is available that identifies the clinical situations where unbound valproic acid serum concentration measurement is useful. As is the case with phenytoin, measurement of unbound valproic acid serum concentrations should be considered in patients with factors known to alter valproic acid plasma protein binding.[8–12] These factors

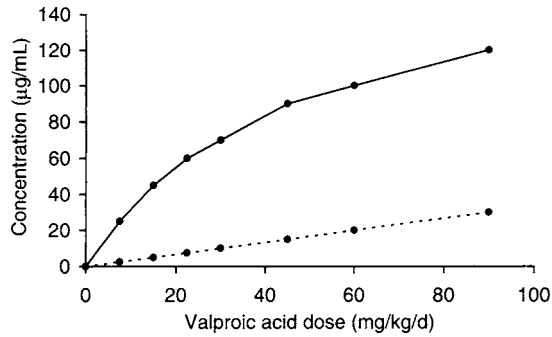

FIGURE 12-2 Although total valproic acid concentrations increase in a nonlinear fashion with dosage increases *(solid line),* unbound, or "free" valproic acid concentrations increase in a linear fashion with dosage increases *(dashed line).* Valproic acid is a low extraction ratio drug, and its unbound serum concentrations are only a function of intrinsic clearance (Cl'_{int}): Css, u = (D/τ) / Cl'_{int}, where D is valproic acid dose in mg, τ is the dosage interval in hours, and Css, u is the unbound steady-state valproic acid concentration.

fall into three broad categories: (1) lack of binding protein where there are insufficient plasma concentrations of albumin, (2) displacement of valproic acid from albumin binding sites by endogenous compounds, and (3) displacement of valproic acid from albumin binding sites by exogenous compounds (Table 12-2).

Low albumin concentrations, known as hypoalbuminemia, can be found in patients with liver disease or nephrotic syndrome, pregnant women, cystic fibrosis patients, burn patients, trauma patients, malnourished individuals, and the elderly. Albumin concentrations below 3 g/dL are associated with high valproic acid unbound fractions in the plasma. Albumin is manufactured by the liver so patients with hepatic disease may have difficulty synthesizing the protein. Patients with nephrotic syndrome waste albumin by eliminating it in the urine. Malnourished patients can be so nutritionally deprived that albumin production is impeded. Malnourishment is the reason for hypoalbuminemia in some elderly patients, although there is a general downtrend in albumin concentrations in older patients. However, the unbound fraction of valproic acid is higher in elderly patients even if albumin concentrations are within the normal range. While recovering from their injuries, burn and trauma patients can become hypermetabolic and albumin concentrations can decrease if enough calories are not supplied during this phase of their disease state. Albumin concentrations may decline during pregnancy as maternal reserves are shifted to the developing fetus and are especially prevalent during the third trimester.

Displacement of valproic acid from plasma protein binding sites by endogenous substances can occur in patients with hepatic or renal dysfunction. The mechanism is competition for albumin plasma protein binding sites between the exogenous substances and valproic acid. Bilirubin (a by-product of heme metabolism) is broken down by the liver, so patients with hepatic disease can have excessive bilirubin concentrations. Total bilirubin concentrations in excess of 2 mg/dL are associated with abnormal valproic acid plasma protein binding. End-stage renal disease patients (creatinine clearance <10–15 mL/min) with uremia (blood urea nitrogen concentrations >80–100 mg/dL) accumulate unidentified compound(s) in their blood that displace valproic acid from plasma protein binding sites. Abnormal valproic acid binding persists in these patients even when dialysis procedures are instituted.

Valproic acid plasma protein binding displacement can also occur because of exogenously administered compounds such as drugs. In this case, the mechanism is competition for albumin binding sites between valproic acid and other agents. Other drugs that

TABLE 12-2 Disease States and Conditions that Alter Valproic Acid Plasma Protein Binding

INSUFFICIENT ALBUMIN CONCENTRATION (HYPOALBUMINEMIA)	DISPLACEMENT BY ENDOGENOUS COMPOUNDS	DISPLACEMENT BY EXOGENOUS COMPOUNDS
Liver disease	Hyperbilirubinemia	Drug interactions
Nephrotic syndrome	Jaundice	Warfarin
Pregnancy	Liver disease	Phenytoin
Cystic fibrosis	Renal dysfunction	Aspirin (>2 g/d)
Burns		NSAIDs with high albumin binding
Trauma		
Malnourishment		
Elderly		

are highly bound to albumin and cause plasma protein binding displacement drug interactions with valproic acid include warfarin, phenytoin, aspirin (>2 g/d), and some highly bound nonsteroidal antiinflammatory agents.

In the upper end of the therapeutic range (>75 μg/mL) some patients will begin to experience the concentration-dependent adverse effects of valproic acid therapy: ataxia, sedation, lethargy, and tiredness. In many individuals, these side effects dissipate with continued dosing, and slow dosage titration may assist in minimizing these adverse reactions in newly treated patients. Other concentration-related side effects of valproic acid therapy include tremor at concentrations >100 μg/mL, and stupor or coma at concentrations >175 μg/mL. Additionally, valproic acid–associated thrombocytopenia can usually be limited by a decrease in drug dose.

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects. While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (ataxia, sedation, lethargy, tiredness, tremor, stupor, coma, thrombocytopenia) as well as gastrointestinal upset associated with local irritation of gastric mucosa (nausea, vomiting, anorexia).[13] Elevated liver function tests, increased serum ammonia, alopecia, and weight gain have been reported during chronic valproic acid treatment. Serious, but rare, idiosyncratic side effects include hepatotoxicity, pancreatitis, pitting edema, systemic lupus-like reactions, and leukopenia with bone marrow changes.

Valproic acid serum concentrations should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Valproic acid serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Valproic acid is primarily eliminated by hepatic metabolism (>95%). Hepatic metabolism is via glucuronidation, β-oxidation, and α-hydroxylation. Glucuronidation is mediated principally by UGT1A6, UGT1A9, and UGT2B7.[14] Over 10 metabolites have been identified for valproic acid, and the 4-en-valproic acid metabolite may be associated with the drug's propensity to cause hepatotoxicity. About 1–5% of a valproic acid dose is recovered in the urine as unchanged drug. Valproic acid follows nonlinear pharmacokinetics owing to saturable, or concentration-dependent, plasma protein binding. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates albumin's ability to bind the drug in the plasma. When this occurs, total steady-state drug serum concentrations increase in a disproportionate manner after a

dosage increase, but unbound steady-state drug serum concentrations increase in a proportional fashion (Figure 12-2). Valproic acid is eliminated almost completely by hepatic metabolism, and it is a low hepatic extraction ratio drug. In this case the hepatic clearance rate is described by the classic relationship that is used to describe hepatic clearance: $Cl_H = [LBF \cdot (f_B Cl'_{int})] / (LBF + f_B Cl'_{int})$, where LBF is liver blood flow, f_B is the unbound fraction of drug in the blood, and Cl'_{int} is the intrinsic ability of the enzyme system to metabolize the drug. Since valproic acid has a low hepatic extraction ratio, this expression for hepatic clearance simplifies to $Cl_H = f_B Cl'_{int}$.

The clinical implication of concentration-dependent plasma protein binding pharmacokinetics is that the clearance of valproic acid is not a constant as it is with linear pharmacokinetics, but is concentration or dose dependent. As the dose or concentration of valproic acid increases, the clearance rate (Cl) increases because more unbound drug is available to hepatic enzymes for metabolism: $\uparrow Cl_H = \uparrow f_B Cl'_{int}$. This is the reason total steady-state concentrations increase disproportionately after a valproic acid dosage increase: $\uparrow Css = [F(\Uparrow D/\tau)] / \uparrow Cl_H$, where F is valproic acid bioavailability, D is valproic acid dose, τ is the dosage interval, and Cl_H is hepatic clearance. When valproic acid dose is increased, the unbound fraction increases and causes an increase in hepatic clearance. Because both dose and hepatic clearance simultaneously increase, total valproic acid concentrations increase, but by a smaller than expected amount. For example, valproic acid follows concentration-dependent plasma protein binding pharmacokinetics with average unbound fractions of 5% in the lower end of the therapeutic range (50 µg/mL) and 10% in the upper end of the therapeutic range (100 µg/mL). When the dose is increased and steady-state concentration of valproic acid increases from 50 µg/mL to 100 µg/mL, the unbound fraction increases by a factor of 2 from 5% to 10% and hepatic clearance of total drug will double within the therapeutic range: $2Cl_H = 2f_B Cl'_{int}$. Unfortunately, there is so much interpatient variability in concentration-dependent plasma protein binding parameters for valproic acid that predicting changes in unbound fraction and hepatic clearance is extremely difficult. However, since unbound steady-state concentrations are only influenced by intrinsic clearance, unbound concentrations increase in a proportional amount to dose: $Css, u = [F(D/\tau)] / Cl'_{int}$.

Valproic acid volume of distribution (V = 0.15 – 0.2 L/kg) is also affected by concentration-dependent plasma protein binding and is determined by the physiologic volume of blood (V_B) and tissues (V_T) as well as the unbound fraction of drug in the blood (f_B) and tissues (f_T): $V = V_B + (f_B/f_T)V_T$. As valproic acid concentrations increase, unbound fraction of drug in the blood increases which causes an increase in the volume of distribution for the drug: $\uparrow V = V_B + (\uparrow f_B / f_T)V_T$. Half-life ($t_{1/2}$) is related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t_{1/2} = (0.693 \cdot V) / Cl$. However, since clearance and volume of distribution are a function of dose- or concentration-dependent plasma protein binding for valproic acid, half-life also changes with drug dosage or concentration changes. As doses or concentrations increase for a drug that follows concentration-dependent plasma protein binding pharmacokinetics, clearance and volume of distribution simultaneously increase, and half-life changes are variable depending on the relative changes in clearance and volume of distribution: $\leftrightarrow t_{1/2} = (0.693 \cdot \uparrow V) / \uparrow Cl$. Using the average clearance and the volume of distribution for an adult (V = 0.15 L/kg, Cl = 10 mL/h/kg or 0.010 L/h/kg), half-life remains at 10 h [$t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 0.15$ L/kg) / 0.010 L/h/kg = 10 h. Clearance and volume

of distribution increase to 0.30 L/kg and 0.020 L/h/kg, respectively, because of decreased protein binding: $t_{1/2}$ = [(0.693 · 0.30 L) / (0.020 L/h/kg = 10 h)] as valproic acid serum concentrations increase from 50 μg/mL to 100 μg/mL. The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is variable as the dose or concentration is increased for valproic acid. On average, valproic acid half-life is 12–18 hours in adult patients with total concentrations within the therapeutic range.

Valproic acid is available as three different entities, and all of them are prescribed as valproic acid equivalents: valproic acid, sodium valproate (the sodium salt of valproic acid), and divalproex sodium (a stable coordination compound consisting of a 1:1 ratio of valproic acid and sodium valproate). For parenteral use, valproic acid is available as a 100 mg/mL solution. When given intravenously, it should be diluted in at least 50 mL of intravenous solution, and given over 1 hour (injection rates should not exceed 20 mg/min). For oral use, a syrup (50 mg/mL), soft capsule (250 mg), enteric coated capsules (125 mg, 250 mg, and 500 mg), sustained-release tablets (250 mg and 500 mg) and sprinkle capsule (125 mg, used to sprinkle into foods) are available. The enteric coated capsules are not sustained-release products, but only delay the absorption of drug after ingestion. As a result, there are less gastrointestinal side effects with the enteric coated product.

The oral bioavailability of valproic acid is very good for all dosage forms and ranges from 90% for the sustained-release tablets to 100% for the other oral dosage forms. Sustained-release tablets produce an AUC that is about 10% less than other oral dosage forms, and drug serum concentrations should be measured for patients converted between sustained-release and other oral dosage forms.[15,16] If a patient is stabilized on an oral valproic acid product, and it is necessary to switch the patient to intravenous drug, the same total daily dose of injectable valproic acid can be given to the individual. Usually, valproic acid doses are not fine-tuned to the point of directly accounting for the difference in valproic acid bioavailability. Rather, clinicians are aware that when valproic acid dosage forms are changed, the serum concentration versus time profile may change. Because of this, most individuals recheck valproic acid steady-state serum concentrations after a dosage form change is instituted.

The typical maintenance dose for valproic acid is 15 mg/kg/d resulting in 1000 mg or 500 mg twice daily for most adult patients. However, because age and coadministration of other antiepileptic drugs that are enzyme inducers (e.g., carbamazepine, phenytoin, phenobarbital) affect valproic acid pharmacokinetics, many clinicians recommend the administration of 7.5 mg/kg/d for adults or 10 mg/kg/d for children under 12 years of age receiving monotherapy and 15 mg/kg/d for adults or 20 mg/kg/d for children under 12 years of age receiving other drugs that are enzyme inducers.[17]

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

For valproic acid, oral clearance (Cl/F) is 7–12 mL/h/kg and half-life is 12–18 hours for adults.[18] In children 6–12 years old, oral clearance and half-life equal 10–20 mL/h/kg and 6–8 hours, respectively.[19] Clearance rates can be higher and half-lives shorter in patients receiving other hepatic drug–metabolizing enzyme inducers (phenytoin, phenobarbital, carbamazepine). For adults receiving other antiepileptic drugs that are enzyme

inducers, valproic acid clearance for adults is 15–18 mL/h/kg and half-lives range from 4 to 12 hours. Similarly, if children receive therapy with other antiepileptic drugs that are enzyme inducers, clearance is 20–30 mL/h/kg and half-life is 4–6 h.[20,21] Valproic acid volume of distribution (V/F) is 0.15–0.2 L/kg.[18,22]

Patients with liver cirrhosis or acute hepatitis have reduced valproic acid clearance because of destruction of liver parenchyma.[23] This loss of functional hepatic cells reduces the amount of enzymes available to metabolize the drug and decreases clearance. Valproic acid clearance in patients with liver disease is 3–4 mL/h/kg. The volume of distribution may be larger because of reduced plasma protein binding (free fraction ≈29%). Protein binding may be reduced and unbound fraction may be increased owing to hypoalbuminemia and/or hyperbilirubinemia (especially albumin ≤3 g/dL and/or total bilirubin ≥2 mg/dL). Average half-life for valproic acid in patients with liver disease is 25 hours. However, the effects that liver disease has on valproic acid pharmacokinetics are highly variable and difficult to accurately predict. It is possible for a patient with liver disease to have relatively normal or grossly abnormal valproic acid clearance and volume of distribution. For example, a liver disease patient who has relatively normal albumin and bilirubin concentrations can have a normal volume of distribution for valproic acid. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 12-3).[24] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 12-3), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for valproic acid. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Since the drug has been associated with hepatic damage, valproic acid therapy should be avoided in patients with liver disease whenever possible. Valproic acid serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Elderly patients have lower valproic acid oral clearance rates and higher unbound fractions than younger adults so lower initial doses may be used in older individuals.[8] During

TABLE 12-3 Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

the third trimester of pregnancy, oral clearance of valproic acid may decrease and require dosage adjustment.[25] Valproic acid serum concentrations exhibit some diurnal variation in patients, so the time that steady-state serum concentrations should be noted when comparing multiple values.[8,26] Doses of valproic acid do not require adjustment for patients with renal failure, and the drug is not removed by dialysis.[27] Breast milk concentrations of valproic acid are about 10% of concurrent serum concentrations.

DRUG INTERACTIONS

Valproic acid is a potent inhibitor of hepatic drug metabolizing enzyme systems and glucuronidation.[28–30] Other antiepileptic drugs that have their clearance rates decreased and steady-state concentrations increased by valproic acid-related enzyme inhibition include clonazepam, carbamazepine, phenytoin, primidone, lamotrigine, and ethosuximide. Valproic acid therapy also decreases the clearance and increases steady-state concentrations of other drugs including zidovudine, amitriptyline, and nortriptyline. As a general rule, when valproic acid is added to a patient's drug regimen, an adverse effect from one of the other drugs must be considered as a possible drug interaction with valproic acid.

Additionally, other drugs can affect valproic acid clearance and steady-state serum concentrations.[28] Phenytoin, lamotrigine, rifampin, and carbamazepine can increase valproic acid clearance and decrease valproic acid steady-state serum concentrations. Cimetidine, chlorpromazine, and felbamate are examples of drugs that decrease valproic acid clearance and increase valproic acid steady-state concentrations.

Because valproic acid is highly protein bound, plasma protein binding drug interactions can occur with other drugs that are highly bound to albumin.[28] Aspirin, warfarin, and phenytoin all have plasma protein binding drug interactions with valproic acid, and these drugs have higher unbound fractions when given concurrently with valproic acid. The drug interaction between valproic acid and phenytoin deserves special examination because of its complexity and because these two agents are regularly used together for the treatment of seizures.[31–34] The drug interaction involves the plasma protein binding displacement and intrinsic clearance inhibition of phenytoin by valproic acid. What makes this interaction so difficult to detect and understand is that these two changes do not occur simultaneously, so the impression left by the drug interaction depends on when in time it is observed in a patient. For example, a patient is stabilized on phenytoin therapy (Figure 12-3), but because adequate control of seizures has not been attained, valproic acid is added to the regimen. As valproic acid concentrations accumulate, the first interaction observed is phenytoin plasma protein binding as the two drugs compete for binding sites on albumin. The result of this portion of the drug interaction is an increase in phenytoin unbound fraction and a decrease in phenytoin total serum concentration, but the unbound phenytoin serum concentration remains the same. As valproic acid serum concentrations achieve steady-state conditions, the higher concentrations of the drug bathe the hepatic microsomal enzyme system and inhibit the intrinsic clearance of phenytoin. This portion of the interaction decreases intrinsic clearance and hepatic clearance for phenytoin, so both unbound and total phenytoin concentrations increase. When phenytoin concentrations finally equilibrate and reach steady-state under the new plasma protein binding and intrinsic clearance conditions imposed by concurrent valproic acid therapy, the total concentration of phenytoin is oftentimes

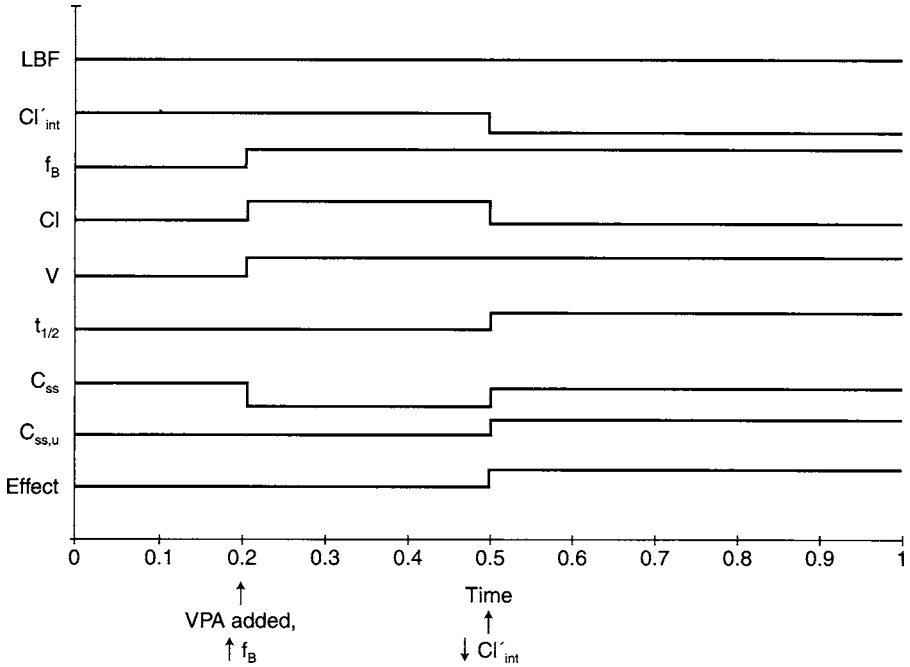

FIGURE 12-3 Schematic representation of the effect on physiologic (*LBF* = liver blood flow, Cl'_{int} = intrinsic or unbound clearance, f_B = unbound fraction of drug in blood/plasma), pharmacokinetic (*Cl* = clearance; *V* = volume of distribution; $t_{1/2}$ = half-life; *Css* = total steady-state drug concentration; *Css, u* = unbound steady-state drug concentration), and pharmacodynamic (*Effect* = pharmacodynamic effect) parameters that occur when initiating valproic acid *(VPA)* treatment in an individual stabilized on phenytoin therapy. Initially, valproic acid decreases phenytoin plasma protein binding via competitive displacement for binding sites on albumin (arrow denotes $\uparrow f_B$). As valproic acid concentrations increase, the hepatic enzyme inhibition component of the drug interaction comes into play (arrow denotes $\downarrow Cl'_{int}$). The net result is total phenytoin concentrations are largely unchanged from baseline, but unbound phenytoin concentrations and pharmacologic effect increase.

at about the same level as before the drug interaction occurred, but unbound phenytoin concentrations are much higher. If only total phenytoin concentrations are measured at this point in time, clinicians will be under the impression that total concentrations did not change and no drug interaction occurred. However, if unbound phenytoin concentrations are simultaneously measured, it will be found that these concentrations have risen and that the phenytoin unbound fraction is twice or more (≥20%) of the baseline amount. In this situation, the patient may have unbound phenytoin concentrations that are toxic and a decrease in phenytoin dosage may be in order.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate valproic acid therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be

customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of valproic acid. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of valproic acid is to compute the best dose possible for the patient given their set of disease states and conditions that influence valproic acid pharmacokinetics and the epileptic disorder being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Valproic acid is predominately metabolized by liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change valproic acid clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance. For example, for a 70-kg adult patient with liver cirrhosis or acute hepatitis, valproic acid clearance would be assumed to equal 3–4 mL/h/kg: 70 kg · 3.5 mL/h/kg = 245 mL/h or 0.245 L/h. To produce the most conservative valproic acid doses in patients with multiple concurrent disease states or conditions that affect valproic acid pharmacokinetics, the disease state or condition with the smallest clearance should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible.

VOLUME OF DISTRIBUTION ESTIMATE

Valproic acid volume of distribution is assumed to equal 0.15 L/kg for adults and 0.2 L/kg for children under 12 years of age. Thus, for an 80-kg adult patient, the estimated valproic volume of distribution would be 12 L: V = 0.15 L/kg · 80 kg = 12 L. Patients with cirrhosis or renal failure may have larger volumes of distribution as a result of decreased plasma protein binding.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl$, $k = 0.693/t_{1/2} = Cl/V$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous injection or orally, valproic acid follows a one-compartment pharmacokinetic model. When oral therapy is required, valproic acid has good bioavailability (F = 1), and every 8–12 hour dosing provides a relatively smooth serum concentration/time curve that emulates an intravenous infusion. Because of this, a very simple pharmacokinetic equation that computes the average valproic acid steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance

dosage calculation: Css = [F(D/τ)] / Cl or D = (Css · Cl · τ) / F, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral rapid-release products, F = 0.9 for oral sustained-release tablets), D is the dose of valproic acid in milligrams, and τ is the dosage interval in hours. Cl is valproic acid clearance in liters per hour. When intravenous therapy is required, the same pharmacokinetic equation is widely used: Css = (D/τ) / Cl or D = Css · Cl · τ, where D is the dose of valproic acid in milligrams, and τ is the dosage interval in hours. Cl is valproic acid clearance in liters per hour.

The equation used to calculate an intravenous loading dose (LD in milligrams) is based on a simple one-compartment model: LD = Css · V, where Css is the desired valproic acid steady-state concentration in micrograms per milliliter which is equivalent to milligrams per liter, and V is the valproic acid volume of distribution. Intravenous valproic acid doses should be infusions over at least 60 minutes (≤20 mg/min).

Example 1 KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an adult patient not taking other drugs that induce hepatic drug metabolism is 7–12 mL/h/kg. Using a value of 10 mL/h/kg, the estimated clearance would equal 0.75 L/h: Cl = 75 kg · 10 mL/h/kg = 750 mL/h or 0.75 L/h. Using 0.15 L/kg, the estimated volume of distribution would be 11 L: 75 kg · 0.15 L/kg = 11 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 11\ L) / 0.75\ L/h = 10\ h$, $k = 0.693/t_{1/2} = 0.693/10\ h = 0.069\ h^{-1}$.

3. *Compute dosage regimen.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is D = (Css · Cl · τ) / F = (50 mg/L· 0.75 L/h · 12 h) / 1 = 450 mg, rounded to 500 every 12 hours.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 2 UO is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral valproic acid. He has normal liver function and currently takes carbamazepine.

Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a child who takes other drugs that induce hepatic drug metabolism is 20–30 mL/h/kg. Using a value of 25 mL/h/kg, the estimated clearance would equal 1 L/h: Cl = 40 kg · 25 mL/h/kg = 1000 mL/h or 1 L/h. Using 0.2 L/kg, the estimated volume of distribution would be 8 L: 40 kg · 0.2 L/kg = 8 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 8\ L) / 1\ L/h = 6\ h$, $k = 0.693/t_{1/2} = 0.693/6\ h = 0.116\ h^{-1}$.

3. *Compute dosage regimen.*

Oral valproic acid syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 1\ L/h \cdot 8\ h) / 1 = 400\ mg$, or 400 mg every 8 h.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 6 hours, the valproic acid steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 6 h = 30 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 3 HU is a 25-year-old, 85-kg (6 ft 2 in) male with tonic-clonic seizures who requires therapy with intravenous valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 75 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an adult patient not taking other drugs that induce hepatic drug metabolism is 7–12 mL/h/kg. Using a value of 10 mL/h/kg, the estimated clearance would equal 0.85 L/h: Cl = 85 kg · 10 mL/h/kg = 850 mL/h or 0.85 L/h. Using 0.15 L/kg, the estimated volume of distribution would be 13 L: 85 kg · 0.15 L/kg = 13 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 13\ L) / 0.85\ L/h = 11\ h$, $k = 0.693/t_{1/2} = 0.693/11\ h = 0.063\ h^{-1}$.

3. *Compute dosage regimen.*

Valproic acid injection will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The maintenance dosage equation for valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (75 \text{ mg/L} \cdot 0.85 \text{ L/h} \cdot 8 \text{ h}) / 1 = 510$ mg, rounded to 500 every 8 hours. The loading dose equation for valproic acid is $LD = Css \cdot V = 75 \text{ mg/L} \cdot 13 \text{ L} = 975$ mg, rounded to 1000 mg. Intravenous doses should be given over 1 hour (≤20 mg/minute).

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 11 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 11 h = 55 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in valproic acid pharmacokinetics, even when concurrent disease states and conditions are identified, most clinicians believe that the use of standard valproic acid doses for various situations is warranted. The original computation of these doses were based on the pharmacokinetic dosing methods, and subsequently modified based on clinical experience. In general, the expected valproic acid steady-state serum concentrations used to compute these doses was 50 μg/mL. Usual initial maintenance doses for pediatric patients are 10 mg/kg/d if the child is not taking a hepatic enzyme inducer (phenytoin, phenobarbital, carbamazepine, and rifampin) or 20 mg/kg/d if the child is taking a hepatic enzyme inducer. For adults, initial maintenance doses are 7.5 mg/kg/d if the patient is not taking hepatic enzyme inducers or 15 mg/kg/d if a hepatic enzyme inducer is concurrently administered. Two or three divided daily doses are initially used for these total doses. To avoid gastrointestinal side effects, doses over 1500 mg given at one time should be avoided. Dosage increases of 5–10 mg/kg/d are made every 1–2 weeks depending on response and adverse effects. Most adults will require 1500–3000 mg/d of valproic acid. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses prescribed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 4 KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen for this patient.

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid in an adult patient not taking

enzyme inducers is 7.5 mg/kg/d: 75 kg · 7.5 mg/kg/d = 563 mg/d or 250 mg every 12 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 5 UO is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral valproic acid. He has normal liver function and currently takes carbamazepine. Suggest an initial valproic acid dosage regimen for this patient.

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral valproic acid syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid for a child taking enzyme inducers is 20 mg/kg/d: 40 kg · 20 mg/kg/d = 800 mg/d or 250 mg every 8 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 6 HU is a 25-year-old, 85-kg (6 ft 2 in) male with tonic-clonic seizures who requires therapy with intravenous valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen for this patient.

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Intravenous valproic acid injection will be prescribed to this patient. The suggested initial maintenance dosage rate for an adult patient not taking enzyme inducers is 7.5 mg/kg/d: 85 kg · 7.5 mg/kg/d = 638 mg/d, rounded to 750 mg/d or 250 mg every 12 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. If needed, a loading dose of 7.5 mg/kg could be given as the first dose: 85 kg · 7.5 mg/kg/d = 638 mg, rounded to 750 mg. Intravenous doses should be administered over 1 hour (≤20 mg/min). The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

USE OF VALPROIC ACID SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce valproic acid serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the nonlinear pharmacokinetics followed by the drug owing to concentration-dependent plasma protein binding, the narrow therapeutic index of valproic acid, and the desire to avoid adverse side effects of valproic acid, measurement of valproic acid serum concentrations is conducted for most patients to ensure that therapeutic, nontoxic levels are present.

In addition to valproic acid serum concentrations, important patient parameters (seizure frequency, potential valproic acid side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions. When valproic acid serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change valproic acid doses by temporarily assuming valproic acid follows linear pharmacokinetics (*pseudolinear pharmacokinetics method*). An empiric adjustment is made in the estimated steady-state concentrations to adjust for nonlinear, concentration-dependent plasma protein binding. In some situations, it may be necessary or desirable to compute the valproic acid *pharmacokinetic parameters* for the patient and utilize these to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Pseudolinear Pharmacokinetics Method

A simple, easy way to approximate new total serum concentrations after a dosage adjustment with valproic acid is to temporarily assume linear pharmacokinetics, then subtract 10–20% for a dosage increase or add 10–20% for a dosage decrease to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics: $D_{new} = (Css_{new}/Css_{old})\ D_{old}$, where Css_{new} is the expected steady-state concentration from the new valproic acid dose in μg/mL, Css_{old} is the measured steady-state concentration from the old valproic acid dose in μg/mL, D_{new} is the new valproic acid dose to be prescribed in mg/d, and D_{old} is the currently prescribed valproic acid dose in mg/d. *Note:* This method is only intended to provide a rough approximation of the resulting valproic acid total steady-state concentration after an appropriate dosage adjustment has been made. Of course, as expected, unbound steady-state concentrations increase or decrease in a linear fashion with dose.

Example 7 KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets (1000 mg/d) for 1 month, and the steady-state valproic acid total concentration equals 38 μg/mL. The patient is assessed

to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 80 μg/mL.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (80 μg/mL / 38 μg/mL) 1000 mg/d = 2105 mg/d, rounded to 2000 mg/d or 1000 mg every 12 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 80 μg/mL · 0.90 = 72 μg/mL and Css = 80 μg/mL · 0.80 = 64 μg/mL. Thus, a dosage rate of 2000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 64–72 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 8 UO is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral valproic acid. He has normal liver function. After dosage titration, the patient was prescribed 400 mg three times daily (1200 mg/d) of valproic acid syrup for 1 month, and the steady-state valproic acid total concentration equals 130 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 75 μg/mL.

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage decrease, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (75 μg/mL / 130 μg/mL) 1200 mg/d = 692 mg/d, rounded to 750 mg/d or 250 mg every 8 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% greater, or 1.10 times, to 20% greater, or 1.2 times, than that predicted by linear pharmacokinetics: Css = 75 μg/mL · 1.10 = 83 μg/mL and Css = 75 μg/mL · 1.20 = 90 μg/mL. Thus, a dosage rate of 750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 83–90 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose

that achieves desired valproic acid concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state valproic acid concentration (Css). During an intravenous dosing, the following equation is used to compute valproic acid clearance (Cl): $Cl = (D/\tau) / Css$, where D is the dose of valproic acid in milligrams, Css is the steady-state valproic acid concentration in milligrams per liter, and τ is the dosage interval in hours. If the patient is receiving oral valproic acid therapy, valproic acid clearance (Cl) can be calculated using the following formula: $Cl = [F(D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral valproic acid products), D is the dose of valproic acid in milligrams, Css is the steady-state valproic acid concentration in milligrams per liter, and τ is the dosage interval in hours.

Occasionally, valproic acid serum concentrations are obtained before and after an intravenous dose. Assuming a one-compartment model, the volume of distribution (V) is calculated using the following equation: $V = D/(C_{postdose} - C_{predose})$ where D is the dose of valproic acid in milligrams, $C_{postdose}$ is the postloading dose concentration in milligrams per liter, and $C_{predose}$ is the concentration before the loading dose was administered in milligrams per liter. ($C_{predose}$ should be obtained within 30 minutes of dosage administration; $C_{postdose}$ should be obtained 30–60 minutes after the end of infusion to avoid the distribution phase.) If the predose concentration was also a steady-state concentration, valproic acid clearance can also be computed. If both clearance (Cl) and volume of distribution (V) have been measured using these techniques, the half-life ($t_{1/2} = (0.693 \cdot V) / Cl$) and elimination rate constant ($k = 0.693/t_{1/2} = Cl/V$) can be computed. The clearance, volume of distribution, elimination rate constant, and half-life measured using these techniques are the patient's own, unique valproic acid pharmacokinetic constants and can be used in one-compartment model equations to compute the required dose to achieve any desired serum concentration. Because this method also assumes linear pharmacokinetics, valproic acid doses computed using the pharmacokinetic parameter method and the pseudolinear pharmacokinetic method should be identical. As with the previous method, to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics, 10–20% for a dosage increase can be subtracted or 10–20% for a dosage decrease can be added to the expected steady-state serum concentration.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic parameter method, the same examples used in the previous section will be used.

Example 9 KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets (1000 mg/d) for 1 month, and the steady-state valproic acid total concentration equals 38 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 80 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: $Cl = [F(D/\tau)] / Css = [1(500 \text{ mg}/12 \text{ h})] / (38 \text{ mg/L}) = 1.1 \text{ L/h}$. (Note: μg/mL = mg/L

and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (80\ mg/L \cdot 1.1\ L/h \cdot 12\ h) / 1 = 1056$ mg, rounded to 1000 mg every 12 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: $Css = 80\ \mu g/mL \cdot 0.90 = 72\ \mu g/mL$ and $Css = 80\ \mu g/mL \cdot 0.80 = 64\ \mu g/mL$. Thus, a dosage rate of 2000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 64–72 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 10 UO is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral valproic acid. He has normal liver function. After dosage titration, the patient was prescribed 400 mg three times daily (1200 mg/d) of valproic acid syrup for 1 month, and the steady-state valproic acid total concentration equals 130 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 75 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: $Cl = [F(D/\tau)] / Css = [1(400\ mg/8\ h)] / (130\ mg/L) = 0.38$ L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (75\ mg/L \cdot 0.38\ L/h \cdot 8\ h) / 1 = 228$ mg, rounded to 250 mg every 8 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% more, or 1.10 times, to 20%, or 1.20 times, more than that predicted by linear pharmacokinetics: $Css = 75\ \mu g/mL \cdot 1.10 = 83\ \mu g/mL$ and $Css = 75\ \mu g/mL \cdot 1.2 = 90\ \mu g/mL$. Thus, a dosage rate of 750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 83–90 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be

measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Example 11 PP is a 59-year-old, 65-kg (5 ft 8 in) male with tonic-clonic seizures who is receiving valproic acid injection 500 mg every 8 hours. The current steady-state valproic acid concentration (obtained 30 minutes before "booster" dose administration) equals 40 μg/mL. Compute a valproic acid maintenance dose that will provide a steady-state concentration of 75 μg/mL. Additionally, in an attempt to boost valproic acid concentrations as soon as possible, an additional, single valproic acid "booster" dose of 500 mg over 60 minutes was given before the maintenance dosage rate was increased. The valproic acid total serum concentration 30 minutes after the additional dose was 105 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: Cl = [F(D/τ)] / Css = [1(500 mg/8 h)] / (40 mg/L) = 1.6 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

Valproic acid volume of distribution can be computed using the prebolus dose (Css = 40 μg/mL) and postbolus dose concentrations: $V = D/(C_{postdose} - C_{predose})$ = 500 mg / (105 mg/L − 40 mg/L) = 8 L. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

Valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) can also be computed: $t_{1/2}$ = (0.693 · V) / Cl = (0.693 · 8 L) / (1.6 L/h) = 3.5 h; k = Cl/V = (1.6 L/h) / (8 L) = 0.20 h^{-1}.

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new valproic acid maintenance dose: D = (Css · Cl · τ) = (75 mg/L · 1.6 L/h · 8 h) = 960 mg, rounded to 1000 mg every 8 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 75 μg/mL · 0.90 = 68 μg/mL and Css = 75 μg/mL · 0.80 = 60 μg/mL. Thus, a dosage rate of 3000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 60–68 μg/mL.

The new valproic acid maintenance dose would be instituted one dosage interval after the additional "booster" dose was given.

A valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient has a half-life equal to 3.5 hours, the valproic acid steady-state concentration could be obtained after 1 day of continuous dosing (5 half-lives = 5 · 3.5 h = 17.5 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem.[35] Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[35]

Example 12 LK is a 50-year-old, 75-kg (5 ft 10 in) male with complex partial seizures who is receiving 500 mg every 8 hours of oral enteric-coated valproic acid tablets. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) function, and also takes 1200 mg/d of carbamazepine. The current steady-state valproic acid concentration equals 31 μg/mL. Compute a valproic acid dose that will provide a steady-state concentration of 70 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 8.6 L, a half-life equal to 5.2 hours, and a clearance equal to 1.13 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1000 mg every 8 hours will produce a steady-state valproic acid concentration of 68 μg/mL.

Example 13 HJ is a 62-year-old, 87-kg (6 ft 1 in) male with tonic-clonic seizures who was given a new prescription of 500 mg every 12 hours of an oral valproic acid capsules. He has liver cirrhosis (Child-Pugh score = 12, bilirubin = 3.2 mg/dL, albumin = 2.5 g/dL). The trough valproic acid concentration before the seventh dose equals 72 μg/mL, and he is experiencing some minor adverse effects (sedation, lethargy, tiredness). Compute a valproic acid dose that will provide a total steady-state concentration of 50 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the Linear Pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 12.5 L, a half-life equal to 19 hours, and a clearance equal to 0.46 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicate that a dose of 750 mg every 24 hours will produce a steady-state concentration of 46 μg/mL.

Example 14 JB is a 50-year-old, 60-kg (5 ft 7 in) male with tonic-clonic seizures was started on valproic acid 500 mg every 8 hours intravenously after being administered an intravenous loading dose of valproic acid 750 mg at 0800 H over 60 minutes. The valproic acid concentration was 30 μg/mL before the third maintenance dose. What valproic acid dose is needed to achieve Css = 75 μg/mL?

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. Valproic acid doses will be input as intravenous bolus doses.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 8.9 L, a half-life equal to 15 hours, and clearance equal to 0.42 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model intravenous bolus equations used by the program to compute doses indicates that a dose of valproic acid 300 mg every 8 hours will produce a steady-state concentration of 75 μg/mL.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 12-4.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current anticonvulsant therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with valproic acid exists.

1. CD is a 42-year-old, 85-kg (6 ft 1 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 μg/mL.
2. Patient CD (please see problem 1) was prescribed 750 mg every 12 hours of enteric-coated divalproex sodium tablets for 1 month, and the steady-state valproic acid total

TABLE 12-4 Dosing Strategies

DOSING APPROACH/PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameters/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concepts	Literature-based recommended dosing	Empiric dosing changes with pseudolinear pharmacokinetic method
Computerized	Bayesian computer programs	Bayesian computer programs

concentration equals 40 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 75 μg/mL.

3. BP is a 9-year-old, 35-kg female (4 ft 6 in) with absence seizures who requires therapy with oral valproic acid. She has normal liver function. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 75 μg/mL.

4. Patient BP (please see problem 3) was prescribed 150 mg three times daily (450 mg/d) of valproic acid syrup for 2 weeks, and the steady-state valproic acid total concentration equals 55 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 90 μg/mL.

5. PH is a 4-year-old, 22-kg male (3 ft 4 in) with tonic-clonic seizures who requires therapy with valproic acid syrup. He has normal liver function and is also treated with carbamazepine. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 μg/mL.

6. Patient PH (please see problem 5) was prescribed 100 mg three times daily (300 mg/d) of valproic acid syrup for 1 week, and the steady-state valproic acid total concentration equals 40 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 60 μg/mL.

7. FL is a 29-year-old, 75-kg (5 ft 11 in) male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function and is also receiving phenytoin therapy. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 μg/mL.

8. Patient FL (please see problem 1) was prescribed 750 mg every 8 hours of enteric-coated divalproex sodium tablets for 2 weeks, and the steady-state valproic acid total concentration equals 55 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration of 90 μg/mL.

9. WE is a 55-year-old, 68-kg (5 ft 8 in) male with complex partial seizures who is receiving 500 mg every 8 hours of an oral enteric-coated divalproex sodium tablets. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) function, and also takes 800 mg/d of carbamazepine. The total valproic acid concentration equals 22 μg/mL before the fourth dose. Compute a valproic acid dose that will provide a steady-state concentration of 50 μg/mL.

10. YF is a 5-year-old, 20-kg (3 ft 6 in) female with tonic-clonic seizures who was given a new prescription of 250 mg every 12 hours of oral valproic acid capsules. She has normal liver function and is receiving no enzyme inducers. The trough valproic acid concentration before the third dose equals 42 μg/mL. Compute a valproic acid dose that will provide a total steady-state concentration of 75 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an adult patient not taking other drugs that induce hepatic drug metabolism is 7–12 mL/h/kg. Using a value of 10 mL/h/kg, the estimated clearance would equal 0.85 L/h: Cl = 85 kg · 10 mL/h/kg = 850 mL/h or 0.85 L/h. Using 0.15 L/kg, the estimated volume of distribution would be 13 L: 85 kg · 0.15 L/kg = 13 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 13\ L) / 0.85\ L/h = 11\ h$, $k = 0.693/t_{1/2} = 0.693/11\ h = 0.063\ h^{-1}$.

3. *Compute dosage regimen.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient (F = 1). (Note: µg/mL= mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 0.85\ L/h \cdot 12\ h) / 1 = 510\ mg$, rounded to 500 mg every 12 hours.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 11 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 11 h = 55 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Literature-Based Recommended Dosing

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid in an adult patient not taking enzyme inducers is 7.5 mg/kg/d: 85 kg · 7.5 mg/kg/d = 638 mg/d, rounded to 750 mg or 250 mg every 8 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should

also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

2. *Solution to problem 2.*

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (75 μg/mL / 40 μg/mL) 1500 mg/d = 2813 mg/d, rounded to 3000 mg/d or 1000 mg every 8 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 75 μg/mL · 0.90 = 68 μg/mL and Css = 75 μg/mL · 0.80 = 60 μg/mL. Thus, a dosage rate of 3000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 60–68 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: Cl = [F(D/τ)] / Css = [1(750 mg / 12 h)] / (40 mg/L) = 1.6 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (75 mg/L · 1.6 L/h · 8 h) / 1 = 960 mg, rounded to 1000 mg every 8 hours. (Note: Dosage interval was changed to every 8 hours to avoid large single doses and gastrointestinal upset.)

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 75 μg/mL · 0.90 = 68 μg/mL and Css = 75 μg/mL · 0.80 = 60 μg/mL. Thus, a dosage rate of 3000 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 60–68 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 10.7 L, a half-life equal to 8.1 hours, and a clearance equal to 0.91 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 750 mg every 8 hours will produce a steady-state valproic acid concentration of 78 μg/mL.

3. *Solution to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a pediatric patient not taking other drugs that induce hepatic drug metabolism is 10–20 mL/h/kg. Using a value of 15 mL/h/kg, the estimated clearance would equal 0.53 L/h: Cl = 35 kg · 15 mL/h/kg = 525 mL/h or 0.53 L/h. Using 0.2 L/kg, the estimated volume of distribution would be 7 L: 35 kg · 0.2 L/kg = 7 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 7\ L) / 0.53\ L/h = 9\ h$, $k = 0.693/t_{1/2} = 0.693/9\ h = 0.077\ h^{-1}$.

3. *Compute dosage regimen.*

Oral valproic acid syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (75\ mg/L \cdot 0.53\ L/h \cdot 8\ h) / 1 = 318$ mg, rounded to 300 every 8 hours.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 9 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 9 h = 45 h). Valproic acid

serum concentrations should also be measured if the patient experiences an exacerbation of their seizures, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Literature-Based Recommended Dosing

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral valproic acid syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid in an adult patient not taking enzyme inducers is 10 mg/kg/d: 35 kg · 10 mg/kg/d = 350 mg/d, rounded to 400 mg or 200 mg every 12 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

4. *Solution to problem 4.*

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (90 μg/mL / 55 μg/mL) 450 mg/d = 736 mg/d, rounded to 750 mg/d or 250 mg every 8 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 90 μg/mL · 0.90 = 81 μg/mL and Css = 90 μg/mL · 0.80 = 72 μg/mL. Thus, a dosage rate of 750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 72–81 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: Cl = [F(D/τ)] / Css = [1(150 mg/8 h)] / (55 mg/L) = 0.34 L/h. (Note: μg/mL = mg/L

and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (90\ mg/L \cdot 0.34\ L/h \cdot 8\ h) / 1 = 245\ mg$, rounded to 250 mg every 8 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: $Css = 90\ \mu g/mL \cdot 0.90 = 81\ \mu g/mL$ and $Css = 90\ \mu g/mL \cdot 0.80 = 72\ \mu g/mL$. Thus, a dosage rate of 750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 72–81 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 2 L, a half-life equal to 6.4 hours, and a clearance equal to 0.21 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 250 mg every 8 hours will produce a steady-state valproic acid concentration of 100 μg/mL.

5. *Solution to problem 5.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an pediatric patient that takes other drugs that induce hepatic drug metabolism is 20–30 mL/h/kg. Using a value of 25 mL/h/kg, the estimated clearance would equal 0.55 L/h: $Cl = 22\ kg \cdot 25\ mL/h/kg = 550\ mL/h$ or 0.55 L/h. Using 0.2 L/kg, the estimated volume of distribution would be 4.4 L: $22\ kg \cdot 0.2\ L/kg = 4.4\ L$.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination

rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 4.4\ L) / 0.55\ L/h = 5.5\ h$, $k = 0.693/t_{1/2} = 0.693/5.5\ h = 0.126\ h^{-1}$.

3. *Compute dosage regimen.*

Oral valproic acid syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 0.55\ L/h \cdot 8\ h) / 1 = 220\ mg$, rounded to 250 mg every 8 hours.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5.5 hours, the valproic acid steady-state concentration could be obtained any time after the first day of dosing (5 half-lives = 5 · 5.5 h = 28 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their seizures, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Literature-Based Recommended Dosing

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral valproic acid syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid in an adult patient not taking enzyme inducers is 20 mg/kg/d: 22 kg · 20 mg/kg/d = 440 mg/d, rounded to 400 mg or 200 mg every 12 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

6. *Solution to problem 6.*

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (60\ \mu g/mL / 40\ \mu g/mL)$ 300 mg/d = 450 mg/d, 150 mg every 8 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: $Css = 60\ \mu g/mL \cdot 0.90 = 54\ \mu g/mL$ and $Css = 60\ \mu g/mL \cdot 0.80 = 48\ \mu g/mL$. Thus, a dosage rate of 450 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 48–54 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: $Cl = [F(D/\tau)] / Css = [1(100\ mg/8\ h)] / (40\ mg/L) = 0.31\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (60\ mg/L \cdot 0.31\ L/h \cdot 8\ h) / 1 = 149\ mg$, rounded to 150 mg every 8 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: $Css = 60\ \mu g/mL \cdot 0.90 = 54\ \mu g/mL$ and $Css = 60\ \mu g/mL \cdot 0.80 = 48\ \mu g/mL$. Thus, a dosage rate of 450 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 48–54 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 2.9 L, a half-life equal to 8.9 hours, and a clearance equal to 0.23 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 150 mg every 8 hours will produce a steady-state valproic acid concentration of 64 μg/mL.

7. *Solution to problem 7.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an adult patient taking other drugs that induce hepatic drug metabolism is 15–18 mL/h/kg. Using a value of 16 mL/h/kg, the estimated clearance would equal 1.2 L/h: Cl = 75 kg · 16 mL/h/kg = 1200 mL/h or 1.2 L/h. Using 0.15 L/kg, the estimated volume of distribution would be 11 L: 75 kg · 0.15 L/kg = 11 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the valproic acid half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 11\ L) / 1.2\ L/h = 6\ h$, $k = 0.693/t_{1/2} = 0.693/6\ h = 0.116\ h^{-1}$.

2. *Compute dosage regimen.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral valproic acid is $D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 1.2\ L/h \cdot 8\ h) / 1 = 480\ mg$, rounded to 500 mg every 8 hours.

A steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 6 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 5 · 6 h = 30 h). Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Literature-Based Recommended Dosing

1. *Estimate valproic acid dose according to disease states and conditions present in the patient.*

Oral enteric-coated divalproex sodium tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for valproic acid in an adult patient taking enzyme inducers is 15 mg/kg/d: 75 kg · 15 mg/kg/d = 1125 mg/d, rounded to 1000 mg or 500 mg every 12 hours. This dose would be titrated upward in 5–10 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

8. *Solution to problem 8.*

Pseudolinear Pharmacokinetics Method

1. *Use pseudolinear pharmacokinetics to predict new concentration for a dosage increase, then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics.*

Using pseudolinear pharmacokinetics, the resulting total steady-state valproic acid serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (90\ \mu g/mL / 55\ \mu g/mL)$ 2250 mg/d = 3682 mg/d, rounded to 3750 mg/d or 1250 mg every 8 hours. Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 90 μg/mL · 0.90 = 81 μg/mL and Css = 90 μg/mL · 0.80 = 72 μg/mL. Thus, a dosage rate of 3750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 72–81 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2–3 days of therapy.

Valproic acid clearance can be computed using a steady-state valproic acid concentration: Cl = [F(D/τ)] / Css = [1(750 mg/8 h)] / (55 mg/L) = 1.7 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute valproic acid dose.*

Valproic acid clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (90 mg/L · 1.7 L/h · 8 h) / 1 = 1224 mg, rounded to 1250 mg every 8 hours.

Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics: Css = 90 μg/mL · 0.90 = 81 μg/mL and Css = 90 μg/mL · 0.80 = 72 μg/mL. Thus, a dosage rate of 3750 mg/d would be expected to yield a total valproic acid steady-state serum concentration between 72–81 μg/mL.

A steady-state trough total valproic acid serum concentration should be measured after steady state is attained in 1–2 weeks. Valproic acid serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 9 L, a half-life equal to 6.1 hours, and a clearance equal to 1 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1000 mg every 8 hours will produce a steady-state valproic acid concentration of 82 μg/mL.

9. *Solution to problem 9*.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 6.8 L, a half-life equal to 3.9 hours, and a clearance equal to 1.2 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1000 mg every 8 hours will produce a steady-state valproic acid concentration of 50 μg/mL.

10. *Solution to problem 10.*

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 4.3 L, a half-life equal to 9.2 hours, and a clearance equal to 0.32 L/h.

3. *Compute dose required to achieve desired valproic acid serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 250 mg every 8 hours will produce a steady-state valproic acid concentration of 70 μg/mL. (Note: Dosage interval was decreased to avoid excessive doses and gastrointestinal side effects.)

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13

PHENOBARBITAL/PRIMIDONE

INTRODUCTION

Phenobarbital is a barbiturate and primidone is a deoxybarbiturate that are effective in the treatment of generalized tonic-clonic and partial seizures (Table 13-1).[1,2] Phenobarbital is available as a separate agent, but is also an active metabolite produced via hepatic metabolism during primidone treatment. Because of this, and because they share a similar antiseizure spectrum, these two drugs are considered together in this chapter. The probable mechanism of action for phenobarbital is elevation of seizure threshold by interacting with γ-aminobutyric $acid_A$ ($GABA_A$) postsynaptic receptors which potentiates synaptic inhibition.[3,4] While the exact mechanism of action is not known for the antiepileptic effect of primidone, a portion of its antiseizure activity is produced by the active metabolites phenobarbital and phenylethylmalonamide (PEMA).[3,4]

THERAPEUTIC AND TOXIC CONCENTRATIONS

The therapeutic ranges for phenobarbital and primidone are defined by most laboratories as 15–40 μg/mL and 5–12 μg/mL, respectively. When primidone is given, sufficient doses are usually administered to produce therapeutic concentrations of both phenobarbital and primidone. At present, concentrations of the other possible active metabolite of primidone, PEMA, are not routinely measured. While animal experiments indicate that primidone has inherent antiseizure activity, some clinicians believe that phenobarbital is the predominant species responsible for the therapeutic effect of primidone in humans.[5] Because phenobarbital and PEMA are produced via hepatic metabolism of primidone, it is very difficult to study the antiepileptic activity of primidone alone in patients.

The most common concentration-related adverse effects of phenobarbital involve the central nervous system: ataxia, headache, unsteadiness, sedation, confusion, and lethargy.[4,6] Other concentration-related side effects are nausea, and in children, irritability and hyperactivity. At phenobarbital concentrations >60 μg/mL, stupor and coma have been reported.

TABLE 13-1 International Classification of Epileptic Seizures with Treatment Recommendations[1,2]

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	*Drugs of choice* Carbamazepine Phenytoin Lamotrigine Oxcarbazepine *Alternatives* Valproic acid Gabapentin Topiramate Tiagabine Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)	*Drugs of choice* Ethosuximide Valproic acid *Alternatives* Lamotrigine Clonazepam Zonisamide Levetiracetam
	2. Tonic-clonic seizures (also known as grand mal seizures)	*Drugs of choice* Valproic acid Phenytoin Carbamazepine *Alternatives* Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

During long-term treatment with phenobarbital, changes in behavior, porphyria, decreased cognitive function, and osteomalacia can occur. For primidone, concentration-related side effects include nausea, vomiting, diplopia, dizziness, sedation, unsteadiness, and ataxia.[4,6] Generally, slow dosage titration, administration of smaller doses and more frequent dosing of the drug produce relief from these side effects. Long-term treatment with primidone is associated with behavioral changes, decreased cognitive function, and disorders of the connective tissue. Obviously, some of the adverse effects noted during treatment with primidone may, in fact, be attributed to phenobarbital. Idiosyncratic side effects that are independent of concentration for both drugs include skin rashes and blood dyscrasias.

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects. While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (diplopia, ataxia, dizziness, headache, unsteadiness, sedation, confusion, lethargy) as well as gastrointestinal upset (nausea, vomiting) when receiving these drugs. Serious, but rare, idiosyncratic side effects include connective tissue disorders, blood dyscrasias, and skin rashes.

Phenobarbital serum concentrations, or primidone plus phenobarbital serum concentrations for those patients receiving primidone therapy, should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Phenobarbital is eliminated primarily by hepatic metabolism (65–70%) to inactive metabolites.[7] About 30–35% of a phenobarbital dose is recovered as unchanged drug in the urine. Renal excretion of unchanged phenobarbital is pH dependent with alkaline urine increasing renal clearance. Phenobarbital is about 50% bound to plasma proteins. The absolute bioavailability of oral phenobarbital in humans approaches 100%.[8] Phenobarbital is available in tablet (15, 16, 30, 60, 100 mg), capsule (16 mg), elixir (15 mg/5 mL, 20 mg/5 mL), and injectable (30 mg/mL, 60 mg/mL, 65 mg/mL, and 130 mg/mL for intravenous or intramuscular use) forms. The typical maintenance dose for phenobarbital is 2.5–5 mg/kg/d for neonates, 3–4.5 mg/kg/d for pediatric patients (<10 years old), and 1.5–2 mg/kg/d for older patients.[4,6] For the acute treatment of status epilepticus, intravenous phenobarbital doses of 15–20 mg/kg are used.

Primidone is eliminated by hepatic metabolism (40–60%) and renal excretion of unchanged drug (40–60%).[9] In adults, approximately 15–20% of a primidone dose is converted by the liver into phenobarbital. PEMA is another active metabolite of primidone.[9,10] When starting treatment with primidone, PEMA concentrations are detectable after the first dose, but phenobarbital concentrations may not be measurable for 5–7 days

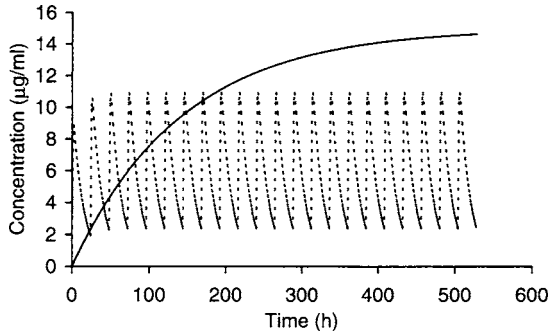

FIGURE 13-1 Primidone and phenobarbital concentrations after administration of primidone. Primidone concentrations fluctuate over the dosage interval with half-lives of 8–15 hours, but phenobarbital concentrations accumulate slowly with an average half-life of 100 hours in adults as primidone is converted to phenobarbital. Because of this, primidone concentrations achieve steady-state conditions long before phenobarbital concentrations reach steady state. In order to measure steady-state serum concentrations of both drugs, one must wait at least 3–4 weeks after a primidone dosage change.

(Figure 13-1). Primidone does not significantly bind to plasma proteins in humans. Because an intravenous form of the drug is not commercially available, the absolute bioavailability of primidone in humans is not known. Primidone is available as 50-mg and 250-mg tablets. Usual maintenance doses for primidone are 12–20 mg/kg/d for neonates, 12–23 mg/kg/d for pediatric patients (<15 years old), and 10–25 mg/kg/d for older patients.

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

Phenobarbital clearance rate (Cl) for older children (≥12 years old) and adults is 4 mL/h/kg, and for younger children is 8 mL/h/kg.[6,8,11] Phenobarbital volume of distribution (V) equals 0.7 L/kg, and its half life averages 120 hours in neonates (0–4 weeks old), 60 hours in children (≥2 months old) and 100 hours in adults. Although only limited studies in patients with hepatic disease are available, a 50% increase in half-life is seen in adults with liver cirrhosis or acute viral hepatitis.[12] Based on this information, patients with liver cirrhosis or acute hepatitis may have reduced phenobarbital clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of enzymes available to metabolize the drug and decreases clearance. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 13-2).[13] Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 13-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal

TABLE 13-2 Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for phenobarbital. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Phenobarbital serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Similarly, because phenobarbital is also eliminated by the kidney, patients with renal dysfunction (creatinine clearance <30 mL/min) receiving phenobarbital should be closely monitored. Phenobarbital is significantly removed (~30% of total body amount) by hemodialysis, and supplemental doses may need to be given after a dialysis session. Phenobarbital is significantly removed by hemoperfusion with a sieving coefficient equal to 0.8.[14,15] Supplemental dosing during hemoperfusion should be guided by serum concentration monitoring. Phenobarbital enters the breast milk so nursing infants should be monitored for possible adverse drug reactions.[16]

The primidone clearance rate (Cl/F) for older patients (≥12 years old) taking primidone alone is 35 mL/h/kg.[17] However, the primidone clearance rate increases to 50 mL/h/kg for older patients if they are receiving concurrent therapy with phenytoin or carbamazepine.[17] For children, primidone clearance averages 125 mL/h/kg.[18] Primidone volume of distribution (V/F) equals 0.7 L/kg, and its half life averages 8 hours in adults taking concurrent phenytoin or carbamazepine or children (<12 years old), and 15 hours in adults taking primidone alone.[6,17,18] Although no studies in patients with hepatic or renal disease are available, because almost equal amounts of primidone are eliminated by the liver and kidney, patients with renal or hepatic dysfunction receiving primidone should be closely monitored. A Child-Pugh score >8 or creatinine clearance <30 mL/min are grounds for a decrease of 25–50% in the initial daily drug dose for primidone. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Primidone and phenobarbital serum concentrations as well as the presence of adverse drug effects should be monitored frequently in patients with liver or kidney disease taking primidone. Primidone is significantly removed (~30% of total body amount) by hemodialysis, and supplemental doses may need to be given after a dialysis session.

DRUG INTERACTIONS

Phenobarbital is a potent inducer of hepatic drug metabolism for the CYP1A2, CYP2C9, and CYP3A4 enzyme systems.[19] Because phenobarbital is also a metabolite produced during primidone therapy, primidone has similar drug interaction potential. Because phenobarbital is such a broad-based hepatic enzyme inducer, patients should be monitored closely for drug interactions whenever either of these agents is added to their therapeutic regimen. A brief list of the compounds whose metabolism and clearance are increased by concurrent phenobarbital treatment includes carbamazepine, lamotrigine, valproic acid, cyclosporin, nifedipine, diltiazem, verapamil, oral contraceptives, tricyclic antidepressants, quinidine, theophylline, and warfarin. Other anticonvulsants that decrease the metabolism and clearance of phenobarbital are felbamate and valproic acid. Phenytoin may also exhibit an interaction with phenobarbital where both agents change the metabolism and clearance of each other. The net result of this drug interaction is quite variable and can result in an increase, decrease, or no change in the steady-state concentration of both drugs. Primidone metabolism and clearance are increased by carbamazepine and phenytoin treatment while valproic acid therapy decreases primidone metabolism and clearance.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate phenobarbital or primidone therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of phenobarbital or primidone. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of phenobarbital or primidone is to compute the best dose possible for the patient given their set of disease states and conditions that influence pharmacokinetics of the drugs and the epileptic disorder being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Phenobarbital is predominately metabolized by liver while primidone is about 50% hepatically eliminated. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change drug clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance. For example, for a 70-kg adult patient, phenobarbital

clearance would be assumed to equal 4 mL/h/kg: 70 kg · 4 mL/h/kg = 280 mL/h or 0.28 L/h. To produce the most conservative phenobarbital or primidone doses in patients with multiple concurrent disease states or conditions that affect their respective pharmacokinetics, the disease state or condition with the smallest clearance should be used to compute doses. This approach will avoid accidental overdosage has much as currently possible.

VOLUME OF DISTRIBUTION ESTIMATE

The volume of distribution of both drugs is assumed to equal 0.7 L/kg for adults and children. Thus, for a 70-kg adult patient, the estimated volume of distribution would be 49 L: V = 0.7 L/kg · 70 kg = 49 L.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl$, $k = 0.693/t_{1/2} = Cl/V$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

Primidone and phenobarbital follow a one-compartment pharmacokinetic model. When oral therapy for either drug or intramuscular treatment with phenobarbital is required, both anticonvulsants have good bioavailability (assume F = 1), and once daily dosing for phenobarbital or multiple daily dosing for primidone provides a relatively smooth serum concentration/time curve that emulates an intravenous infusion. Because of this, a very simple pharmacokinetic equation that computes the average phenobarbital or primidone steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation: $Css = [F(D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau)/F$, where F is the bioavailability fraction for the oral dosage form (F = 1 for both drugs), D is the dose of the anticonvulsant in mg, Cl is anticonvulsant clearance in L/h, and τ is the dosage interval in hours.

When intravenous therapy with phenobarbital is required, a similar pharmacokinetic equation is widely used: $Css = (D/\tau) / Cl$ or $D = Css \cdot Cl \cdot \tau$, where D is the dose of phenobarbital in milligrams, and τ is the dosage interval in hours, Cl is phenobarbital clearance in liters per hour. The equation used to calculate an intravenous loading dose for phenobarbital (LD in milligrams) is based on a simple one-compartment model: LD = Css · V, where Css is the desired phenobarbital steady-state concentration in μg/mL which is equivalent to mg/L, and V is the phenobarbital volume of distribution. Intravenous phenobarbital doses should be administered no faster than 100 mg/minute.

Example 1 GO is a 50-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state concentration equal to 20 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an older patient is 4 mL/h/kg. Using this value, the estimated clearance would equal 0.3 L/h: Cl = 75 kg · 4 mL/h/kg = 300 mL/h or 0.3 L/h. The estimated volume of distribution would be 53 L: 75 kg · 0.7 L/kg = 53 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the phenobarbital half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V)/Cl = (0.693 \cdot 53\ L)/0.3\ L/h = 122\ h$, $k = Cl/V = 0.3\ L/h / 53\ L = 0.0057\ h^{-1}$.

3. *Compute dosage regimen.*

Oral phenobarbital tablets will be prescribed to this patient (F = 1). (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral phenobarbital is $D = (Css \cdot Cl \cdot \tau) / F = (20\ mg/L \cdot 0.3\ L/h \cdot 24\ h) / 1 = 144$ mg, rounded to 120 every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 122 hours, the phenobarbital steady-state concentration could be obtained any time after 4 weeks of dosing (5 half-lives = 5 · 122 h = 610 h or 25 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Example 2 GO is a 50-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with intravenous phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state concentration equal to 20 µg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an older patient is 4 mL/h/kg. Using this value, the estimated clearance would equal 0.3 L/h: $Cl = 75\ kg \cdot 4\ mL/h/kg = 300\ mL/h$ or 0.3 L/h. The estimated volume of distribution would be 53 L: 75 kg · 0.7 L/kg = 53 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the phenobarbital half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 53\ L)/0.3\ L/h = 122\ h$, $k = Cl/V = 0.3\ L/h / 53\ L = 0.0057\ h^{-1}$.

3. *Compute dosage regimen.*

Intravenous phenobarbital will be prescribed to this patient. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous phenobarbital is $D = Css \cdot Cl \cdot \tau = 20\ mg/L \cdot 0.3\ L/h \cdot 24\ h = 144$ mg, rounded to 120 every 24 hours. If needed, an intravenous loading dose could also be computed for the patient: $LD = Css \cdot V = 20\ mg/L \cdot 53\ L = 1060$ mg, rounded to 1000 mg. Intravenous loading doses should be administered no faster than 100 mg/min.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life

equal to 122 hours, the phenobarbital steady-state concentration could be obtained any time after 4 weeks of dosing (5 half-lives = 5 · 122 h = 610 h or 25 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Example 3 BI is a 23-year-old, 65-kg male with complex partial seizures who requires therapy with oral primidone. He has normal liver and renal function and takes carbamazepine. Suggest an initial primidone dosage regimen designed to achieve a steady-state primidone concentration equal to 6 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an adult patient taking carbamazepine is 50 mL/h/kg. Using this value, the estimated clearance would equal 3.25 L/h: Cl = 65 kg · 50 mL/h/kg = 3250 mL/h or 3.25 L/h. The estimated volume of distribution would be 46 L: 65 kg · 0.7 L/kg = 46 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the primidone half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 46\ L)/3.25\ L/h = 10\ h$, $k = Cl/V = 3.25\ L/h / 46\ L = 0.071\ h^{-1}$.

3. *Compute dosage regimen.*

Oral primidone tablets will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral primidone is $D = (Css \cdot Cl \cdot \tau) / F = (6\ mg/L \cdot 3.25\ L/h \cdot 12\ h) / 1 = 234$ mg, rounded to 250 mg every 12 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (125 mg every 12 hours) and would be titrated to the full dose over 1–2 weeks.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after a 3–4 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in phenobarbital and primidone pharmacokinetics, even when concurrent disease states and conditions are identified, most clinicians believe that the use of standard drug doses for various situations are warranted. The original computation of these doses were based on the pharmacokinetic dosing methods, and subsequently modified based on clinical experience. In general, the expected steady-state serum concentrations used to compute these doses was in the lower end of the therapeutic range for each drug (Table 13-3). Phenobarbital is usually administered once or twice daily while

TABLE 13-3 Literature-Based Initial Doses for Phenobarbital and Primidone

PATIENT PROFILE	PHENOBARBITAL DOSE (mg/kg/d)	PRIMIDONE DOSE (mg/kg/d)
Neonate	2.5–5	12–20
Children	3–4.5	12–23
Adult	1.5–2	10–25

Note: Intravenous loading doses for phenobarbital are 15–20 mg/kg for status epilepticus.

primidone is given 2–4 times daily. To avoid side effects, primidone doses are started at 25–50% of the ultimate desired maintenance dose with dosage increases made every 1–2 weeks depending on response and adverse effects. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8) or renal disease (creatinine clearance <30 mL/min), maintenance doses prescribed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 4 GO is a 50-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state concentration equal to 20 μg/mL.

1. *Estimate phenobarbital dose according to disease states and conditions present in the patient.*

Oral phenobarbital tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for phenobarbital in an adult patient is 1.5–2 mg/kg/d. Using 1.5 mg/kg/d, the dose would be 75 kg · 1.5 mg/kg/d = 113 mg/d, rounded to 120 mg/d.

Trough phenobarbital serum concentrations should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after a 3–4 weeks of dosing (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Example 5 GO is a 50-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with intravenous phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state concentration equal to 20 μg/mL.

1. *Estimate phenobarbital dose according to disease states and conditions present in the patient.*

Intravenous phenobarbital will be prescribed to this patient. The suggested initial maintenance dosage rate for phenobarbital in an adult patient is 1.5–2 mg/kg/d. Using 1.5 mg/kg/d, the maintenance dose would be 75 kg · 1.5 mg/kg/d = 113 mg/d, rounded to 120 mg/d. If needed, the loading dose range is 15–20 mg/kg. Using 15 mg/kg, the loading dose would be 75 kg · 15 mg/kg = 1125 mg, rounded to 1000 mg.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Example 6 BI is a 23-year-old, 65-kg male with complex partial seizures who requires therapy with oral primidone. He has normal liver and renal function and takes carbamazepine. Suggest an initial primidone dosage regimen designed to achieve a steady-state primidone concentration equal to 6 μg/mL.

1. *Estimate primidone dose according to disease states and conditions present in the patient.*

Oral primidone tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for primidone in an adult patient is 10–25 mg/kg/d. Because the patient is taking carbamazepine, which is known to induce primidone metabolism, a dose of 15 mg/kg/d will be used to compute the initial dose: 65 kg · 15 mg/kg/d = 975 mg/d, rounded to 1000 mg/d and given as 250 mg every 6 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (125 mg every 6 hours) and would be titrated to the full dose over 1–2 weeks according to response and adverse effects.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after a 3–4 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

USE OF PHENOBARBITAL AND PRIMIDONE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce phenobarbital or primidone serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the narrow therapeutic index of phenobarbital and primidone, and the desire to avoid adverse side effects, measurement of serum concentrations for these anticonvulsants is conducted for most patients to ensure that therapeutic, nontoxic levels are present. In addition to phenobarbital or primidone serum concentrations, important patient parameters (seizure frequency, potential side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When phenobarbital or primidone serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change doses since phenobarbital and primidone follows *linear pharmacokinetics*. Sometimes, it is not possible to simply change the dose because of the limited number of oral dosage strengths, and the dosage interval must also be changed. In some situations, it may be necessary or desirable to compute the phenobarbital or primidone *pharmacokinetic parameters* for the patient and utilize these to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. An additional benefit of this dosing method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because phenobarbital and primidone follow linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and primidone may undergo some induction of its hepatic clearance at higher doses as phenobarbital concentrations increase. This method works for phenobarbital regardless of the route of administration. When primidone is administered to the patient, phenobarbital is produced as an active metabolite, and the new phenobarbital concentration resulting from a primidone dosage changes in a linear fashion. The phenobarbital concentration resulting from a primidone dosage change can be estimated using a rearrangement of the above equation: $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old}$, where D is the primidone dose, Css is the steady-state phenobarbital concentration, old indicates the primidone dose that produced the steady-state phenobarbital concentration that the patient is currently receiving, and new denotes the primidone dose necessary to produce the desired steady-state phenobarbital concentration.

Example 7 LK is a 13-year-old, 47-kg (5 ft 1 in) female with complex partial seizures who requires therapy with oral primidone. After dosage titration, the patient was prescribed 250 mg every 8 hours of primidone tablets (750 mg/d) for 1 month, and the steady-state primidone and phenobarbital steady-state concentrations equal 3 μg/mL and 15 μg/mL, respectively. The patient is assessed to be compliant with her dosage regimen. Suggest a primidone dosage regimen designed to achieve a steady-state primidone concentration of 6 μg/mL.

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the primidone dose necessary to cause the change in steady-state concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (6\ \mu g/mL / 3\ \mu g/mL)$

750 mg/d = 1500 mg/d, or 500 mg every 8 hours. The dosage regimen would be titrated to this value over a period of 1–2 weeks to avoid adverse effects. Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ Css_{old} = (1500\ mg/d / 750\ mg/d)\ 15\ \mu g/mL = 30\ \mu g/mL$.

A steady-state trough primidone and phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Example 8 HI is a 42-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. After dosage titration, the patient was prescribed 120 mg daily of phenobarbital tablets for 1 month, and the steady-state phenobarbital concentration equals 20 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration of 30 μg/mL.

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (30\ \mu g/mL / 20\ \mu g/mL)\ 120\ mg/d = 180\ mg/d$.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired phenobarbital or primidone concentrations. For patients receiving oral phenobarbital, the pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state phenobarbital concentration (Css). Phenobarbital clearance (Cl) can be calculated using the following formula: $Cl = [F(D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral phenobarbital products), D is the dose of phenobarbital in milligrams, Css is the steady-state phenobarbital concentration in milligrams per liter, and τ is the dosage interval in hours. Similarly, phenobarbital clearance during intravenous therapy can be computed using the equivalent formula: $Cl = (D/\tau) / Css$, where D is the dose of phenobarbital in milligrams, Css is the steady-state phenobarbital concentration in milligrams per liter, and τ is the dosage interval in hours.

If the patient is receiving oral primidone, primidone clearance (Cl) is computed using the same equation: $Cl = [F(D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral primidone products), D is the dose of primidone in milligrams, Css is the steady-state primidone concentration in milligrams per liter, and τ is the dosage interval in hours. As with the linear pharmacokinetics method discussed previously, phenobarbital concentrations that occur during primidone treatment can be easily

calculated. The phenobarbital concentration resulting from a primidone dosage change can be estimated using the following equation: $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old}$, where D is the primidone dose, Css is the steady-state phenobarbital concentration, old indicates the primidone dose that produced the steady-state phenobarbital concentration that the patient is currently receiving, and new denotes the primidone dose necessary to produce the desired steady-state phenobarbital concentration.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic parameter method, the same examples used in the previous section will be used.

Example 9 LK is a 13-year-old, 47-kg (5 ft 1 in) female with complex partial seizures who requires therapy with oral primidone. After dosage titration, the patient was prescribed 250 mg every 8 hours of primidone tablets (750 mg/d) for one month, and the steady-state primidone and phenobarbital steady-state concentrations equal 3 μg/mL and 15 μg/mL, respectively. The patient is assessed to be compliant with her dosage regimen. Suggest a primidone dosage regimen designed to achieve a steady-state primidone concentration of 6 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions for both primidone and phenobarbital after 3–4 weeks of therapy.

Primidone clearance can be computed using a steady-state primidone concentration: $Cl = [F(D/\tau)] / Css = [1(250\ mg/8\ h)] / (3\ mg/L) = 10\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute primidone dose and resulting phenobarbital concentration.*

Primidone clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (6\ mg/L \cdot 10\ L/h \cdot 8\ h) / 1 = 480\ mg$, rounded to 500 mg every 8 hours. Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old} = (1500\ mg/d / 750\ mg/d)\ 15\ \mu g/mL = 30\ \mu g/mL$.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state is attained in 3–4 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Example 10 HI is a 42-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. After dosage titration, the patient was prescribed 120 mg daily of phenobarbital tablets for 1 month, and the steady-state phenobarbital concentration equals 20 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration of 30 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 3–4 weeks of therapy.

Phenobarbital clearance can be computed using a steady-state phenobarbital concentration: Cl = [F(D/τ)] / Css = [1(120 mg/24 h)] / (20 mg/L) = 0.25 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute phenobarbital dose.*

Phenobarbital clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (30 mg/L · 0.25 L/h · 24 h) / 1 = 180 mg every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations,

many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[20] Currently, this program is available only for phenobarbital.

Example 11 HI is a 42-year-old, 75-kg (5 ft 10 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. After dosage titration, the patient was prescribed 120 mg daily of phenobarbital tablets for 1 month, and the steady-state phenobarbital concentration equals 20 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration of 30 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 51 L, a half-life equal to 185 h, and a clearance equal to 0.19 L/h.

3. *Compute dose required to achieve desired phenobarbital serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 180 mg every 24 hours will produce a steady-state phenobarbital concentration of 36 μg/mL.

Example 12 JB is an 8-year-old, 35-kg male (4 ft 2 in) with complex partial seizures who was started on phenobarbital syrup 100 mg every 24 hours. The phenobarbital concentration was 12 μg/mL before the tenth maintenance dose. What phenobarbital dose is needed to achieve Css = 25 μg/mL?

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 26 L, a half-life equal to 82 h, and clearance equal to 0.22 L/h.

3. *Compute dose required to achieve desired phenobarbital serum concentrations.*

The one-compartment model oral equations used by the program to compute doses indicates that a dose of phenobarbital 175 mg every 24 hours will produce a steady-state concentration of 26 μg/mL.

TABLE 13-4 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 13–4.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current anticonvulsant therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with phenobarbital or primidone exists.

1. FH is a 37-year-old, 85-kg (6 ft 1 in) male with tonic-clonic seizures who requires therapy with oral phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration equal to 15 μg/mL.

2. Patient FH (please see problem 1) was prescribed 90 mg every 24 hours of phenobarbital tablets for 1 month, and the steady-state phenobarbital concentration equals 12 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration of 20 μg/mL.

3. AS is a 9-year-old, 35-kg female (4 ft 6 in) with complex partial seizures who requires therapy with oral phenobarbital. She has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration equal to 20 μg/mL.

4. Patient AS (please see problem 3) was prescribed 30 mg twice daily (60 mg/d) of phenobarbital elixir for 3 weeks, and the steady-state phenobarbital concentration

equals 8.3 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a phenobarbital dosage regimen designed to achieve a steady-state phenobarbital concentration equal to 15 μg/mL.

5. FL is a 29-year-old, 75-kg (5 ft 11 in) male with tonic-clonic seizures who requires therapy with oral primidone. He has normal liver function and is also receiving phenytoin therapy. Suggest an initial primidone dosage regimen designed to achieve a steady-state primidone concentration equal to 5 μg/mL.

6. Patient FL (please see problem 5) was prescribed 500 mg every 12 hours of primidone tablets for 4 weeks, and the steady-state primidone and phenobarbital total concentrations equal 4.3 μg/mL and 11.6 μg/mL, respectively. The patient is assessed to be compliant with his dosage regimen. Suggest a primidone dosage regimen designed to achieve a steady-state primidone concentration of 6 μg/mL and estimate the resulting phenobarbital concentration.

7. PH is a 4-year-old, 22-kg male (3 ft 4 in) with tonic-clonic seizures who requires therapy with oral primidone. He has normal liver and renal function and is also treated with carbamazepine. Suggest an initial primidone dosage regimen designed to achieve a steady-state primidone concentration equal to 5 μg/mL.

8. Patient PH (please see problem 7) was prescribed 75 mg 3 times daily (225 mg/d) of primidone tablets for 3 weeks, and the steady-state primidone and phenobarbital concentrations equal 5.5 μg/mL and 18 μg/mL, respectively. The patient is assessed to be compliant with his dosage regimen. Suggest a primidone dosage regimen designed to achieve a steady-state primidone concentration of 8 μg/mL and estimate the resulting phenobarbital concentration.

9. PU is a 55-year old, 68-kg (5 ft 8 in) male with complex partial seizures who is receiving 90 mg daily of phenobarbital. He has normal liver and renal (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL, serum creatinine = 1.1 mg/dL) function, and also takes 800 mg/d of carbamazepine. The phenobarbital concentration equals 14 μg/mL before the eighth dose. Compute a phenobarbital dose that will provide a steady-state concentration of 25 μg/mL.

10. LH is a 25-year-old, 60-kg (5 ft 3 in) female with tonic-clonic seizures who was given a new prescription of 120 mg daily of phenobarbital tablets. She has normal liver and renal function and is also being treated with phenytoin. The trough phenobarbital concentration before the tenth dose equals 10 μg/mL. Compute a phenobarbital dose that will provide a steady-state concentration of 30 μg/mL.

ANSWERS TO PROBLEMS

1. *Answer to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an older patient is 4 mL/h/kg. Using this value, the estimated clearance would equal 0.34 L/h: Cl = 85 kg · 4 mL/h/kg = 340 mL/h or 0.34 L/h. The estimated volume of distribution would be 60 L: 85 kg · 0.7 L/kg = 60 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the phenobarbital half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 60\ L) / 0.34\ L/h = 122$ h, $k = Cl/V = 0.34\ L/h / 60\ L = 0.0057\ h^{-1}$.

3. *Compute dosage regimen.*

Oral phenobarbital tablets will be prescribed to this patient (F = 1). (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral phenobarbital is $D = (Css \cdot Cl \cdot \tau) / F = (15\ mg/L \cdot 0.34\ L/h \cdot 24\ h) / 1 = 122$ mg, rounded to 120 every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 122 hours, the phenobarbital steady-state concentration could be obtained any time after 4 weeks of dosing (5 half-lives = 5 · 122 h = 610 h or 25 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Literature-Based Recommended Dosing

1. *Estimate phenobarbital dose according to disease states and conditions present in the patient.*

Oral phenobarbital tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for phenobarbital in an adult patient is 1.5–2 mg/kg/d. Using 1.5 mg/kg/d, the dose would be 85 kg · 1.5 mg/kg/d = 128 mg/d, rounded to 120 mg/d.

Trough phenobarbital serum concentrations should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after 3–4 weeks of dosing (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

2. *Answer to problem 2.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (20\ µg/mL / 12\ µg/mL)\ 90\ mg/d = 150$ mg/d.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 3–4 weeks of therapy.

Phenobarbital clearance can be computed using a steady-state phenobarbital concentration: Cl = [F(D/τ)] / Css = [1(90 mg/24 h)] / (12 mg/L) = 0.31 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute phenobarbital dose.*

Phenobarbital clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (20 mg/L · 0.31 L/h · 24 h) / 1 = 149 mg, rounded to 150 mg every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

3. *Answer to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a pediatric patient is 8 mL/h/kg. Using this value, the estimated clearance would equal 0.28 L/h: Cl = 35 kg · 8 mL/h/kg = 280 mL/h or 0.28 L/h. The estimated volume of distribution would be 25 L: 35 kg · 0.7 L/kg = 25 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the phenobarbital half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2}$ = (0.693 · V) / Cl = (0.693 · 25 L) / 0.28 L/h = 62 h, k = Cl/V = 0.28 L/h / 25 L= 0.011 h^{-1}.

3. *Compute dosage regimen.*

Oral phenobarbital elixir will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral phenobarbital is D = (Css · Cl · τ) / F = (20 mg/L · 0.28 L/h · 24 h) / 1 = 134 mg, rounded to 120 every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life

equal to 62 hours, the phenobarbital steady-state concentration could be obtained any time after 2 weeks of dosing (5 half-lives = 5 · 62 h = 310 h or 13 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Literature-Based Recommended Dosing

1. *Estimate phenobarbital dose according to disease states and conditions present in the patient.*

Oral phenobarbital elixir will be prescribed to this patient. The suggested initial maintenance dosage rate for phenobarbital in a pediatric patient is 3–4.5 mg/kg/d. Using 3 mg/kg/d, the dose would be 35 kg · 3 mg/kg/d = 105 mg/d, rounded to 100 mg/d.

Trough phenobarbital serum concentrations should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 60 hours, the steady-state concentrations could be obtained any time after 2 weeks of dosing (5 phenobarbital half-lives = 5 · 60 h = 300 h or 13 d). Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

4. *Answer to problem 4.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (15 μg/mL / 8.3 μg/mL) 60 mg/d = 108 mg/d, rounded to 100 mg every 24 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 2 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 2 weeks of therapy.

Phenobarbital clearance can be computed using a steady-state phenobarbital concentration: Cl = [F(D/τ)] / Css = [1(30 mg/12 h)] / (8.3 mg/L) = 0.30 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute phenobarbital dose.*

Phenobarbital clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (15 mg/L · 0.30 L/h · 12 h) / 1 = 54 mg, rounded to 60 mg every 12 hours.

A steady-state trough phenobarbital serum concentration should be measured after steady state is attained in 2 weeks. Phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of phenobarbital toxicity.

5. *Answer to problem 5.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The primidone clearance rate for an adult patient taking phenytoin is 50 mL/h/kg. Using this value, the estimated clearance would equal 3.75 L/h: Cl = 75 kg · 50 mL/h/kg = 3750 mL/h or 3.75 L/h. The estimated volume of distribution would be 53 L: 75 kg · 0.7 L/kg = 53 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the primidone half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 53\ L) / 3.75\ L/h = 10\ h$, $k = Cl/V = 3.75\ L/h / 53\ L = 0.071\ h^{-1}$.

3. *Compute dosage regimen.*

Oral primidone tablets will be prescribed to this patient (F = 1). (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral primidone is $D = (Css \cdot Cl \cdot \tau) / F = (5\ mg/L \cdot 3.75\ L/h \cdot 12\ h) / 1 = 225\ mg$, rounded to 250 mg every 12 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (125 mg every 12 hours) and would be titrated to the full dose over 1–2 weeks.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after 3–4 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Literature-Based Recommended Dosing

1. *Estimate primidone dose according to disease states and conditions present in the patient.*

Oral primidone tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for primidone in an adult patient is 10–25 mg/kg/d. Because the patient is taking phenytoin, which is known to induce primidone metabolism, a dose of 15 mg/kg/d will be used to compute the initial dose: 75 kg · 15 mg/kg/d = 1125 mg/d,

rounded to 1000 mg/d and given as 250 mg every 6 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (125 mg every 6 hours) and would be titrated to the full dose over 1–2 weeks according to response and adverse effects.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 100 hours or more, the steady-state concentrations could be obtained any time after a 3–4 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 100 h = 500 h or 21 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

6. *Answer to problem 6.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the primidone dose necessary to cause the change in steady-state concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (6\ \mu g/mL / 4.3\ \mu g/mL)\ 1000\ mg/d = 1395\ mg/d$, rounded to 1500 mg/d or 500 mg every 8 hours. The dosage regimen would be titrated to this value over a period of 1–2 weeks to avoid adverse effects. Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old} = (1500\ mg/d / 1000\ mg/d)\ 11.6\ \mu g/mL = 17.4\ \mu g/mL$.

A steady-state trough primidone and phenobarbital serum concentration should be measured after steady state is attained in 3–4 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions for both primidone and phenobarbital after 3–4 weeks of therapy.

Primidone clearance can be computed using a steady-state primidone concentration: $Cl = [F(D/\tau)] / Css = [1(500\ mg/12\ h)] / (4.3\ mg/L) = 9.7\ L/h$. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute primidone dose and resulting phenobarbital concentration.*

Primidone clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (6\ mg/L \cdot 9.7\ L/h \cdot 8\ h) / 1 = 466\ mg$, rounded to 500 mg every 8 hours. Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old} = (1500\ mg/d / 1000\ mg/d)\ 11.6\ \mu g/mL = 17.4\ \mu g/mL$.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state is attained in 3–4 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

7. *Answer to problem 7.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a pediatric patient is 125 mL/h/kg. Using this value, the estimated clearance would equal 2.75 L/h: Cl = 22 kg · 125 mL/h/kg = 2750 mL/h or 2.75 L/h. The estimated volume of distribution would be 15 L: 22 kg · 0.7 L/kg = 15 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the primidone half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V)/Cl = (0.693 \cdot 15\ L) / 2.75\ L/h = 4\ h$, $k = Cl/V = 2.75\ L/h / 15\ L = 0.183\ h^{-1}$.

3. *Compute dosage regimen.*

Primidone tablets will be prescribed to this patient (F = 1). (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral primidone is $D = (Css \cdot Cl \cdot \tau) / F = (5\ mg/L \cdot 2.75\ L/h \cdot 6\ h) / 1 = 82.5\ mg$, rounded to 100 mg every 6 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (50 mg every 6 hours) and would be titrated to the full dose over 1–2 weeks.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 60 hours or more, the steady-state concentrations could be obtained any time after 2 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 60 h = 300 h or 13 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Literature-Based Recommended Dosing

1. *Estimate primidone dose according to disease states and conditions present in the patient.*

Primidone tablets will be prescribed to this patient. The suggested initial maintenance dosage rate for primidone in a pediatric patient is 12–23 mg/kg/d. Because the patient is taking phenytoin, which is known to induce primidone metabolism, a dose

of 15 mg/kg/d will be used to compute the initial dose: 22 kg · 15 mg/kg/d = 330 mg/d, rounded to 300 mg/d and given as 100 mg every 8 hours. To avoid side effects, the starting dose would be 50% of this anticipated maintenance dose (50 mg every 8 hours) and would be titrated to the full dose over 1–2 weeks according to response and adverse effects.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state for both agents is attained in 3–5 half-lives. Since the patient is expected to have a phenobarbital half-life equal to 60 hours or more, the steady-state concentrations could be obtained any time after 2 weeks of dosing at the full primidone maintenance dose (5 phenobarbital half-lives = 5 · 60 h = 300 h or 13 d). Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

8. *Answer to problem 8.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the primidone dose necessary to cause the change in steady-state concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (8 μg/mL / 5.5 μg/mL) 225 mg/d = 327 mg/d, rounded to 300 mg/d or 100 mg every 8 hours. The dosage regimen would be titrated to this value over a period of 1–2 weeks to avoid adverse effects. Using linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old}$ = (300 mg/d / 225 mg/d) 18 μg/mL = 24 μg/mL.

A steady-state trough primidone and phenobarbital serum concentration should be measured after steady state is attained in 2 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions for both primidone and phenobarbital after 2 weeks of therapy.

Primidone clearance can be computed using a steady-state primidone concentration: $Cl = [F(D/\tau)] / Css = [1(75\ mg/8\ h)] / (5.5\ mg/L) = 1.7\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute primidone dose and resulting phenobarbital concentration.*

Primidone clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F$ = (8 mg/L · 1.7 L/h · 8 h) / 1 = 109 mg, rounded to 100 mg every 8 hours. Using linear

pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal $C_{ss,new} = (D_{new}/D_{old})\ C_{ss,old} = (300\ mg/d / 225\ mg/d)\ 18\ \mu g/mL = 24\ \mu g/mL$.

Steady-state trough primidone and phenobarbital serum concentrations should be measured after steady state is attained in 2 weeks. Primidone and phenobarbital serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of primidone toxicity.

9. *Solution to problem 9.*

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

After receiving phenobarbital for less than 4 weeks, it is unlikely the patient is at steady state.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 36 L, a half-life equal to 217 hours, and a clearance equal to 0.11 L/h.

3. *Compute dose required to achieve desired phenobarbital serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 60 mg every 24 hours will produce a steady-state phenobarbital concentration of 21 μg/mL.

10. *Solution to problem 10.*

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

After receiving phenobarbital for less than 4 weeks, it is unlikely the patient is at steady state.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 44 L, a half-life equal to 97 hours, and a clearance equal to 0.31 L/h.

3. *Compute dose required to achieve desired phenobarbital serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 240 mg every 24 hours will produce a steady-state phenobarbital concentration of 29 μg/mL.

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14

ETHOSUXIMIDE

INTRODUCTION

Ethosuximide is succinimide compound that is effective in the treatment of absence (petit mal) seizures (Table 14-1).[1,2] It is the product of an intense structure-activity research effort to find an specific agent to suppress absence seizures with a relatively low side effect profile. While the exact mechanism of action is not known, the antiepileptic effect of ethosuximide is thought to result from its ability to decrease low-threshold calcium currents in thalamic neurons.[3] The thalamus has a key role in the production of 3-Hz spike-wave rhythms that are a hallmark of absence seizures. Ethosuximide may also inhibit the sodium-potassium ATPase system and NADPH-linked aldehyde reductase.[4]

THERAPEUTIC AND TOXIC CONCENTRATIONS

The therapeutic range for ethosuximide is defined by most laboratories as 40–100 μg/mL, although some clinicians suggest drug concentrations as high as 150 μg/mL with appropriate monitoring of serum concentrations and possible side effects.[5] The most common adverse effects of ethosuximide are gastric distress, nausea, vomiting, and anorexia, but these gastrointestinal problems appear to be caused by local irritation of gastric mucosa. Generally, administration of smaller doses and more frequent dosing of the drug produce relief from these side effects. In the upper end of the therapeutic range (>70 μg/mL) some patients will begin to experience the concentration-dependent adverse effects of ethosuximide treatment: drowsiness, fatigue, lethargy, dizziness, ataxia, hiccups, euphoria, and headaches. Idiosyncratic side effects that are independent of concentration include rash, systemic lupus-like syndromes, and blood dyscrasias (leukopenia, pancytopenia).

TABLE 14-1 International Classification of Epileptic Seizures with Treatment Recommendations

MAJOR CLASS	SUBSET OF CLASS	DRUG TREATMENT FOR SELECTED SEIZURE TYPE
Partial seizures (beginning locally)	1. Simple partial seizures (without impaired consciousness) a. With motor symptoms b. With somatosensory or special sensory symptoms c. With autonomic symptoms d. With psychological symptoms 2. Complex partial seizures (with impaired consciousness) a. Simple partial onset followed by impaired consciousness b. Impaired consciousness at onset 3. Partial seizures evolving into secondary generalized seizures	*Drugs of choice* Carbamazepine Phenytoin Lamotrigine Oxcarbazepine *Alternatives* Valproic acid Gabapentin Topiramate Tiagabine Zonisamide Levetiracetam Primidone Phenobarbital Pregabalin Felbamate
Generalized seizures (convulsive or nonconvulsive)	1. Absence seizures (typical or atypical; also known as petit mal seizures)	*Drugs of choice* Ethosuximide Valproic acid *Alternatives* Lamotrigine Clonazepam Zonisamide Levetiracetam
	2. Tonic-clonic seizures (also known as grand mal seizures)	*Drugs of choice* Valproic acid Phenytoin Carbamazepine *Alternatives* Lamotrigine Topiramate Zonisamide Oxcarbazepine Levetiracetam Primidone Phenobarbital

CLINICAL MONITORING PARAMETERS

The goal of therapy with anticonvulsants is to reduce seizure frequency and maximize quality of life with a minimum of adverse drug effects. While it is desirable to entirely abolish all seizure episodes, it may not be possible to accomplish this in many patients. Patients should be monitored for concentration-related side effects (drowsiness, fatigue, lethargy, dizziness, ataxia, hiccups, euphoria, headaches) as well as gastrointestinal upset associated with local irritation of gastric mucosa (gastric distress, nausea, vomiting, anorexia). Serious, but rare, idiosyncratic side effects include systemic lupus-like syndromes, leukopenia, and pancytopenia.

Ethosuximide serum concentrations should be measured in most patients. Because epilepsy is an episodic disease state, patients do not experience seizures on a continuous basis. Thus, during dosage titration it is difficult to tell if the patient is responding to drug therapy or simply is not experiencing any abnormal central nervous system discharges at that time. Ethosuximide serum concentrations are also valuable tools to avoid adverse drug effects. Patients are more likely to accept drug therapy if adverse reactions are held to the absolute minimum.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Ethosuximide is eliminated primarily by hepatic metabolism (70–80%) via hydroxylation and then conjugated to inactive metabolites.[6] About 20–30% of an ethosuximide dose is recovered as unchanged drug in the urine.[7] Ethosuximide is not significantly bound to plasma proteins. At concentrations exceeding 100 μg/mL, the drug may follow nonlinear pharmacokinetics, presumably owing to Michaelis-Menten (concentration dependent or saturable) metabolism.[8] Because an intravenous form of the drug is not commercially available, the absolute bioavailability in humans is not known. However, based on animal studies, ethosuximide oral bioavailability of capsules (250 mg) and syrup (250 mg/5 mL) is assumed to be 100%.[5] The typical maintenance dose for ethosuximide is 20 mg/kg/d for pediatric patients (<12 years old) and 15 mg/kg/d for older patients.[5]

EFFECTS OF DISEASE STATES AND CONDITIONS ON PHARMACOKINETICS AND DOSING

Ethosuximide oral clearance rate (Cl/F) for older children (≥12 years old) and adults is 12 mL/h/kg and for younger children is 16 mL/h/kg.[5] Ethosuximide volume of distribution (V/F) equals 0.7 L/kg, and its half life averages 30 hours in children and 60 hours in adults.[5] Although studies in patients with hepatic disease are not available, 70–80% of the drug is eliminated by hepatic metabolism. Because of this, patients with liver cirrhosis or acute hepatitis may have reduced ethosuximide clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of enzymes available to metabolize the drug and decreases clearance. An index of liver dysfunction can be gained by applying the Child-Pugh clinical classification system to the patient (Table 14-2).[9] Child-Pugh scores are completely discussed in Chapter 3 but will be briefly discussed here.

TABLE 14-2 Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 14-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease of 25–50% in the initial daily drug dose for ethosuximide. As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Ethosuximide serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Similarly, a small amount (20–30%) of ethosuximide is usually eliminated unchanged by the kidneys so patients with renal dysfunction (creatinine clearance <30 mL/min) receiving ethosuximide should be closely monitored.[7] Ethosuximide is significantly removed by hemodialysis, and supplemental doses may need to be given after a dialysis session.[10] The drug crosses into the placenta and enters breast milk, achieving concentrations at both sites similar to concurrent maternal serum concentrations.[11–13]

DRUG INTERACTIONS

Unlike other antiepileptic drugs, ethosuximide is not a hepatic enzyme inducer or inhibitor, and appears to cause no clinically important drug interactions.[14] Valproic acid can inhibit ethosuximide metabolism and increase steady-state concentrations, especially when ethosuximide serum concentrations are in the upper end of the therapeutic range.[8]

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate ethosuximide therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based*

recommended dosing is a very commonly used method to prescribe initial doses of ethosuximide. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of ethosuximide is to compute the best dose possible for the patient given their set of disease states and conditions that influence ethosuximide pharmacokinetics and the epileptic disorder being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Ethosuximide is predominately metabolized by liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change ethosuximide clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance. For example, for a 20-kg pediatric patient, ethosuximide clearance would be assumed to equal 16 mL/h/kg: 20 kg · 16 mL/h/kg = 320 mL/h or 0.32 L/h. To produce the most conservative ethosuximide doses in patients with multiple concurrent disease states or conditions that affect ethosuximide pharmacokinetics, the disease state or condition with the smallest clearance should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible.

VOLUME OF DISTRIBUTION ESTIMATE

Ethosuximide volume of distribution is assumed to equal 0.7 L/kg for adults and children. Thus, for a 20-kg pediatric patient, the estimated ethosuximide volume of distribution would be 14 L: V = 0.7 L/kg · 20 kg = 14 L.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl$, $k = 0.693/t_{1/2} = Cl/V$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

Ethosuximide follows a one-compartment pharmacokinetic model. When oral therapy is required, ethosuximide has good bioavailability (F = 1), and once or twice dosing provides a relatively smooth serum concentration/time curve that emulates an intravenous infusion. Because of this, a very simple pharmacokinetic equation that computes the average ethosuximide steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation: $Css = [F(D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau) / F$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral ethosuximide products), D is the dose of ethosuximide in milligrams, Cl is ethosuximide clearance in liters per hour, and τ is the dosage interval in hours.

Example 1 LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral ethosuximide. She has normal liver and renal function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an older patient is 12 mL/h/kg. Using this value, the estimated clearance would equal 0.564 L/h: Cl = 47 kg · 12 mL/h/kg = 564 mL/h or 0.564 L/h. The estimated volume of distribution would be 33 L: 47 kg · 0.7 L/kg = 33 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 33$ L)/ 0.564 L/h = 41 h, $k = Cl/V = 0.564$ L/h / 33 L = 0.017 h^{-1}.

3. *Compute dosage regimen.*

Oral ethosuximide capsules will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral ethosuximide is $D = (Css \cdot Cl \cdot \tau) / F = (50$ mg/L · 0.564 L/h · 12 h) / 1 = 338 mg, rounded to 250 every 12 hours.

A steady-state trough ethosuximide serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 41 hours, the ethosuximide steady-state concentration could be obtained any time after the ninth day of dosing (5 half-lives = 5 · 41 h = 205 h or 9 d). Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Example 2 CT is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral ethosuximide. He has normal liver and renal function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a child is 16 mL/h/kg. Using this value, the estimated clearance would equal 0.640 L/h: Cl = 40 kg · 16 mL/h/kg = 640 mL/h or 0.640 L/h. Using 0.7 L/kg, the estimated volume of distribution would be 28 L: 40 kg · 0.7 L/kg = 28 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 28$ L)/ 0.640 L/h = 30 h, $k = Cl/V = 0.640$ L/h / 28 L = 0.023 h^{-1}.

3. *Compute dosage regimen.*

Oral ethosuximide syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral ethosuximide is $D = (Css \cdot Cl \cdot \tau) / F = (50 \text{ mg/L} \cdot 0.640 \text{ L/h} \cdot 12 \text{ h}) / 1 = 384$ mg, rounded to 400 mg every 12 h.

A steady-state trough ethosuximide serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 30 hours, the ethosuximide steady-state concentration could be obtained any time after the sixth day of dosing (5 half-lives = 5 · 30 h = 150 h or 6 d). Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in ethosuximide pharmacokinetics, even when concurrent disease states and conditions are identified, most clinicians believe that the use of standard ethosuximide doses for various situations are warranted. The original computation of these doses were based on the pharmacokinetic dosing methods, and subsequently modified based on clinical experience. In general, the expected ethosuximide steady-state serum concentrations used to compute these doses was 40–50 μg/mL. The usual initial maintenance dose for pediatric patients (<12 years old) is 20 mg/kg/d. For older patients, the initial maintenance dose is 15 mg/kg/d. One or two divided daily doses are initially used for these total doses. To avoid gastrointestinal side effects, doses over 1500 mg given at one time should be avoided. Dosage increases of 3–7 mg/kg/d are made every 1–2 weeks depending on response and adverse effects. While maximal doses are 40 mg/kg/d for children less than 12 years old and 30 mg/kg/d for older patients, ethosuximide serum concentrations and adverse effects should be used to judge optimal response to the drug. If the patient has significant hepatic dysfunction (Child-Pugh score ≥8), maintenance doses prescribed using this method should be decreased by 25–50% depending on how aggressive therapy is required to be for the individual.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 3 LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral ethosuximide. She has normal liver and renal function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

1. *Estimate ethosuximide dose according to disease states and conditions present in the patient.*

Oral ethosuximide capsules will be prescribed to this patient. The suggested initial maintenance dosage rate for ethosuximide in an older patient is 15 mg/kg/d: 47 kg · 15 mg/kg/d = 705 mg/d, rounded to 750 mg/d. This dose could be given as 250 mg in the morning and 500 mg in the evening. This dose would be titrated upward in 3–7 mg/kg/d increments

every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Example 4 CT is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral ethosuximide. He has normal liver and renal function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

1. *Estimate ethosuximide dose according to disease states and conditions present in the patient.*

Oral ethosuximide syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for ethosuximide for a child is 20 mg/kg/d: 40 kg · 20 mg/kg/d = 800 mg/d or 400 mg every 12 hours. This dose would be titrated upward in 3–7 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

USE OF ETHOSUXIMIDE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce ethosuximide serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the possible nonlinear pharmacokinetics followed by the drug at high concentrations, the narrow therapeutic index of ethosuximide and the desire to avoid adverse side effects of ethosuximide, measurement of ethosuximide serum concentrations is conducted for most patients to ensure that therapeutic, nontoxic levels are present. In addition to ethosuximide serum concentrations, important patient parameters (seizure frequency, potential ethosuximide side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When ethosuximide serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change doses since ethosuximide follows *linear pharmacokinetics*. Sometimes, it is not possible to simply change the dose because of the limited number of oral dosage strengths, and the dosage interval must also be changed. In some situations, it may be necessary or desirable to compute the ethosuximide

pharmacokinetic parameters for the patient and utilize these to calculate the best drug dose. Computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because ethosuximide follows linear, dose-proportional pharmacokinetics in most patients with concentrations within and below the therapeutic range, steady-state serum concentrations change in proportion to dose according to the following equation:

$$D_{new}/C_{ss,new} = D_{old}/C_{ss,old} \text{ or } D_{new} = (C_{ss,new}/C_{ss,old})D_{old},$$

where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and the assumption of linear pharmacokinetics may not be valid in all patients. When steady-state serum concentrations increase more than expected after a dosage increase or decrease less than expected after a dosage decrease, nonlinear ethosuximide pharmacokinetics is a possible explanation for the observation. Because of this, suggested dosage increases greater than 75% using this method should be scrutinized by the prescribing clinician, and the risk versus benefit for the patient assessed before initiating large dosage increases (>75% over current dose).

Example 5 LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral ethosuximide. After dosage titration, the patient was prescribed 500 mg every 12 hours of ethosuximide capsules (1000 mg/d) for 1 month, and the steady-state ethosuximide total concentration equals 38 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 80 μg/mL.

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting total steady-state ethosuximide serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old}$ = (80 μg/mL / 38 μg/mL) 1000 mg/d = 2105 mg/d, rounded to 2000 mg/d or 1000 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Example 6 CT is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral ethosuximide. After dosage titration, the patient was prescribed 500 mg twice daily (1000 mg/d) of ethosuximide syrup for 1 month, and the steady-state ethosuximide total concentration equals 130 μg/mL. The patient is assessed to be compliant with

his dosage regimen. Suggest a ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 75 μg/mL.

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting total steady-state ethosuximide serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (75\ \mu g/mL / 130\ \mu g/mL)\ 1000$ mg/d = 577 mg/d, rounded to 500 mg/d or 250 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired ethosuximide concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state ethosuximide concentration (Css). Ethosuximide clearance (Cl) can be calculated using the following formula: $Cl = [F(D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral ethosuximide products), D is the dose of ethosuximide in milligrams, Css is the steady-state ethosuximide concentration in milligrams per liter, and τ is the dosage interval in hours.

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic parameter method, the same examples used in the previous section will be used.

Example 7 LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral ethosuximide. After dosage titration, the patient was prescribed 500 mg every 12 hours of ethosuximide capsules (1000 mg/d) for 1 month, and the steady-state ethosuximide total concentration equals 38 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 80 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady state conditions after 1–2 weeks of therapy.

Ethosuximide clearance can be computed using a steady-state ethosuximide concentration: $Cl = [F(D/\tau)] / Css = [1(500\ mg/12\ h)] / (38\ mg/L) = 1.1$ L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute ethosuximide dose.*

Ethosuximide clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (80\ mg/L \cdot 1.1\ L/h \cdot 12\ h) / 1 = 1056$ mg, rounded to 1000 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Example 8 CT is a 10-year-old, 40-kg male with absence seizures who requires therapy with oral ethosuximide. After dosage titration, the patient was prescribed 500 mg twice daily (1000 mg/d) of ethosuximide syrup for 1 month, and the steady-state ethosuximide total concentration equals 130 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 75 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 1–2 weeks of therapy.

Ethosuximide clearance can be computed using a steady-state ethosuximide concentration: $Cl = [F(D/\tau)] / Css = [1(500\ mg/12\ h)] / (130\ mg/L) = 0.32\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute ethosuximide dose.*

Ethosuximide clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (75\ mg/L \cdot 0.32\ L/h \cdot 12\ h) / 1 = 288\ mg$, rounded to 250 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem.[15] Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program,

and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[15]

Example 9 LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral ethosuximide. The patient has normal liver and renal function (bilirubin = 0.5 mg/dL, albumin 4.6 mg/dL, serum creatinine = 0.5 mg/dL). After dosage titration, the patient was prescribed 500 mg every 12 hours of ethosuximide capsules (1000 mg/d) for 2 weeks, and the steady-state ethosuximide total concentration equals 38 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 80 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 46 L, a half-life equal to 26 h, and a clearance equal to 1.24 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1000 mg every 12 hours will produce a steady-state ethosuximide concentration of 68 μg/mL.

Example 10 JB is an 8-year-old, 35-kg male (4 ft 2 in) with absence seizures who was started on ethosuximide syrup 350 mg every 12 hours. The ethosuximide concentration was 25 μg/mL before the fifth maintenance dose. What ethosuximide dose is needed to achieve Css = 75 μg/mL?

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 30 L, a half-life equal to 18 h, and clearance equal to 1.12 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model oral equations used by the program to compute doses indicates that a dose of ethosuximide 1000 mg every 12 hours will produce a steady-state concentration of 69 μg/mL.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 14-3.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current anticonvulsant therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with ethosuximide exists.

1. YH is a 4-year-old, 16-kg (3 ft 4 in) male with absence seizures who requires therapy with oral ethosuximide. He has normal liver function. Suggest an initial ethosuximide

TABLE 14-3 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

2. Patient YH (please see problem 1) was prescribed 300 mg every day of ethosuximide syrup for 1 month, and the steady-state ethosuximide total concentration equals 40 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 75 μg/mL.

3. FD is a 9-year-old, 35-kg female (4 ft 6 in) with absence seizures who requires therapy with oral ethosuximide. She has normal liver function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 75 μg/mL.

4. Patient FD (please see problem 3) was prescribed 350 mg every 12 hours (700 mg/d) of ethosuximide syrup for 2 weeks, and the steady-state ethosuximide total concentration equals 55 μg/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 90 μg/mL.

5. LK is a 14-year-old, 60-kg male (5 ft 6 in) with absence seizures who requires therapy with ethosuximide capsules. He has normal liver and renal function. Suggest an initial ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration equal to 50 μg/mL.

6. Patient LK (please see problem 5) was prescribed 500 mg every 12 hours (1000 mg/d) of ethosuximide capsules for 2 weeks, and the steady-state ethosuximide total concentration equals 40 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an ethosuximide dosage regimen designed to achieve a steady-state ethosuximide concentration of 60 μg/mL.

7. DG is a 15-year-old, 68-kg (5 ft 8 in) male with absence seizures who is receiving 1000 mg daily of ethosuximide capsules. He has normal liver and renal function. The total ethosuximide concentration equals 22 μg/mL before the fourth dose. Compute an ethosuximide dose that will provide a steady-state concentration of 50 μg/mL.

8. YF is a 5-year-old, 20-kg (3 ft 6 in) female with absence seizures who was given a new prescription of 250 mg every 12 hours of oral ethosuximide syrup. She has normal liver and renal function. The trough ethosuximide concentration before the fifth dose equals 42 μg/mL. Compute an ethosuximide dose that will provide a total steady-state concentration of 75 μg/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a pediatric patient is 16 mL/h/kg. Using this value, the estimated clearance would equal 0.256 L/h: Cl = 16 kg · 16 mL/h/kg = 256 mL/h or 0.256 L/h. Using 0.7 L/kg, the estimated volume of distribution would be 11 L: 16 kg · 0.7 L/kg = 11 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 11\ L) / 0.256\ L/h = 30\ h$, $k = Cl/V = 0.256\ L/h / 11\ L = 0.023\ h^{-1}$.

3. *Compute dosage regimen.*

Oral ethosuximide syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral ethosuximide is $D = (Css \cdot Cl \cdot \tau) / F = (50\ mg/L \cdot 0.256\ L/h \cdot 12\ h) / 1 = 154$ mg, rounded to 150 every 12 hours.

A steady-state trough ethosuximide serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 30 hours, the ethosuximide steady-state concentration could be obtained any time after the sixth day of dosing (5 half-lives = 5 · 30 h = 150 h or 6 d). Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Literature-Based Recommended Dosing

1. *Estimate ethosuximide dose according to disease states and conditions present in the patient.*

Oral ethosuximide syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for ethosuximide in a pediatric patient is 20 mg/kg/d: 16 kg · 20 mg/kg/d = 320 mg/d, rounded to 300 mg/d or 150 mg every 12 hours. This dose would be titrated upward in 3–7 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

2. *Solution to problem 2.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting total steady-state ethosuximide serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (75\ \mu g/mL / 40\ \mu g/mL)\ 300\ mg/d = 563$ mg/d, rounded to 600 mg/d.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 1–2 weeks of therapy.

Ethosuximide clearance can be computed using a steady-state ethosuximide concentration: $Cl = [F(D/\tau)] / Css = [1(300\ mg/24\ h)]/(40\ mg/L) = 0.31\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute ethosuximide dose.*

Ethosuximide clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (75\ mg/L \cdot 0.31\ L/h \cdot 24\ h) / 1 = 558\ mg$, rounded to 600 mg every 24 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 11.3 L, a half-life equal to 32 h, and a clearance equal to 0.24 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 500 mg every day will produce a steady-state ethosuximide concentration of 68 μg/mL.

3. *Solution to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for a pediatric patient is 16 mL/h/kg. Using this value, the estimated clearance would equal 0.560 L/h: $Cl = 35\ kg \cdot 16\ mL/h/kg = 560\ mL/h$ or 0.560 L/h. Using 0.7 L/kg, the estimated volume of distribution would be 25 L: $35\ kg \cdot 0.7\ L/kg = 25\ L$.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2} = (0.693 \cdot V) / Cl = (0.693 \cdot 25\ L) / 0.560\ L/h = 31\ h$, $k = Cl/V = 0.560\ L/h / 25\ L = 0.022\ h^{-1}$.

3. *Compute dosage regimen.*

Oral ethosuximide syrup will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral ethosuximide is $D = (Css \cdot Cl \cdot \tau) / F = (75\ mg/L \cdot 0.560\ L/h \cdot 12\ h) / 1 = 504$ mg, rounded to 500 every 12 hours.

A steady-state trough ethosuximide serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 31 hours, the ethosuximide steady-state concentration could be obtained any time after the sixth day of dosing (5 half-lives = 5 · 31 h = 155 h or 6 d). Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Literature-Based Recommended Dosing

1. *Estimate ethosuximide dose according to disease states and conditions present in the patient.*

Oral ethosuximide syrup will be prescribed to this patient. The suggested initial maintenance dosage rate for ethosuximide in a pediatric patient is 20 mg/kg/d: 35 kg · 20 mg/kg/d = 700 mg/d, 350 mg every 12 hours. This dose would be titrated upward in 3–7 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

4. *Solution to problem 4.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting total steady-state ethosuximide serum concentration would equal $D_{new} = (Css_{new}/Css_{old})\ D_{old} = (90\ \mu g/mL / 55\ \mu g/mL)\ 700\ mg/d = 1145$ mg/d, rounded to 1100 mg/d or 550 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 1–2 weeks of therapy.

Ethosuximide clearance can be computed using a steady-state ethosuximide concentration: Cl = [F(D/τ)] / Css = [1(350 mg/12 h)] / (55 mg/L) = 0.53 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute ethosuximide dose.*

Ethosuximide clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (90 mg/L · 0.53 L/h · 12 h) / 1 = 572 mg, rounded to 600 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 25 L, a half-life equal to 36 h, and a clearance equal to 0.48 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 600 mg every 12 hours will produce a steady-state ethosuximide concentration of 95 μg/mL.

5. *Solution to problem 5.*

Pharmacokinetic Dosing Method

1. *Estimate clearance and volume of distribution according to disease states and conditions present in the patient.*

The clearance rate for an older patient is 12 mL/h/kg. Using this value, the estimated clearance would equal 0.720 L/h: Cl = 60 kg · 12 mL/h/kg = 720 mL/h or 0.720 L/h. Using 0.7 L/kg, the estimated volume of distribution would be 42 L: 60 kg · 0.7 L/kg = 42 L.

2. *Estimate half-life and elimination rate constant.*

Once the correct clearance and volume of distribution estimates are identified for the patient, they can be converted into the ethosuximide half-life ($t_{1/2}$) and elimination rate constant (k) estimates using the following equations: $t_{1/2}$ = (0.693 · V) / Cl = (0.693 · 42 L) / 0.720 L/h = 40 h, k = Cl/V = 0.720 L/h / 42 L = 0.017 h^{-1}.

3. *Compute dosage regimen.*

Oral ethosuximide capsules will be prescribed to this patient (F = 1). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral ethosuximide is $D = (Css \cdot Cl \cdot \tau) / F = (50 \text{ mg/L} \cdot 0.720 \text{ L/h} \cdot 24 \text{ h}) / 1 = 864$ mg, rounded to 750 every day.

A steady-state trough ethosuximide serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 40 hours, the ethosuximide steady-state concentration could be obtained any time after the sixth day of dosing (5 half-lives = 5 · 40 h = 200 h or 8 d). Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Literature-Based Recommended Dosing

1. *Estimate ethosuximide dose according to disease states and conditions present in the patient.*

Oral ethosuximide capsules will be prescribed to this patient. The suggested initial maintenance dosage rate for ethosuximide in an older patient is 15 mg/kg/d: 60 kg · 15 mg/kg/d = 900 mg/d, rounded to 1000 mg daily. This dose would be titrated upward in 3–7 mg/kg/d increments every 1–2 weeks while monitoring for adverse and therapeutic effects. The goals of therapy include maximal suppression of seizures and avoidance of side effects.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

6. *Solution to problem 6.*

Linear Pharmacokinetics Method

1. *Compute a new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the resulting total steady-state ethosuximide serum concentration would equal $D_{new} = (Css_{new}/Css_{old}) D_{old} = (60 \text{ μg/mL} / 40 \text{ μg/mL}) 1000$ mg/d = 1500 mg/d, or 750 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after 1–2 weeks of therapy.

Ethosuximide clearance can be computed using a steady-state ethosuximide concentration: Cl = [F(D/τ)] / Css = [1(500 mg/12 h)] / (40 mg/L) = 1.0 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute ethosuximide dose.*

Ethosuximide clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (60 mg/L · 1.0 L/h · 12 h) / 1 = 720 mg, rounded to 750 mg every 12 hours.

A steady-state trough total ethosuximide serum concentration should be measured after steady state is attained in 1–2 weeks. Ethosuximide serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of ethosuximide toxicity.

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 42 L, a half-life equal to 32 h, and a clearance equal to 0.93 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 750 mg every 12 hours will produce a steady-state ethosuximide concentration of 61 μg/mL.

7. *Solution to problem 7.*

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

This patient is not at steady state, so linear pharmacokinetics cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 48 L, a half-life equal to 29 h, and a clearance equal to 1.2 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1750 mg every 24 hours will produce a steady-state ethosuximide concentration of 48 μg/mL. To avoid possible gastrointestinal side effects, this daily dose should be given in as a divided dose of 750 mg in the morning and 1000 mg in the evening.

8. *Solution to problem 8*

Bayesian Pharmacokinetic Computer Programs

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 13 L, a half-life equal to 31 hours, and a clearance equal to 0.30 L/h.

3. *Compute dose required to achieve desired ethosuximide serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 300 mg every 12 hours will produce a steady-state ethosuximide concentration of 76 μg/mL.

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Part V

IMMUNOSUPPRESSANTS

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15

CYCLOSPORINE

INTRODUCTION

Cyclosporine is a cyclic polypeptide with immunosuppressant properties that is used for the prevention of graft-versus-host disease in hematopoietic stem cell transplantation patients, for the prevention of graft rejection in solid organ transplant patients, and for the treatment of psoriasis, rheumatoid arthritis and a variety of other autoimmune diseases.[1,2] The immunomodulating properties of cyclosporine are a result of its ability to block the production of interleukin-2 and other cytokines secreted by T-lymphocytes.[3] Cyclosporine binds to cyclophilin, an intracellular cytoplasmic protein found in T-cells. The cyclosporine-cyclophilin complex interacts with calcineurin, inhibits the catalytic activity of calcineurin, and prevents the production of intermediaries involved with the expression of genes regulating the production of cytokines.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The therapeutic range of cyclosporine used by clinicians varies greatly according to the type of assay used to measure cyclosporine and whether blood or serum concentrations are determined by the clinical laboratory (Table 15-1).[1,2,4,5] Because cyclosporine is bound to red blood cells, blood concentrations are higher than simultaneously measured serum or plasma concentrations. High pressure liquid chromatography (HPLC) assay techniques are specific for cyclosporine measurement in blood, serum, or plasma. However, older immunoassays conducted via fluorescence polarization (polyclonal TDx assay, Abbott Diagnostics) or radioimmunoassay (polyclonal RIA, various manufacturers) are nonspecific and measure both cyclosporine and its metabolites. Newer monoclonal fluorescence polarization (monoclonal TDx assay) and radioimmunoassays (various) are now available that are relatively specific for cyclosporine and produce results similar to the HPLC assay. As a result, cyclosporine concentrations measured simultaneously in a patient using the specific high pressure liquid chromatography technique or one of the

TABLE 15-1 Cyclosporine Therapeutic Concentrations for Different Assay Techniques and Biologic Fluids

ASSAY	BIOLOGIC FLUID	THERAPEUTIC CONCENTRATIONS (ng/mL)
High pressure liquid chromatography (HPLC), monoclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or monoclonal radioimmunoassay (various manufacturers)	Blood	100–400
High pressure liquid chromatography (HPLC), monoclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or monoclonal radioimmunoassay (various manufacturers)	Plasma	50–150
Polyclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or polyclonal radioimmunoassay (various manufacturers)	Blood	200–800
Polyclonal fluorescence polarization immunoassay (monoclonal TDx assay, Abbott Diagnostics), or polyclonal radioimmunoassay (various manufacturers)	Plasma	100–400

specific immunoassays will be lower than that determined using a nonspecific immunoassay. Since cyclosporine metabolites are excreted in the bile, liver transplant patients immediately after surgery can have very high cyclosporine metabolite concentrations in the blood, serum, and plasma because bile production has not begun yet in the newly transplanted organ. If nonspecific immunoassays are used to measure cyclosporine concentrations in liver transplant patients immediately after surgery before the graft has begun to produce bile, the predominate species measured with this assay methodology may be cyclosporine metabolites and not cyclosporine. One reason some laboratories favor the use of immunoassays for the measurement of cyclosporine concentrations, even though they are less specific for the parent compound, is that it takes less time to conduct the technique so that cyclosporine concentrations can be returned to clinicians more rapidly. For the purposes of the pharmacokinetic calculations and problems presented in this book, cyclosporine concentrations in the blood using the cyclosporine-specific high pressure liquid chromatograph assay results will be used.

Often, desired cyclosporine concentrations differ between the various types of organ transplants, change with time during the posttransplantation phase, and are determined by protocols specific to the transplantation service and institution.[1,2,4,5] Thus, it is especially important for clinicians to be aware of these various factors, as acceptable cyclosporine concentrations under these different circumstances may be different than those listed by their clinical laboratory or those given in this text.

For patients receiving cyclosporine after a hematopoietic stem cell transplantation, the goal of therapy is to prevent graft-versus-host disease while avoiding adverse effects of immunosuppressant therapy.[1,4,5] Graft-versus-host disease is a result of donor T-lymphocytes detecting antigens on host tissues and producing an immunologic response against these antigens and host tissues. Acute graft-versus-host disease usually occurs

within the first 100 days after transplantation of donor cells, and causes epithelial tissue damage in organs. The most common tissues attacked are skin, gastrointestinal tract, and liver. To prevent acute graft-versus-host disease from occurring in allogenic hematopoietic stem cell transplantation patients with HLA-identical sibling donors, cyclosporine therapy is usually instituted on the day of stem cell transplant (day 0), and doses are adjusted to provide therapeutic trough concentrations. Methotrexate and/or glucocorticoids are usually also given in conjunction with cyclosporine treatment to hematopoietic stem cell transplantation patients. If prophylaxis of acute graft-versus-host disease is successful, cyclosporine doses start to be tapered on about posttransplant day 50, with the goal of drug discontinuation by about posttransplant day 180. For allogeneic hematopoietic stem cell transplantation patients with HLA-mismatched or HLA-identical unrelated donors, the risk of acute graft-versus-host disease is higher, so cyclosporine therapy may be more prolonged for these patients. After post-transplantation day 100, chronic graft-versus-host disease may occur and can also be treated with cyclosporine therapy.

For patients receiving solid organ transplants such as kidney, liver, heart, lung, or heart-lung transplantation, the goal of cyclosporine therapy is to prevent acute or chronic rejection of the transplanted organ while minimizing drug side effects.[2,4,5] In this case, the recipient's immune system detects foreign antigens on the donor organ which produces an immunologic response against the graft. This leads to inflammatory and cytotoxic effects directed against the transplanted tissue, and produces the risk of organ tissue damage and failure. In the case of a rejected kidney transplant, it is possible to remove the graft and place the patient on a form of dialysis to sustain their life. However, for other solid organ transplantation patients, graft rejection can result in death. Because cyclosporine can cause nephrotoxicity, many centers delay cyclosporine therapy in renal transplant patients for a few days or until the kidney begins functioning to avoid untoward effects on the newly transplanted organ. Also, desired cyclosporine concentrations in renal transplant patients are generally lower to avoid toxicity in the new renal graft than for other transplant patients (typically 100–200 ng/mL versus 150–300 ng/mL using whole blood with a specific, high pressure liquid chromatograph assay). For other solid organ transplant patients, cyclosporine therapy may be started several hours before surgery or, for patients with poor kidney function, held until after transplantation to avoid nephrotoxicity. During the immediate postoperative phase, intravenous cyclosporine may be given to these patients. For long-term management of immunosuppression in solid organ tissue transplant patients, cyclosporine doses are gradually tapered to the lowest concentration and dose possible over a 6- to 12-month time period as long as rejection episodes do not occur.

Hypertension, nephrotoxicity, hyperlipidemia, tremor, hirsutism, and gingival hyperplasia are all typical adverse effects of cyclosporine treatment.[1–5] Hypertension is the most common side effect associated with cyclosporine therapy, and is treated with traditional antihypertensive drug therapy. Nephrotoxicity is separated into acute and chronic varieties. Acute nephrotoxicity is concentration or dose dependent and reverses with a dosage decrease. Renal damage in this situation is thought to result from renal vasoconstriction which results in increased renal vascular resistance, decreased renal blood flow, and reduced glomerular filtration rate. Chronic nephrotoxicity is accompanied by kidney tissue damage, including interstitial fibrosis, nonspecific tubular vacuolization, and structural changes in arteries, arterioles, and proximal tubular epithelium. Increased serum

creatinine and blood urea nitrogen (BUN) values, hyperkalemia, hyperuricemia, proteinuria, and increased renal sodium excretion occur with cyclosporine-induced nephrotoxicity. The clinical features of cyclosporine nephrotoxicity and acute graft rejection in renal transplant patients are similar, so renal biopsies may be conducted to differentiate between these possibilities.[2] Because biopsy findings are similar between cyclosporine-induced nephrotoxicity and chronic rejection of kidney transplants, this technique is of less help in this situation. Hyperlipidemia is treated using dietary counseling and antilipid drug therapy. Cyclosporine dosage decreases may be necessary to decrease tremor associated with drug therapy while hirsutism is usually addressed using patient counseling. Gingival hyperplasia can be minimized through the use of appropriate and regular dental hygiene and care.

CLINICAL MONITORING PARAMETERS

Hematopoietic stem cell transplantation patients should be monitored for the signs and symptoms associated with graft-versus-host disease.[1] These include a generalized maculopapular skin rash, diarrhea, abdominal pain, ileus, hyperbilirubinemia, and increased liver function tests (serum transaminases and alkaline phosphatase). Patients with severe chronic graft-versus-host disease may have involvement of the skin, liver, eyes, mouth, esophagus, or other organs similar to what might be seen with systemic autoimmune diseases.

Solid organ transplant patients should be monitored for graft rejection consistent with the transplanted organ. For renal transplant patients, increased serum creatinine, azotemia, hypertension, edema, weight gain secondary to fluid retention, graft tenderness, fever, and malaise may result from an acute rejection episode.[2] Hypertension, proteinuria, a continuous decline in renal function (increases in serum creatinine and blood urea nitrogen levels), and uremia are indicative of chronic rejection in renal transplant patients. For hepatic transplant patients, acute rejection signs and symptoms include fever, lethargy, graft tenderness, increased white blood cell count, change in bile color or amount, hyperbilirubinemia, and increased liver function tests.[2] Chronic rejection in a liver transplant patient may be accompanied only by increased liver function tests and jaundice. For heart transplant patients, acute rejection is accompanied by low-grade fever, malaise, heart failure (presence of S_3 heart sound), or atrial arrhythmia.[2] Chronic rejection in heart transplant patients, also known as cardiac allograft vasculopathy which is characterized by accelerated coronary artery atherosclerosis, may include the following symptoms: arrhythmias, decreased left ventricular function, heart failure, myocardial infarction, and sudden cardiac death. For all solid organ transplant patients, tissue biopsies may be taken from the transplanted tissue to confirm the diagnosis of organ rejection.[2]

Typical adverse effects of cyclosporine treatment include hypertension, nephrotoxicity, hyperlipidemia, tremor, hirsutism, and gingival hyperplasia.[1–5] The management of these more common drug side effects are discussed in the previous section. Other cyclosporine adverse drug reactions that occur less frequently include gastrointestinal side effects (nausea, vomiting, diarrhea), headache, hepatotoxicity, hyperglycemia, acne, leukopenia, hyperkalemia, and hypomagnesemia.

Because of the pivotal role that cyclosporine plays as an immunosuppressant in transplant patients, as well as the severity of its concentration- and dose-dependent side

effects, cyclosporine concentrations should be measured in every patient receiving the drug. If a patient experiences signs or symptoms of graft-versus-host disease or organ rejection, a cyclosporine concentration should be checked to ensure that levels have not fallen below the therapeutic range. If a patient encounters a possible clinical problem that could be an adverse drug effect of cyclosporine therapy, a cyclosporine concentration should be measured to determine if levels are in the toxic range. During the immediate post-transplantation phase, cyclosporine concentrations are measured daily in most patients even though steady state may not yet have been achieved in order to prevent acute rejection in solid organ transplant patients or acute graft-versus-host disease in hematopoietic stem cell transplantation patients.

After discharge from the hospital, cyclosporine concentrations continue to be obtained at most clinic visits. In patients receiving allogeneic hematopoietic stem cell transplantations from HLA-identical sibling donors, it is usually possible to decrease cyclosporine doses and concentrations about 2 months after the transplant and stop cyclosporine therapy altogether after about 6 months posttransplant if no or mild acute rejection episodes have taken place. However, in allogeneic hematopoietic stem cell transplantation patients with HLA-mismatched related or HLA-identical unrelated donors and all solid organ transplant patients, chronic cyclosporine therapy is usually required. In these cases, cyclosporine doses and concentrations are decreased to the minimum required to prevent graft-versus-host reactions or rejection episodes in order to decrease drug adverse effects. Methods to adjust cyclosporine doses using cyclosporine concentrations are discussed later in this chapter. Although newer data are available that suggest determination of cyclosporine area under the concentration/time curve using multiple concentrations[6–10] or 2-hour postdose cyclosporine concentrations[11–14] may provide better outcomes for some transplant types, many transplant centers continue to use predose trough cyclosporine concentration determinations to adjust drug doses.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Cyclosporine is almost completely eliminated by hepatic metabolism (>99%).[15] Hepatic metabolism is mainly via the CYP3A4 enzyme system, and the drug is a substrate for P-glycoprotein. There are more than 25 identified cyclosporine metabolites.[5,16] None of these metabolites appear to have significant immunosuppressive effects in humans. Most of the metabolites are eliminated in the bile. Less than 1% of a cyclosporine dose is recovered as unchanged drug in the urine. Within the therapeutic range, cyclosporine follows linear pharmacokinetics.[17]

There is a large amount of intrasubject variability in cyclosporine concentrations obtained on a day-to-day basis, even when the patient should be at steady state. There are many reasons for this variability. Cyclosporine has low water solubility, and its gastrointestinal absorption can be influenced by many variables.[5,16,18,19] To improve the consistency of absorption rate and bioavailability for original dosage form (Sandimmune, Novartis), a microemulsion version of the drug (Neoral, Novartis) was marketed to help reduce absorption variability. While use of microemulsion cyclosporine does decrease steady-state concentration variability (10–30% for Neoral versus 16–38% for Sandimmune for trough concentrations), there are still substantial day-to-day changes in

cyclosporine concentrations regardless of the dosage form used.[20] The fat content of meals has an influence on the absorption of oral cyclosporine.[21] Food containing a large amount of fat enhances the absorption of cyclosporine. Oral cyclosporine solution is prepared with olive oil and alcohol to enhance the solubility of the drug. The solution is mixed in milk, chocolate milk, or orange juice using a glass container immediately before swallowing. When the entire dose has been given, the glass container should be rinsed with the diluting liquid and immediately consumed. If microemulsion cyclosporine solution is administered, it should be mixed in a similar fashion using apple or orange juice. In either case, grapefruit juice should not be used since this vehicle inhibits CYP3A4 and/or P-glycoprotein contained in the gastrointestinal tract and markedly increases bioavailability. Variation in cyclosporine solution absorption is dependent on how accurately the administration technique for each dose is reproduced. After liver transplantation, bile production and flow may not begin immediately, or bile flow may be diverted from the gastrointestinal tract using a T-tube.[22,23] In the absence of bile salts, the absorption of cyclosporine can be greatly decreased. Bile appears to assist in the dissolution of cyclosporine which increases the absorption of the drug. Diarrhea also impairs cyclosporine absorption,[24,25] and hematopoietic stem cell transplantation patients may experience diarrhea as a part of graph-versus-host disease.[1] Other drug therapy can also increase or decrease the intestinal first-pass clearance of cyclosporine.[26]

Cyclosporine is a low-to-moderate hepatic extraction ratio drug with an average liver extraction ratio of ~30%.[27] Because of this, its hepatic clearance is influenced by unbound fraction in the blood (f_B), intrinsic clearance (Cl'_{int}), and liver blood flow (LBF). Cyclosporine binds primarily to erythrocytes and lipoproteins, yielding unbound fractions in the blood that are highly variable (1.4–12%).[28–33] Erythrocyte concentrations vary in transplant patients, especially those who have received hematopoietic stem cell transplantation or kidney transplants. Lipoprotein concentrations also vary among patients, and hyperlipidemia is an adverse effect of cyclosporine. Hepatic intrinsic clearance is different among individuals, and there is a large amount of variability in this value within individual liver transplant patients that changes according to the viability of the graft and time after transplantation surgery. Other drug therapy can also increase or decrease the hepatic intrinsic clearance of cyclosporine.[26] Liver blood flow exhibits a great deal of day-to-day intrasubject variability which will also change the hepatic clearance of cyclosporine. Of course, changing the unbound fraction in the blood, hepatic intrinsic clearance, or liver blood flow will also change the hepatic first-pass metabolism of cyclosporine. Taking all of these possible factors into consideration that alter absorption and clearance allows one to gain a better appreciation of why cyclosporine concentrations change on a day-to-day basis.

Cyclosporine capsules and solution are available in regular (25-mg, 50-mg, and 100-mg capsules; 100-mg/mL solution) and microemulsion (25-mg and 100-mg capsules; 100-mg/mL solution) form. Although the oral absorption characteristics are more consistent and bioavailability higher for microemulsion forms of cyclosporine, it is recommended that patients switched from cyclosporine to microemulsion cyclosporine have doses converted on a 1:1 basis. Subsequent microemulsion cyclosporine dosage adjustments are based on concentration monitoring. Cyclosporine injection for intravenous administration is available at a concentration of 50 mg/mL. Before administration, each milliliter of the concentrate should be diluted in 20–100 mL of normal saline or 5% dextrose, and the total dose infused over 2–6 hours. For patients stabilized on oral

cyclosporine, the initial intravenous dose should be about 33% of the oral dose. Anaphylactic reactions have occurred with this dosage form, possibly because of the castor oil diluent used to enhance dissolution of the drug. The initial dose of cyclosporine varies greatly among various transplant centers. Cyclosporine therapy is commonly started 4–12 hours before the transplantation procedure. According to a survey of transplant centers in the United States, the average initial oral dose (± standard deviation) for renal, liver, and heart transplant patients were 9 ± 3mg/kg/d, 8 ± 4mg/kg/d, and 7 ± 3 mg/kg/d.[20] For both rheumatoid arthritis and psoriasis, the recommended initial dose is 2.5 mg/kg/d administered twice daily as divided doses with maximal recommended doses of 4 mg/kg/d.

EFFECTS OF DISEASE STATES AND CONDITIONS ON CYCLOSPORINE PHARMACOKINETICS AND DOSING

Transplantation type does not appear to have a substantial effect on cyclosporine pharmacokinetics. The overall mean for all transplant groups is a clearance of 6 mL/min/kg, a volume of distribution equal to 5 L/kg, and a half-life of 10 hours for adults.[5,16,18,19] Average clearance is higher (10 mL/min/kg) and mean half-life is shorter (6 hours) in children (≤16 years old).[5,16,18,19] The determination of cyclosporine half-life is difficult for patients receiving the drug on a twice daily dosage schedule because only a few concentrations can be measured in the postabsorption, postdistribution phase. Because of this, half-life measurements were taken from studies that allowed at least 24 hours between doses. These results, as with the other pharmacokinetic parameters discussed in this chapter, are based on a specific high-pressure liquid chromatography assay method conducted using whole blood samples. As discussed in a previous section, nonspecific cyclosporine assays measure metabolite concentrations in addition to parent drug, and concurrently measured plasma or serum concentrations are lower than whole blood concentrations.

Because the drug is primarily eliminated by hepatic metabolism, clearance is lower (3 mL/min/kg) and half-life prolonged (20 hours) in patients with liver failure.[5,16,34] Immediately after liver transplantation, cyclosporine metabolism is depressed until the graft begins functioning in a stable manner. Additionally, patients with transient liver dysfunction, regardless of transplantation type, will have decreased cyclosporine clearance and increased half-life values. Immediately after transplantation surgery, oral absorption of cyclosporine, especially in liver transplant patients with T-tubes, is highly variable.[22,23] Obesity does not influence cyclosporine pharmacokinetics, so doses should be based on ideal body weight for these individuals.[35–39]

Renal failure does not change cyclosporine pharmacokinetics, and the drug is not significantly removed by hemodialysis or peritoneal dialysis.[40–42] The hemofiltration sieving coefficient for cyclosporine is 0.58, which indicates significant removal.[43,44] Replacement doses during hemoperfusion should be determined using cyclosporine concentrations.

DRUG INTERACTIONS

Drug interactions with cyclosporine fall into two basic categories. The first are agents known to cause nephrotoxicity when administered by themselves.[26] The fear is that administration of a known nephrotoxin with cyclosporine will increase the incidence of

renal damage over that observed when cyclosporine or the other agent is given separately. Drugs in this category of drug interactions include aminoglycoside antibiotics, vancomycin, cotrimoxazole (trimethoprim-sulfamethoxazole), amphotericin B, and antiinflammatory drugs (azapropazone, diclofenac, naproxen, other nonsteroidal antiinflammatory drugs). Other agents are melphalan, ketoconazole, cimetidine, ranitidine, and tacrolimus.

The second category of drug interactions involves inhibition or induction of cyclosporine metabolism. Cyclosporine is metabolized by CYP3A4 and is a substrate for P-glycoprotein, so the potential for many pharmacokinetic drug interactions exists with agents that inhibit these pathways or are also cleared by these mechanisms.[26] Because both of these drug elimination systems also exist in the gastrointestinal tract, inhibition drug interactions may also enhance cyclosporine oral bioavailability by diminishing the intestinal and hepatic first-pass effects. Drugs that inhibit cyclosporine clearance include the calcium channel blockers (verapamil, diltiazem, nicardipine), azole antifungals (fluconazole, itraconazole, ketoconazole), macrolide antibiotics (erythromycin, clarithromycin), antivirals (indinavir, nelfinavir, ritonavir, saquinavir), steroids (methylprednisolone, oral contraceptives, androgens), psychotropic agents (fluvoxamine, nefazodone) as well as other agents (amiodarone, chloroquine, allopurinol, bromocriptine, metoclopramide, cimetidine, grapefruit juice). Inducing agents include other antibiotics (nafcillin, rifampin, rifabutin), anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), barbiturates, aminoglutethimide, troglitazone, octreotide, and ticlopidine. Because of the large number of interacting agents, and the critical nature of the drugs involved in the treatment of transplant patients, complete avoidance of drug interactions with cyclosporine is not possible. Thus, most drug interactions with cyclosporine are managed using appropriate cyclosporine dosage modification with cyclosporine concentration monitoring as a guide.

Cyclosporine can also change the clearance of other drugs via competitive inhibition of CYP3A4 and/or P-glycoprotein.[26] Drugs that may experience decreased clearance and increased serum concentrations when given with cyclosporine include prednisolone, digoxin, calcium channel blockers (verapamil, diltiazem, bepridil, nifedipine and most other dihydropyridine analogues, sildenafil), ergot alkaloids, vinca alkaloids, simvastatin, and lovastatin.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate cyclosporine therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of cyclosporine. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of cyclosporine is to compute the best dose possible for the patient in order to prevent graft rejection or graft versus host disease given their set of

disease states and conditions that influence cyclosporine pharmacokinetics, while avoiding adverse drug reactions. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Cyclosporine is almost completely metabolized by the liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same fashion that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change cyclosporine clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance rate. For example, an adult transplant patient with normal liver function would be assigned a cyclosporine clearance rate equal to 6 mL/min/kg, while a pediatric transplant patient with the same profile would be assumed to have a cyclosporine clearance of 10 mL/min/kg.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous infusion or orally, cyclosporine follows a two-compartment model.[42] When oral therapy is chosen, the drug is often erratically absorbed with variable absorption rates, and some patients may have a "double-peak" phenomenon occur where a maximum concentration is achieved 2–3 hours after dosage administration with a second maximum concentration 2–4 hours after that.[21,45] Because of the complex absorption profile and the fact that the drug is usually administered twice daily, a very simple pharmacokinetic equation that calculates the average cyclosporine steady-state serum concentration (Css in ng/mL = μg/L) is widely used and allows maintenance dose computation: $Css = [F(D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau) / F$, where F is the bioavailability fraction for the oral dosage form (F averages 0.3 or 30% for most patient populations and oral dosage forms), D is the dose of cyclosporine in milligrams, Cl is cyclosporine clearance in liters per hour, and τ is the dosage interval in hours. If the drug is to be given intravenously as intermittent infusions, the equivalent equation for that route of administration is $Css = (D/\tau) / Cl$ or $D = Css \cdot Cl \cdot \tau$. If the drug is to be given as a continuous intravenous infusion, the equation for that method of administration is $Css = k_o/Cl$, or $k_o = Css \cdot Cl$, where k_o is the infusion rate.

STEADY-STATE CONCENTRATION SELECTION

The generally accepted therapeutic ranges for cyclosporine in blood, serum, or plasma using various specific and nonspecific (parent drug + metabolite) assays are given in Table 15-1. More important than these general guidelines are the specific requirements for each graft type as defined by the transplant center where the surgery was conducted. Clinicians should become familiar with the cyclosporine protocols used at the various institutions at which they practice. Although it is unlikely that steady state has been achieved, cyclosporine concentrations are usually obtained on a daily basis, even when dosage changes were made the previous day, owing to the critical nature of the therapeutic effect provided by the drug.

Example 1 HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial

oral cyclosporine dose designed to achieve a steady-state cyclosporine trough blood concentration equal to 250 ng/mL.

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 27 L/h: Cl = 6 mL/min/kg · 75 kg · (60 min/h / 1000 mL/L) = 27 L/h

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is $D = (Css \cdot Cl \cdot \tau) / F$ = (250 μg/L · 27 L/h · 12 h) / (0.3 · 1000 μg/mg) = 270 mg, rounded to 300 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days).

Example 2 Same patient as in example 1, except compute an initial dose using intravenous cyclosporine.

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 27 L/h: Cl = 6 mL/min/kg · 75 kg · (60 min/h / 1000 mL/L) = 27 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for intravenous cyclosporine is $D = Css \cdot Cl \cdot \tau$ = (250 μg/L · 27 L/h · 12 h) / (1000 μg/mg) = 81 mg, rounded to 75 mg every 12 hours.

If the cyclosporine dose is given as a continuous infusion instead of intermittent infusions, the dosage equation is $k_o = Css \cdot Cl$ = (250 μg/L · 27 L/h) / (1000 μg/mg) = 6.8 mg/h, rounded to 7 mg/h.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days).

Literature-Based Recommended Dosing

Because of the large amount of variability in cyclosporine pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard cyclosporine doses for various situations is warranted. Indeed, most transplant centers use doses that are determined using a cyclosporine dosage protocol. The original computations of these doses were based on the pharmacokinetic dosing method

described in the previous section, and subsequently modified based on clinical experience. In general, the expected cyclosporine steady-state concentration used to compute these doses is dependent upon the type of transplanted tissue and the posttransplantation time line. Generally speaking, initial oral doses of 8–18 mg/kg/d or intravenous doses of 3–6 mg/kg/d (1/3 the oral dose to account for ~30% oral bioavailability) are used and vary greatly from institution to institution.[1–5] For obese individuals (>30% over ideal body weight), ideal body weight should be used to compute initial doses.[35–39] To illustrate how this techniques is used, the same patient examples utilized in the previous section will be repeated for this dosage approach for comparison purposes.

Example 3 HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral cyclosporine dose designed to achieve a steady-state cyclosporine trough blood concentration within the therapeutic range.

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine oral dosage range for adult patients is 8–18 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (8 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial cyclosporine dose for this patient is 600 mg/d given as 300 mg every 12 hours: Dose = 8 mg/kg/d · 75 kg = 600 mg/d or 300 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

Example 4 Same patient as in example 3, except compute an initial dose using intravenous cyclosporine.

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine intravenous dosage range for adult patients is 3–6 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (3 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial cyclosporine dose for this patient is 200 mg/d given as 100 mg every 12 hours: Dose = 3 mg/kg/d · 75 kg = 225 mg/d, rounded to 200 mg/d or 100 mg every 12 hours.

If the cyclosporine dose is given as a continuous infusion instead of intermittent infusions, the infusion rate is k_o = (3 mg/kg/d · 75 kg) / (24 h/d) = 9.4 mg/h, rounded to 9 mg/h.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

USE OF CYCLOSPORINE CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce cyclosporine concentrations that are expected or desirable. Because of pharmacokinetic

variability, the narrow therapeutic index of cyclosporine, and the severity of cyclosporine adverse side effects, measurement of cyclosporine concentrations is mandatory for patients to ensure that therapeutic, nontoxic levels are present. In addition to cyclosporine concentrations, important patient parameters (transplanted organ function tests or biopsies, clinical signs and symptoms of graft rejection or graft-versus-host disease, potential cyclosporine side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

For hematopoietic stem cell transplantation patients, steady-state trough concentrations are typically measured for cyclosporine. For solid organ transplant patients, the optimal times and strategies for measurement of steady-state concentrations are somewhat controversial.[4,46] At first, it was assumed that the predose trough concentration would be best as it represents the lowest concentration during the dosage interval. However, recent studies have found that the steady-state cyclosporine concentration 2 hours after a dose (C2) reflects cyclosporine area under the curve better than a trough concentration. Finally, some clinicians believe that since cyclosporine is such a critical component of transplant therapy, that multiple postdose cyclosporine concentrations should be measured to obtain the best estimate of area under the curve that is possible. Currently, most transplant centers measure a single steady-state cyclosporine concentration as either a predose trough or 2 hours postdose, while some conduct multiple measurements to determine cyclosporine area under the curve estimates.

When cyclosporine concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change cyclosporine doses assuming the drug follows *linear pharmacokinetics*. Sometimes, it is useful to compute cyclosporine pharmacokinetic constants for a patient and base dosage adjustments on these. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the cyclosporine dose. Another approach involves measuring several postdose steady-state cyclosporine concentrations to estimate the *area under the concentration-time curve (AUC)* and adjusting the cyclosporine dose to attain a target AUC. Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where concentrations are obtained at suboptimal times or the patient was not at steady state when concentrations were measured.

Linear Pharmacokinetics Method

Because cyclosporine follows linear, dose-proportional pharmacokinetics,[17] steady-state concentrations change in proportion to dose according to the following equation:

$$D_{new}/C_{ss,new} = D_{old}/C_{ss,old} \text{ or } D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$$

where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The C_{ss} can be either a steady-state trough concentration or a steady-state concentration measured 2 hours (+/–15 minutes) after a dose (C2). When C2 levels are used, recommended concentrations vary according to transplant type and posttransplant time (Table 15-2). The advantages of this method are that it is quick and simple. The disadvantage is steady-state concentrations are required.

TABLE 15-2 Recommended 2-Hour (+/–15 Minutes) Post-dose Steady-State Cyclosporine Concentrations (C2) for Various Solid Organ Transplant Types and Post transplant Times[52–54]

RENAL TRANSPLANT	
POSTTRANSPLANT TIME (MONTHS)	**C2 LEVEL (ng/mL)**
1	1500–2000
2	1500
3	1300
4–6	1100
7–12	900
> 12	800
LIVER TRANSPLANT	
POSTTRANSPLANT TIME (MONTHS)	**C2 LEVEL (ng/mL)**
0–3	1000
4–6	800
> 6	600

Example 5A LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current steady-state cyclosporine blood concentration equals 375 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the second day ($5\ t_{1/2} = 5 \cdot 10\ h = 50\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (200\ ng/mL / 375\ ng/mL)\ 800\ mg/d$$
$$= 427\ mg/d, \text{ rounded to } 400\ mg/d$$

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime

after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Example 5B LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is 5 months post transplant and receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current C2 steady-state cyclosporine blood concentration equals 1500 ng/mL. Compute a cyclosporine dose that will provide a C2 steady-state concentration of 800 ng/mL. (*Note: This is the same case as in example 5A in order to illustrate differences between trough and C2 level monitoring.*)

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (800 \text{ ng/mL} / 1500 \text{ ng/mL})\ 800 \text{ mg/d}$$
$$= 427 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Example 6 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 75 mg every 12 hours of intravenous cyclosporine. The current steady-state cyclosporine concentration equals 215 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 350 ng/mL.

1. *Compute new dose to achieve desired concentration.*

The patient recently received a liver transplantation and would be expected to have a longer cyclosporine half-life if the organ is not yet functioning at an optimal level ($t_{1/2}$ = 20 h). Because of this, it could take up to 4 days of consistent cyclosporine therapy to achieve steady-state conditions (5 $t_{1/2}$ = 5 · 20 h = 100 h or ~4 d).

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 75 mg/dose · 2 doses/d = 150 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (350 \text{ ng/mL} / 215 \text{ ng/mL})\ 150 \text{ mg/d}$$
$$= 244 \text{ mg/d, rounded to } 250 \text{ mg/d or } 125 \text{ mg every 12 hours.}$$

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life up to 20 hours, the cyclosporine steady-state concentration could be obtained anytime after the fourth day of dosing (5 half-lives = 5 · 20 h = 100 h or 4 days). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

2. *If the patient in example 6 received cyclosporine as a continuous infusion at a rate of 6 mg/h, the equivalent dosage adjustment computation would be:*

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (350 \text{ ng/mL} / 215 \text{ ng/mL}) \ 6 \text{ mg/h}$$
$$= 9.8 \text{ mg/h, rounded to } 10 \text{ mg/h}$$

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using drug concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired cyclosporine concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady state cyclosporine concentration. Cyclosporine clearance can be measured using a single steady-state cyclosporine concentration and the following formula for orally administered drug: $Cl = [F(D/\tau)] / Css$, where Cl is cyclosporine clearance in liters per hour, F is the bioavailability factor for cyclosporine (F = 0.3), τ is the dosage interval in hours, and Css is the cyclosporine steady-state concentration in nanograms per milliliter which also equals micrograms per liter. If cyclosporine is administered intravenously, it is not necessary to take bioavailability into account: $Cl = (D/\tau) / Css$, where Cl is cyclosporine clearance in liters per hour, τ is the dosage interval in hours, and Css is the cyclosporine steady-state concentration in nanograms per milliliter which also equals micrograms per liter. Although this method does allow computation of cyclosporine clearance, it yields exactly the same cyclosporine dose as that supplied using linear pharmacokinetics. As a result, most clinicians prefer to directly calculate the new dose using the simpler linear pharmacokinetics method. To demonstrate this point, the patient cases used to illustrate the linear pharmacokinetics method will be used as examples for the pharmacokinetic parameter method.

Example 7 LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current steady-state cyclosporine blood concentration equals 375 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day ($5 \ t_{1/2} = 5 \cdot 10$ h = 50 h or 2 days) of therapy.

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: $Cl = [F(D/\tau)] / Css = [0.3 \cdot (400 \text{ mg}/12 \text{ h}) \cdot 1000 \ \mu\text{g/mg}] / (375 \ \mu\text{g/L}) = 26.7$ L/h. (Note: µg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (200\ \mu g/L \cdot 26.7\ L/h \cdot 12h) / (0.3 \cdot 1000\ \mu g/mg) = 214$ mg, rounded to 200 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Example 8 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 75 mg every 12 hours of intravenous cyclosporine. The current steady-state cyclosporine concentration equals 215 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 350 ng/mL.

1. *Compute pharmacokinetic parameters.*

The patient recently received a liver transplantation and would be expected to have a longer cyclosporine half-life if the organ is not yet functioning at an optimal level ($t_{1/2}$ = 20 h). Because of this, it could take up to 4 days of consistent cyclosporine therapy to achieve steady-state conditions (5 $t_{1/2} = 5 \cdot 20$ h = 100 h or ~4 d).

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: $Cl = (D/\tau) / Css = [(75\ mg/12\ h) \cdot 1000\ \mu g/mg] / (215\ \mu g/L) = 29.1$ L/h. (Note: µg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: $D = Css \cdot Cl \cdot \tau = (350\ \mu g/L \cdot 29.1\ L/h \cdot 12h) / 1000\ \mu g/mg = 122$ mg, rounded to 125 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life up to 20 hours, the cyclosporine steady-state concentration could be obtained anytime after the fourth day of dosing (5 half-lives = 5 · 20 h = 100 h or 4 days). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

If the patient in example 8 received cyclosporine as a continuous infusion at a rate of 6 mg/h, the equivalent clearance and dosage adjustment computations would be:

$Cl = k_o/Css = (6\ mg/h \cdot 1000\ \mu g/mg) / (215\ \mu g/L) = 27.9$ L/h

$k_o = Css \cdot Cl = (350\ \mu g/L \cdot 27.9\ L/h) / (1000\ \mu g/mg) = 9.8$ mg/h, rounded to 10 mg/h

Area Under the Concentration-Time Curve Method

Some solid organ transplant centers believe that measurement or estimation of cyclosporine area under the concentration-time curve (AUC) is the best way to optimize

cyclosporine therapy. While AUC can be measured using hourly postdose cyclosporine levels, studies have shown that there is a strong correlation between 3–4 cyclosporine concentrations and the total AUC. Based on this finding, most centers utilizing this method measure several steady-state cyclosporine concentrations and use a published regression equation determined in other patients receiving the same transplanted organ and similar drug therapy (to account for possible drug interactions) in order to convert the concentrations to an estimated AUC. Then, if necessary, adjust the cyclosporine dose using linear pharmacokinetics to achieve the target AUC: $D_{new}/AUC_{new} = D_{old}/AUC_{old}$ or $D_{new} = (AUC_{new}/AUC_{old})D_{old}$, where D is the dose, AUC is the steady-state area under the concentration-time curve, old indicates the dose that produced the steady-state area under the concentration-time curve that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state area under the concentration-time curve.

There are many regression equations from which to choose based on the target transplant population and other concurrent therapy that may cause drug interactions with cyclosporine. The one used for the examples and problems in this book is for renal transplant patients in the immediate 3 month post transplant period that received a variety of other immunosuppressants (prednisone plus mycophenolate mofetil or rapamycin).[47] In this investigation, the steady-state AUC from time 0 hours (predose) to 4 hours after the dose ($AUC_{0–4h}$) strongly correlated with the total steady-state AUC during the dosage interval and was used to adjust cyclosporine doses: $AUC_{0–4h}$ (in [μg · h]/L) = $256 + C_{1h} + (0.9 \cdot C_{2h}) + (1.4 \cdot C_{3h})$, where C_{1h}, C_{2h}, C_{3h} are steady-state cyclosporine concentrations in μg/L obtained 1, 2, and 3 hours, respectively, after a dose. The dose is then adjusted to produce a new steady-state AUC equal to 4400–5500 (μg · h)/L using linear pharmacokinetics.[8]

Example 9 GQ is a 47-year-old, 78-kg (6 ft 1 in) male who has undergone renal transplantation. He is receiving 400 mg every 12 hours of oral cyclosporine. The following cyclosporine steady-state concentrations have been measured to determine an estimated $AUC_{0–4h}$: C_{1h} = 412 ng/mL, C_{2h} = 1251 ng/mL, C_{3h} = 1009 ng/mL. Compute a cyclosporine dose that will provide a steady-state $AUC_{0–4h}$ of 5000 (μg · h)/L.

1. *Compute pharmacokinetic parameters.*

Cyclosporine $AUC_{0–4h}$ can be estimated using the steady-state cyclosporine concentrations: $AUC_{0–4h} = 256 + C_{1h} + (0.9 \cdot C_{2h}) + (1.4 \cdot C_{3h}) = 256 + (412\ \mu g/L) + (0.9 \cdot 1251\ \mu g/L) + (1.4 \cdot 1009\ \mu g/L) = 3206$ (μg · h)/L. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations.)

2. *Compute cyclosporine dose.*

Linear pharmacokinetics is used to compute the new dose (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d): $D_{new} = (AUC_{new}/AUC_{old})D_{old} = \{[5000\ (\mu g \cdot h)/L] / [(3206\ \mu g \cdot h)/L)]\}(800\ mg/d) = 1258$ mg/d, rounded to 600 mg every 12 hours.

Steady-state cyclosporine serum concentrations should be measured after steady state is attained in 3–5 half-lives. Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[48–50] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations is generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. When only a limited number of cyclosporine steady-state concentrations are available, Bayesian pharmacokinetic computer programs can be used to compute a complete patient pharmacokinetic profile that includes clearance, volume of distribution, and half life.

Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[51]

Example 10 LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL). The current steady-state cyclosporine

blood concentration equals 375 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 403 L, a half-life equal to 17.6 hours, and a clearance equal to 15.9 L/h.

3. *Compute dose required to achieve desired cyclosporine serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 200 mg every 12 hours will produce a steady-state cyclosporine concentration of 210 ng/mL. Using the linear pharmacokinetics and pharmacokinetic parameter methods previously described in this chapter produced the same answer for this patient.

Example 11 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 75 mg every 12 hours of intravenous cyclosporine. He has elevated liver function tests (bilirubin = 3.2 mg/dL, albumin = 2.5 g/dL). The current steady-state cyclosporine concentration equals 215 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 350 ng/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 403 L, a half-life equal to 13.8 hours, and a clearance equal to 20.3 L/h.

3. *Compute dose required to achieve desired cyclosporine serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 125 mg every 12 hours will produce a steady-state cyclosporine concentration of 380 ng/mL. Using the linear pharmacokinetics and pharmacokinetic parameter methods previously described in this chapter produced the same answer for this patient.

Example 12 YT is a 25-year-old, 55-kg (5 ft 2 in) female hematopoietic stem cell transplantation recipient who received 300 mg every 12 hours of oral cyclosporine capsules for two doses after transplant, but because her renal function decreased, her dose was empirically changed to 200 mg every 12 hours. She has normal liver function (bilirubin = 0.9 mg/dL, albumin = 3.9 g/dL). The cyclosporine blood concentration obtained 12 hours after her first dose of the lower dosage regimen equaled 280 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 250 ng/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 401 L, a half-life equal to 35 hours, and a clearance equal to 8 L/h.

3. *Compute dose required to achieve desired cyclosporine serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 100 mg every 12 hours will produce a steady-state cyclosporine concentration of 250 ng/mL.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 15-3.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current immunosuppressive therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with cyclosporine exists.

1. VI is a 37-year-old, 85-kg (6 ft 1 in) male heart transplant patient who requires therapy with oral cyclosporine. He has normal liver function. Suggest an initial dosage regimen designed to achieve a steady-state cyclosporine concentration equal to 300 ng/mL.
2. Patient VI (please see problem 1) was prescribed 400 mg every 12 hours of cyclosporine capsules for 4 days, and the steady-state cyclosporine concentration

TABLE 15-3 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/ equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics or AUC method
Computerized	Bayesian computer program	Bayesian computer program

equals 426 ng/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration of 300 ng/mL.

3. AS is a 9-year-old, 35-kg female (4 ft 6 in) hematopoietic stem cell transplantation patient who requires therapy with oral cyclosporine. She has normal liver function. Suggest an initial cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration equal to 250 ng/mL.

4. Patient AS (please see problem 3) was prescribed 150 mg every 12 hours of cyclosporine solution for 3 days, and the steady-state cyclosporine concentration equals 173 ng/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an oral cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration equal to 250 ng/mL.

5. FL is a 29-year-old, 78-kg (5 ft 11 in) male liver transplant patient who requires therapy with oral cyclosporine. He has poor liver function because of his liver disease. Suggest an initial cyclosporine dosage regimen to be started 24 hours before transplant surgery designed to achieve a steady-state cyclosporine concentration equal to 300 ng/mL.

6. Patient FL (please see problem 5) is 10 days postsurgery for a liver transplantation. He was prescribed 400 mg every 12 hours of cyclosporine capsules since transplantation, and the steady-state cyclosporine concentration equals 531 ng/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration of 250 ng/mL.

7. PH is a 22-year-old, 67-kg female (5 ft 5 in) renal transplant patient who requires therapy with oral cyclosporine. She is 36 hours post transplantation procedure, and the transplanted kidney is beginning to function normally. Her liver function is normal. Suggest an initial cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration equal to 200 ng/mL.

8. Patient PH (please see problem 7) was prescribed 200 mg every 12 hours of cyclosporine capsules for 3 days, and the steady-state cyclosporine concentration equals 125 ng/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a cyclosporine dosage regimen designed to achieve a steady-state cyclosporine concentration of 200 ng/mL.

9. PU is a 55-year-old, 68-kg (5 ft 8 in) male heart transplant patient who received two intravenous cyclosporine doses (125 mg every 12 hours) and was switched to oral cyclosporine capsules 300 mg every 12 hours. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) function. The cyclosporine concentration equals 190 ng/mL 12 hours after the first oral dose of the drug. Compute a cyclosporine dose that will provide a steady-state concentration of 325 ng/mL.

10. LH is a 25-year-old, 60-kg (5 ft 3 in) female renal transplant patient who was given a new prescription for cyclosporine capsules 200 mg every 12 hours 2 days after transplantation surgery. She has normal liver function (bilirubin = 0.4 mg/dL, albumin = 3.7 g/dL) and is also being treated with phenytoin. The trough cyclosporine

concentration before the third dose equals 90 ng/mL. Compute a cyclosporine dose that will provide a steady-state concentration of 200 ng/mL.

11. UT is a 28-year-old, 75-kg (5 ft 11 in) male liver transplant patient who is 20-days post-surgery. He was prescribed 400 mg every 12 hours of cyclosporine capsules, and the steady-state C2 cyclosporine concentration equals 2124 ng/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a cyclosporine dosage regimen designed to achieve a steady-state C2 cyclosporine concentration of 1000 ng/mL.

12. KL is a 21-year-old, 67-kg female (5 ft 6 in) renal transplant patient who is 4 months postsurgery. She was prescribed 200 mg every 12 hours of cyclosporine capsules, and the steady-state C2 cyclosporine concentration equals 688 ng/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a cyclosporine dosage regimen designed to achieve a steady-state C2 cyclosporine concentration of 1100 ng/mL.

13. QG is a 51-year-old, 78-kg (6 ft 1 in) male who has undergone renal transplantation. He is receiving 400 mg every 12 hours of oral cyclosporine. The following cyclosporine steady-state concentrations have been measured to determine an estimated AUC_{0-4h}: C_{1h} = 525 ng/mL, C_{2h} = 1399 ng/mL, C_{3h} = 1250 ng/mL. Compute a cyclosporine dose that will provide a steady-state AUC_{0-4h} of 5000 (μg · h)/L.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 30.6 L/h: Cl = 6 mL/min/kg · 85 kg · (60 min/h / 1000 mL/L) = 30.6 L/h

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is D = (Css · Cl · τ) / F = (300 μg/L · 30.6 L/h · 12 h) / (0.3 · 1250 μg/mg) = 367 mg, rounded to 400 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days).

Literature-Based Recommended Dosing

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine oral dosage range for adult patients is 8–18 mg/kg/d. Because this is a heart transplant patient, a dose in the middle of the range (10 mg/kg/d) will be used in order to avoid graft rejection. The initial cyclosporine dose for this patient is 800 mg/d given as 400 mg every 12 hours: Dose = 10 mg/kg/d · 85 kg = 850 mg/d, rounded to 800 mg/d or 400 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

2. *Solution to problem 2.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (300 \text{ ng/mL} / 426 \text{ ng/mL})\ 800 \text{ mg/d}$$
$$= 563 \text{ mg/d, rounded to } 600 \text{ mg/d}$$

The new suggested dose would be 600 mg/d or 300 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h or 2 days) of therapy.

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = [F(D/τ)] / Css = [0.3 · (400 mg/12 h) · 1000 μg/mg] / (426 μg/L) = 23.5 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (300 μg/L · 23.5 L/h · 12 h) / (0.3 · 1000 μg/mg) = 282 mg, rounded to 300 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

3. *Solution to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for pediatric patients is 10 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 21 L/h: Cl = 10 mL/min/kg · 35 kg · (60 min/h / 1000 mL/L) = 21 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is D = (Css · Cl · τ) / F = (250 μg/L · 21 L/h · 12 h) / (0.3 · 1000 μg/mg) = 210 mg, rounded to 200 mg every 12 hours of cyclosporine solution.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 1–2 days (5 half-lives = 5 · 6 h = 30 h).

Literature-Based Recommended Dosing

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine oral dosage range is 8–18 mg/kg/d. Because this is a pediatric patient, a dose in the middle of the range (12 mg/kg/d) will be used in order to avoid graft-versus-host disease. The initial cyclosporine dose for this patient is 400 mg/d given as 200 mg every 12 hours: Dose = 12 mg/kg/d · 35 kg = 420 mg/d, rounded to 400 mg/d or 200 mg every 12 hours of cyclosporine solution.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 1–2 days (5 half-lives = 5 · 6 h = 30 h) of treatment.

4. *Solution to problem 4.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions by the second day (5 $t_{1/2}$ = 5 · 6 h = 30 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 150 mg/dose · 2 doses/d = 300 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (250 \text{ ng/mL} / 173 \text{ ng/mL})\ 300 \text{ mg/d}$$
$$= 434 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine solution to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 6 hours, the cyclosporine steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 6 h = 30 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 6 h = 30 h) of therapy.

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = [F(D/τ)] / Css = [0.3 · (150 mg/12 h) · 1000 μg/mg] / (173 μg/L) = 21.7 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (250 μg/L · 21.7 L/h · 12 h) / (0.3 · 1000 μg/mg) = 217 mg, rounded to 200 mg every 12 hours of cyclosporine solution.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 6 hours, the cyclosporine steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 6 h = 30 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

5. *Solution to problem 5.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 28.1 L/h: Cl = 6 mL/min/kg · 78 kg · (60 min/h / 1000 mL/L) = 28.1 L/h

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is D = (Css · Cl · τ) / F = (300 μg/L · 28.1 L/h · 12 h) / (0.3 · 1000 μg/mg) = 337 mg, rounded to 300 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days).

Literature-Based Recommended Dosing

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine oral dosage range for adult patients is 8–18 mg/kg/d. Because this is a liver transplant patient, a dose in the middle of the range (10 mg/kg/d) will be used in order to avoid graft rejection. The initial cyclosporine dose for this patient is 800 mg/d given as 400 mg every 12 hours: Dose = 10 mg/kg/d · 78 kg = 780 mg/d, rounded to 800 mg/d or 400 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

6. *Solution to problem 6.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (250 \text{ ng/mL} / 531 \text{ ng/mL})\ 800 \text{ mg/d}$$
$$= 377 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h or 2 days) of therapy.

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = [F(D/τ)] / Css = [0.3 · (400 mg/12 h) · 1000 μg/mg] / (531 μg/L) = 18.8 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (250 μg/L · 18.8 L/h · 12 h) / (0.3 · 1000 μg/mg) = 188 mg, rounded to 200 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

7. *Solution to problem 7.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean cyclosporine clearance for adult patients is 6 mL/min/kg. The cyclosporine blood clearance for this patient is expected to be 24.1 L/h: Cl = 6 mL/min/kg · 67 kg · (60 min/h / 1000 mL/L) = 24.1 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral cyclosporine is D = (Css · Cl · τ) / F = (200 μg/L · 24.1 L/h · 12 h) / (0.3 · 1000 μg/mg) = 193 mg, rounded to 200 mg every 12 hours.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur in about 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days).

Literature-Based Recommended Dosing

1. *Choose cyclosporine dose based on disease states and conditions present in the patient and transplant type.*

The cyclosporine oral dosage range for adult patients is 8–18 mg/kg/d. Because this is a kidney transplant patient, a dose in the lower end of the range (8 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial cyclosporine dose for this patient is

500 mg/d: Dose = 8 mg/kg/d · 67 kg = 536 mg/d, rounded to 500 mg/d or 200 mg every morning and 300 mg every evening.

Cyclosporine serum concentrations would be obtained on a daily basis with steady state expected to occur after 2 days (5 half-lives = 5 · 10 h = 50 h, or ~2 days) of treatment.

8. *Solution to problem 8.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 200 mg/dose · 2 doses/d = 400 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (200 \text{ ng/mL} / 125 \text{ ng/mL}) \ 400 \text{ mg/d}$$
$$= 640 \text{ mg/d, rounded to } 600 \text{ mg/d}$$

The new suggested dose would be 600 mg/d or 300 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 10 h = 50 h or 2 days) of therapy.

Cyclosporine clearance can be computed using a steady-state cyclosporine concentration: Cl = [F(D/τ)] / Css = [0.3 · (200 mg/12 h) · 1000 μg/mg] / (125 μg/L) = 40 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute cyclosporine dose.*

Cyclosporine clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (200 μg/L · 40 L/h · 12 h) / (0.3 · 1000 μg/mg) = 320 mg, rounded to 300 mg every 12 hours.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the cyclosporine steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 10 h = 50 h). Cyclosporine concentrations

should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

9. *Solution to problem 9.*

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 401 L, a half-life equal to 35 hours, and a clearance equal to 8 L/h.

3. *Compute dose required to achieve desired cyclosporine serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 100 mg every 12 hours will produce a steady-state cyclosporine concentration of 250 ng/mL.

10. *Solution to problem 10.*

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Because the patient is also being treated with phenytoin, an enzyme-induction drug interaction for cyclosporine should be entered into the program at the appropriate place.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 240 L, a half-life equal to 7 hours, and a clearance equal to 23.7 L/h.

3. *Compute dose required to achieve desired cyclosporine serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 400 mg every 12 hours will produce a steady-state cyclosporine concentration of 200 ng/mL.

11. *Solution to problem 11.*

Linear Pharmacokinetics Method

1. Compute new dose to achieve desired concentration.

Using linear pharmacokinetics, the new dose to attain the desired C2 concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (1000 \text{ ng/mL} / 2124 \text{ ng/mL})\ 800 \text{ mg/d}$$
$$= 377 \text{ mg/d, rounded to } 400 \text{ mg/d}$$

The new suggested dose would be 400 mg/d or 200 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained. Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

12. *Solution to problem 12.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

Using linear pharmacokinetics, the new dose to attain the desired C2 concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 200 mg/dose · 2 doses/d = 400 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (1100 \text{ ng/mL} / 688 \text{ ng/mL})\ 400 \text{ mg/d}$$
$$= 640 \text{ mg/d, rounded to } 600 \text{ mg/d}$$

The new suggested dose would be 600 mg/d or 300 mg every 12 hours of cyclosporine capsules to be started at the next scheduled dosing time.

A steady-state trough cyclosporine serum concentration should be measured after steady state is attained. Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

13. *Solution to problem 13.*

1. *Compute pharmacokinetic parameters.*

Cyclosporine AUC_{0-4h} can be estimated using the steady-state cyclosporine concentrations: $AUC_{0-4h} = 256 + C_{1h} + (0.9 \cdot C_{2h}) + (1.4 \cdot C_{3h}) = 256 + (525\ \mu g/L) + (0.9 \cdot 1399\ \mu g/L) + (1.4 \cdot 1250\ \mu g/L) = 3790\ (\mu g \cdot h)/L$. (Note: µg/L = ng/mL and this concentration unit was substituted for Css in the calculations.)

2. *Compute cyclosporine dose.*

Linear pharmacokinetics is used to compute the new dose (total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d): $D_{new} = (AUC_{new}/AUC_{old})D_{old} = \{[5000\ (\mu g \cdot h)/L] / [(3790\ \mu g \cdot h)/L)]\}(800 \text{ mg/d}) = 1055 \text{ mg/d}$, rounded to 500 mg every 12 hours.

Steady-state cyclosporine serum concentrations should be measured after steady state is attained in 3–5 half-lives. Cyclosporine concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of cyclosporine toxicity.

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TACROLIMUS

INTRODUCTION

Tacrolimus (also known as FK506) is a macrolide compound with immunosuppressant actions that is used for the prevention of graft rejection in solid organ transplant patients.[1,2] Currently, it is approved for use in heart, liver, and renal transplant patients.[1] It is also used in heart-lung and other solid organ transplant recipients, as well as the treatment of graft-versus-host disease in hematopoietic stem cell transplant patients.[1,2] The immunomodulating effects of tacrolimus result from its ability to block the production of intraleukin-2 and other cytokines produced by T-lymphocytes.[3] Tacrolimus binds to FK-binding protein (FKPB), an intracellular cytoplasmic protein found in T-cells. The tacrolimus-FKPB complex interacts with calcineurin, inhibits the catalytic activity of calcineurin, and blocks the production of intermediaries involved with the expression of genes regulating the production of cytokines.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The therapeutic range for tacrolimus used by most transplantation centers is 5–20 ng/mL in blood.[1,4,5] Although, plasma tacrolimus concentrations have been measured and an equivalent therapeutic range in this matrix suggested (0.5–2 ng/mL), the two most widely used assays for the drug use blood samples.[4,5] Because tacrolimus is extensively bound to erythrocytes, blood concentrations average about 15 times greater than concurrently measured serum or plasma concentrations.[5] Two different assay systems are in widespread use. The enzyme-linked immunosorbent assay (ELISA; Pro-Trac, IncStar) and microparticulate enzyme immunoassay (MEIA; IMx, Abbott Diagnostics) incorporate the same monoclonal antibody. Using blood as the assay matrix, these two different assay systems produce similar results.[6–8] For the purposes of the pharmacokinetic computations and problems presented in this book, tacrolimus concentrations in the blood determined with the ELISA or MEIA assay systems will be used. Because predose

trough steady-state concentrations correlate well with steady-state area under the concentration/time curve measurements, tacrolimus trough concentrations are used in patient monitoring situations.[5,9,10]

Desired tacrolimus concentrations differ between the various types of organ transplants, change with time during the post transplantation phase, and are determined by protocols specific to the transplantation service and institution.[1,2,5] Because of these factors, it is very important for clinicians to be aware of these situations since acceptable tacrolimus concentrations under these different circumstances may be different from those given by the clinical laboratory or those suggested in this textbook.

For patients receiving solid organ transplants such as kidney, liver, heart, lung, or heart-lung transplantation, the goal of tacrolimus therapy is to prevent acute or chronic rejection of the transplanted organ while minimizing drug side effects.[1,5] In this case, the recipient's immune system detects foreign antigens on the donor organ which produces an immunologic response against the graft. This leads to inflammatory and cytotoxic effects directed against the transplanted tissue, and produces the risk of organ tissue damage and failure. In the case of a rejected kidney transplant, it is possible to remove the graft and place the patient on a form of dialysis to sustain their life. However, for other solid organ transplantation patients, graft rejection can result in death. Because tacrolimus can cause nephrotoxicity, some centers delay tacrolimus therapy in renal transplant patients for a few days or until the kidney begins functioning to avoid untoward effects on the newly transplanted organ. Also, desired tacrolimus concentrations in renal transplant patients are generally lower to avoid toxicity in the new renal graft than for other transplant patients (typically 5–15 ng/mL versus 5–20 ng/mL using whole blood). For other solid organ transplant patients, tacrolimus therapy may be started several hours before surgery. During the immediate postoperative phase, intravenous tacrolimus may be given to these patients. For long-term management of immunosuppression in solid organ tissue transplant patients, tacrolimus doses are gradually tapered to the lowest concentration and dose possible over a 6- to 12-month time period as long as rejection episodes do not occur.

Although not currently approved for use in hematopoietic stem cell transplant recipients, tacrolimus is used as an immunosuppressant in this patient population.[2] For patients receiving tacrolimus after a hematopoietic stem cell transplant, the goal of therapy is to prevent graft-versus-host disease while avoiding adverse effects of immunosuppressant therapy. Graft-versus-host disease is a result of donor T-lymphocytes detecting antigens on host tissues and producing an immunologic response against these antigens and host tissues. Acute graft-versus-host disease usually occurs within the first 100 days after transplantation of donor stem cells, and causes epithelial tissue damage in organs. The most common tissues attacked are skin, gastrointestinal tract, and liver. To prevent acute graft-versus-host disease from occurring in allogeneic hematopoietic stem cell transplant patients with HLA-identical sibling donors, tacrolimus therapy is usually instituted on the day of stem cell transplant (day 0), and doses are adjusted to provide therapeutic trough concentrations. Methotrexate and/or glucocorticoids are usually also given in conjunction with tacrolimus treatment to hematopoietic stem cell transplantation patients. If prophylaxis of acute graft-versus-host disease is successful, tacrolimus doses start to be tapered on about post transplant day 50, with the goal of drug discontinuation by about post transplant day 180. For allogeneic hematopoietic stem cell transplant patients with HLA-mismatched or HLA-identical unrelated donors, the risk of acute graft-versus-host disease

is higher, so tacrolimus therapy may be more prolonged for these patients. After post transplantation day 100, chronic graft-versus-host disease may occur, and tacrolimus is also used as an agent to treat this type of immunologic response.

Neurotoxicity (coma, delirium, psychosis, encephalopathy, seizures, tremor, confusion, headaches, paresthesias, insomnia, nightmares, photophobia, anxiety), nephrotoxicity, hypertension, electrolyte imbalances (hyperkalemia, hypomagnesemia), glucose intolerance, gastrointestinal upset (diarrhea, nausea, vomiting, anorexia), hepatotoxicity, pruritus, alopecia, and leukocytosis are all typical adverse effects of tacrolimus treatment.[1–3] Neurologic side effects tend to be associated with high (≥25 ng/mL) tacrolimus blood concentrations and usually respond to dosage decreases. Hypertension is a common side effect associated with tacrolimus therapy, and is treated with traditional antihypertensive drug therapy. Glucose intolerance can range from mild increases in glucose concentrations to insulin-dependent post-transplant diabetes mellitus in ~10–20% of patients. Nephrotoxicity is similar to that seen with cyclosporine, and is separated into acute and chronic varieties. Acute nephrotoxicity is concentration or dose dependent and reverses with a dosage decrease. Chronic nephrotoxicity is accompanied by kidney tissue damage, including interstitial fibrosis, nonspecific tubular vacuolization, and structural changes in arteries, arterioles, and proximal tubular epithelium. Increased serum creatinine and blood urea nitrogen (BUN) values and hyperkalemia occur with tacrolimus-induced nephrotoxicity. The clinical features of tacrolimus nephrotoxicity and acute graft rejection in renal transplant patients are similar, so renal biopsies may be conducted to differentiate between these possibilities. Because biopsy findings are similar between tacrolimus-induced nephrotoxicity and chronic rejection of kidney transplants, this technique is less helpful in this situation.[1] Dosage decreases may be necessary to limit adverse drug effects associated with tacrolimus therapy.

CLINICAL MONITORING PARAMETERS

Solid organ transplant patients should be monitored for graft rejection consistent with the transplanted organ.[1] For renal transplant patients, increased serum creatinine, azotemia, hypertension, edema, weight gain secondary to fluid retention, graft tenderness, fever, and malaise may be caused by an acute rejection episode.[1] Hypertension, proteinuria, a continuous decline in renal function (increases in serum creatinine and blood urea nitrogen levels), and uremia are indicative of chronic rejection in renal transplant patients. For hepatic transplant patients, acute rejection signs and symptoms include fever, lethargy, graft tenderness, increased white blood cell count, change in bile color or amount, hyperbilirubinemia, and increased liver function tests.[1] Chronic rejection in a liver transplant patient may be accompanied only by increased liver function tests and jaundice. For heart transplant patients, acute rejection is accompanied by low-grade fever, malaise, heart failure (presence of S_3 heart sound), or atrial arrhythmia.[1] Chronic rejection in heart transplant patients, also known as cardiac allograft vasculopathy which is characterized by accelerated coronary artery atherosclerosis, may include the following symptoms: arrhythmias decreased left ventricular function, heart failure, myocardial infarction, and sudden cardiac death. For all solid organ transplant patients, tissue biopsies may be taken from the transplanted tissue to confirm the diagnosis of organ rejection.[1]

Hematopoietic stem cell transplant patients should be monitored for the signs and symptoms associated with graft-versus-host disease.[2] These include a generalized maculopapular skin rash, diarrhea, abdominal pain, ileus, hyperbilirubinemia, and increased liver function tests (serum transaminases and alkaline phosphatase). Patients with severe chronic graft-versus-host disease may have involvement of the skin, liver, eyes, mouth, esophagus, or other organs similar to what might be seen with systemic autoimmune diseases.

Typical adverse effects of tacrolimus treatment include neurotoxicity, nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, glucose intolerance, gastrointestinal upset, hepatotoxicity, pruritus, alopecia, and leukocytosis.[1–3] The management of these more common drug side effects are discussed in the previous section. Other tacrolimus adverse drug reactions that occur less frequently include hyperlipidemia and thrombocytopenia.

Because of the pivotal role that tacrolimus plays as an immunosuppressant in transplant patients, as well as the severity of its concentration- and dose-dependent side effects, tacrolimus concentrations should be measured in every patient receiving the drug. If a patient experiences signs or symptoms of organ rejection or graft-versus-host disease, a tacrolimus concentration should be checked to ensure that levels have not fallen below the therapeutic range. If a patient encounters a possible clinical problem that could be an adverse drug effect of tacrolimus therapy, a tacrolimus concentration should be measured to determine if levels are in the toxic range. During the immediate post-transplantation phase, tacrolimus concentrations are measured daily in most patients even though steady state may not yet have been achieved in order to prevent acute rejection in solid organ transplant patients or acute graft-versus-host disease in hematopoietic stem cell transplant patients. After discharge from the hospital, tacrolimus concentrations continue to be obtained at most clinic visits. In patients receiving allogeneic hematopoietic stem cell transplants from HLA-identical sibling donors, it is usually possible to decrease tacrolimus doses and concentrations about 2 months after the transplant and stop tacrolimus therapy altogether after about 6 months post transplant if no or mild acute rejection episodes have taken place. However, in allogeneic hematopoietic stem cell transplant patients with HLA-mismatched related or HLA-identical unrelated donors and all solid organ transplant patients, chronic tacrolimus therapy is usually required. In these cases, tacrolimus doses and concentrations are decreased to the minimum required to prevent graft-versus-host reactions or rejection episodes in order to decrease drug adverse effects. Methods to adjust tacrolimus doses using tacrolimus concentrations are discussed later in this chapter. Because of a good correlation with the tacrolimus steady-state area under the concentration/time curve, predose steady-state trough tacrolimus concentration determinations are used by most transplant centers to adjust drug doses.[5,9,10] Because of the success found in using area under the concentration-time curve (AUC) measurements with cyclosporine, some investigators are beginning to suggest that determination of tacrolimus AUC using multiple concentrations may be a useful monitoring technique.[11–14]

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Tacrolimus is almost completely eliminated by hepatic metabolism (>99%). Hepatic metabolism is mainly via the CYP3A4 enzyme system, and the drug is a substrate for P-glycoprotein.[15–18] There are more than 15 identified tacrolimus metabolites.[5] None of

these metabolites appear to have significant immunosuppressive effects in humans. Most of the metabolites are eliminated in the bile.[19] Less than 1% of a tacrolimus dose is recovered as unchanged drug in the urine.[20]

There is a large amount of intrasubject variability in tacrolimus concentrations obtained on a day-to-day basis, even when the patient should be at steady state.[5] There are many reasons for this variability. Tacrolimus has low water solubility, and its gastrointestinal absorption can be influenced by many variables. While oral absorption rate is generally fast for most patients (times to maximum concentration between 0.5 and 1 hour), some patients absorb tacrolimus very slowly which yields a flat concentration/time profile.[9,20–22] Additionally, absorption lag times of up to 2 hours have been reported in liver transplant patients.[9] While the average oral bioavailability is 25%, there is a large amount of variation in this parameter among patients (4–89%).[5] Renal transplant patients may have reduced oral bioavailability for tacrolimus. When given with meals, especially with high fat content food, oral bioavailability of tacrolimus decreases.[5] To avoid the possible effect of food on tacrolimus bioavailability, the drug should be given at a constant time in relation to meals. Oral tacrolimus should not be taken with grapefruit juice since this vehicle inhibits CYP3A4 and/or P-glycoprotein contained in the gastrointestinal tract and markedly increases bioavailability.[23] After liver transplantation, bile production and flow may not begin immediately, or bile flow may be diverted from the gastrointestinal tract using a T-tube. Unlike cyclosporine, tacrolimus gastrointestinal absorption does not seem to be influenced by the presence or absence of bile.[20,24] Other drug therapy can also increase or decrease the intestinal first-pass clearance of tacrolimus.[23]

Tacrolimus is a low hepatic extraction ratio drug.[5] Because of this, its hepatic clearance is influenced by unbound fraction in the blood (f_B) and intrinsic clearance (Cl'_{int}). Tacrolimus binds primarily to erythrocytes, α_1-acid glycoprotein, and albumin.[25–28] The exact value for protein binding (72–99%) depends on the technique used and matrix tested, and these factors have resulted in a large range of reported values for unbound fractions in the blood.[5] Erythrocyte concentrations vary in transplant patients, especially those who have received hematopoietic stem cell or kidney transplants. α_1-Acid glycoprotein concentrations also vary greatly among patients. Hepatic intrinsic clearance is different among individuals, and there is a large amount of variability in this value among individual liver transplant patients that changes according to the viability of the graft and time after transplantation surgery. Other drug therapy can also increase or decrease the hepatic intrinsic clearance of tacrolimus.[23] Taking all of these possible factors into consideration that alter absorption and clearance allows one to gain a better appreciation of why tacrolimus concentrations change on a day-to-day basis.

Tacrolimus capsules are available in 0.5, 1, and 5 mg strengths. Tacrolimus injection for intravenous administration is available at a concentration of 5 mg/mL. Before administration, it should be diluted in normal saline or 5% dextrose to a concentration between 0.004–0.02 mg/L, and the drug should be given as a continuous infusion. Anaphylactic reactions have occurred with this dosage form, possibly because of the castor oil diluent used to enhance dissolution of the drug. The initial dose of tacrolimus varies greatly among various transplant centers with a range of 0.1–0.3 mg/kg/d for orally administered drug and 0.03–0.1 mg/kg/d for intravenously administered drug.[1,5] For patients with liver dysfunction, these doses may be reduced by 25–50%.[24,29,30] Tacrolimus therapy may be started before the transplantation procedure.[1,2] Recommended initial oral doses of

tacrolimus are 0.2 mg/kg/d for adult kidney transplant patients, 0.10–0.15 mg/kg/d for adult liver transplant patients, 0.15–0.2 mg/kg/d for pediatric hepatic transplant recipients, and 0.075 mg/kg/d for adult heart transplant patients. Oral tacrolimus is usually given in two divided daily doses given every 12 hours.

EFFECTS OF DISEASE STATES AND CONDITIONS ON TACROLIMUS PHARMACOKINETICS AND DOSING

Transplantation type does not appear to have a substantial effect on tacrolimus pharmacokinetics.[5] The overall mean for all transplant groups is a clearance of 0.06 L/h/kg, a volume of distribution equal to 1 L/kg, and a half-life of 12 hours for adults.[5] In children (≤16 years old), average clearance and volume of distribution are higher (0.138 L/h/kg and 2.6 L/kg, respectively) but the mean half-life is about the same as adults (12 hours).[5] The determination of tacrolimus half-life is difficult for patients receiving the drug on a twice daily dosage schedule because only a few concentrations can be measured in the postabsorption, postdistribution phase. These results, as with the other pharmacokinetic parameters discussed in this chapter, are based on an enzyme-linked immunosorbent assay (ELISA; Pro-Trac, IncStar) or a microparticulate enzyme immunoassay (MEIA; IMx, Abbott Diagnostics) assay conducted using whole blood samples. As discussed in a previous section, concurrently measured plasma or serum concentrations are lower than whole blood concentrations.

Because the drug is primarily eliminated by hepatic metabolism, average clearance is lower (0.04 L/h/kg) in adult patients with liver dysfunction.[24,29,30] Also, mean volume of distribution is larger (3 L/kg) and half-life prolonged and variable (mean = 60 hours, range 28–141 h) in this patient population. Immediately after liver transplantation, tacrolimus metabolism is depressed until the graft begins functioning in a stable manner. Additionally, patients with transient liver dysfunction, regardless of transplantation type, will have decreased tacrolimus clearance and increased half-life values. Renal failure does not significantly change tacrolimus pharmacokinetics, and tacrolimus dosage adjustments are not necessary for patients receiving hemodialysis or peritoneal dialysis.[31,32]

DRUG INTERACTIONS

Compared with cyclosporine, tacrolimus drug interactions are not as well documented, and many drug interactions that are reported with cyclosporine are assumed to also occur with tacrolimus.[23] Drug interactions with tacrolimus fall into two basic categories. The first are agents known to cause nephrotoxicity when administered by themselves. The fear is that administration of a known nephrotoxin with tacrolimus will increase the incidence of renal damage over that observed when tacrolimus or the other agent is given separately. Compounds in this category of drug interactions include aminoglycoside antibiotics, vancomycin, cotrimoxazole (trimethoprim-sulfamethoxazole), amphotericin B, cisplatin, and nonsteroidal antiinflammatory drugs. Coadministration of tacrolimus with cyclosporine has resulted in augmented nephrotoxic side effects.

The second category of drug interactions involves inhibition or induction of tacrolimus metabolism.[23] Tacrolimus is metabolized by CYP3A4 and is a substrate for P-glycoprotein, so the potential for many pharmacokinetic drug interactions exists with agents that inhibit these pathways or are also cleared by these mechanisms. Because both of these drug elimination systems also exist in the gastrointestinal tract, inhibition drug interactions may also enhance tacrolimus oral bioavailability by diminishing the intestinal and hepatic first-pass effects. Drugs that may inhibit tacrolimus clearance include the calcium channel blockers (verapamil, diltiazem, nicardipine), azole antifungals (fluconazole, itraconazole, ketoconazole), macrolide antibiotics (erythromycin, clarithromycin, troleandomycin), antivirals (indinavir, nelfinavir, ritonavir, saquinavir), steroids (methylprednisolone, oral contraceptives, androgens), and psychotropic agents (fluvoxamine, nefazodone) as well as other compounds (cimetidine, lansoprazole, grapefruit juice). Inducing agents include other antibiotics (nafcillin, caspofungin, rifampin, rifabutin), anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), barbiturates, aminoglutethimide, St. John's Wort, sirolimus, and troglitazone. Because of the large number of potentially interacting agents, and the critical nature of the drugs involved in the treatment of transplant patients, complete avoidance of drug interactions with tacrolimus is not possible. Thus, most drug interactions with tacrolimus are managed using appropriate tacrolimus dosage modification with tacrolimus concentration monitoring as a guide.

If given with antacids, tacrolimus concentrations may decrease.[23] The mechanisms of action for this drug interaction appear to be pH-mediated destruction of tacrolimus for sodium bicarbonate or magnesium oxide and physical adsorption of tacrolimus to the antacid for aluminum hydroxide gel. Gastrointestinal prokinetic agents (cisapride, metoclopramide) may increase tacrolimus concentrations. Tacrolimus also has the potential to change the clearance of other drugs via competitive inhibition of CYP3A4 and/or P-glycoprotein.[23]

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate tacrolimus therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of tacrolimus. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of tacrolimus is to compute the best dose possible for the patient in order to prevent graft rejection or graft-versus-host disease given their set of disease states and conditions that influence tacrolimus pharmacokinetics, while avoiding adverse drug reactions. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Tacrolimus is almost completely metabolized by the liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same fashion that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change tacrolimus clearance, and the clearance previously measured in these studies is used as an estimate of the current patient's clearance rate. For example, an adult transplant patient with normal liver function would be assigned a tacrolimus clearance rate equal to 0.06 L/h/kg, while a pediatric transplant patient with the same profile would be assumed to have a tacrolimus clearance of 0.138 L/h/kg.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by intravenous infusion or orally, tacrolimus follows a two-compartment model. When oral therapy is chosen, the drug is often erratically absorbed with variable absorption rates. Because of the complex absorption profile and the fact that the drug is usually administered twice daily, a very simple pharmacokinetic equation that calculates the average tacrolimus steady-state concentration (Css in ng/mL = μg/L) is widely used and allows maintenance dose computation: $Css = [F(D/\tau)] / Cl$ or $D = (Css \cdot Cl \cdot \tau) / F$, where F is the bioavailability fraction for the oral dosage form (F averages 0.25 or 25% for most patient populations), D is the dose of tacrolimus in milligrams, Cl is tacrolimus clearance in liters per hour, and τ is the dosage interval in hours. If the drug is to be given as a continuous intravenous infusion, the equivalent equation for that route of administration is $Css = k_o/Cl$ or $k_o = Css \cdot Cl$, where k_o is the infusion rate in milligrams per hour.

STEADY-STATE CONCENTRATION SELECTION

The generally accepted therapeutic range for tacrolimus in the blood is 5–20 ng/mL. More important than these general guidelines are the specific requirements for each graft type as defined by the transplant center where the surgery was conducted. Clinicians should become familiar with the tacrolimus protocols used at the various institutions at which they practice. Although it is unlikely that steady state has been achieved, tacrolimus concentrations are usually obtained on a daily basis, even when dosage changes were made the previous day, owing to the critical nature of the therapeutic effect provided by the drug.

Example 1 HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral tacrolimus dose designed to achieve a steady-state tacrolimus trough blood concentration equal to 15 ng/mL.

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for adult patients is 0.06 L/h/kg. The tacrolimus blood clearance for this patient is expected to be 4.5 L/h: $Cl = 0.06 \text{ L/h/kg} \cdot 75 \text{ kg} = 4.5 \text{ L/h}$.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to

change the dose amount to milligrams.) The dosage equation for oral tacrolimus is D = (Css · Cl · τ) / F = (15 μg/L · 4.5 L/h · 12 h) / (0.25 · 1000 μg/mg) = 3.2 mg, rounded to 3 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur in about 3 days (5 half-lives = 5 · 12 h = 60 h).

Example 2 Same patient as in example 1, except compute an initial dose using intravenous tacrolimus.

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for adult patients is 0.06 L/h/kg. The tacrolimus blood clearance for this patient is expected to be 4.5 L/h: Cl = 0.06 L/h/kg · 75 kg = 4.5 L/h

2. *Compute dosage regimen.*

A continuous infusion will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for intravenous tacrolimus is k_o = Css · Cl = (15 μg/L · 4.5 L/h) / (1000 μg/mg) = 0.07 mg/h.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur in about 3 days (5 half-lives = 5 · 12 h = 60 h).

Literature-Based Recommended Dosing

Because of the large amount of variability in tacrolimus pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard tacrolimus doses for various situations is warranted. Indeed, most transplant centers use doses that are determined using a tacrolimus dosage protocol. The original computation of these doses was based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. In general, the expected tacrolimus steady-state concentration used to compute these doses is dependent upon the type of transplanted tissue and the post transplantation time line. Generally speaking, initial oral doses of 0.1–0.3 mg/kg/d are needed to achieve therapeutic tacrolimus steady-state concentrations.[1,5] Usual initial continuous infusion intravenous doses are 0.03–0.1 mg/kg/d.[1,5] For patients with liver dysfunction, these doses may be reduced by 25–50%.[24,29,30] To illustrate how this technique is used, the same patient examples utilized in the previous section will be repeated for this dosage approach for comparison purposes.

Example 3 HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral tacrolimus dose designed to achieve a steady-state tacrolimus trough blood concentration within the therapeutic range.

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus oral dosage range for adult patients is 0.1–0.3 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (0.1 mg/kg/d) will be used

in order to avoid nephrotoxicity. The initial tacrolimus dose for this patient is 8 mg/d given as 4 mg every 12 hours: Dose = 0.1 mg/kg/d · 75 kg = 7.5 mg/d, rounded to 8 mg/d or 4 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after 3 days (5 half-lives = 5 · 12 h = 60 h) of treatment.

Example 4 Same patient as in example 3, except compute an initial dose using intravenous tacrolimus.

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus intravenous dosage range for adult patients is 0.03–0.1 mg/kg/d. Because this is a renal transplant patient, a dose in the lower end of the range (0.03 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial tacrolimus intravenous infusion dose for this patient is 0.09 mg/h: Dose = (0.03 mg/kg/d · 75 kg) / (24 h/d) = 0.09 mg/h.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after 3 days (5 half-lives = 5 · 12 h = 60 h) of treatment.

USE OF TACROLIMUS CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce tacrolimus concentrations that are expected or desirable. Because of pharmacokinetic variability, the narrow therapeutic index of tacrolimus, and the severity of tacrolimus adverse side effects, measurement of tacrolimus concentrations is mandatory for patients to ensure that therapeutic, nontoxic levels are present. In addition to tacrolimus concentrations, important patient parameters (transplanted organ function tests or biopsies, clinical signs and symptoms of graft rejection or graft-versus-host disease, potential tacrolimus side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

For most patients, predose steady-state trough tacrolimus concentrations are typically measured. Since alternate methods to monitor cyclosporine concentrations have met with some success, investigators have begun suggesting similar methods for tacrolimus. Of these methods, estimation of tacrolimus AUC using several measured steady-state concentrations is the one that is gaining use in some transplant centers.

When tacrolimus concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change tacrolimus doses assuming the drug follows *linear pharmacokinetics*. Sometimes, it is useful to compute tacrolimus pharmacokinetic constants for a patient and base dosage adjustments on these. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the tacrolimus dose. Another approach involves measuring several postdose steady-state tacrolimus concentrations to

estimate the *AUC* and adjusting the tacrolimus dose to attain a target AUC. Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where concentrations are obtained at suboptimal times or the patient was not at steady state when concentrations were measured.

Linear Pharmacokinetics Method

Assuming tacrolimus follows linear, dose-proportional pharmacokinetics,[33] steady-state concentrations change in proportion to dose according to the following equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantage is steady-state concentrations are required.

Example 5 LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 5 mg every 12 hours of oral tacrolimus capsules. He has normal liver function. The current steady-state tacrolimus blood concentration equals 24 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the third day ($5\ t_{1/2} = 5 \cdot 12\ h = 60\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 5 mg/dose · 2 doses/d = 10 mg/d):

$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15\ ng/mL / 24\ ng/mL)\ 10\ mg/d = 6.3\ mg/d$, rounded to 6 mg/d

The new suggested dose would be 6 mg/d or 3 mg every 12 hours of tacrolimus capsules to be started at the next scheduled dosing time.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Example 6 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 0.15 mg/h of intravenous tacrolimus as a continuous infusion. The current steady-state tacrolimus concentration equals 9 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the third day ($5\ t_{1/2} = 5 \cdot 12\ h = 60\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15 \text{ ng/mL} / 9 \text{ ng/mL})\ 0.15 \text{ mg/h} = 0.25 \text{ mg/h}$$

A tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using drug concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired tacrolimus concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state tacrolimus concentration. Tacrolimus clearance can be measured using a single steady-state tacrolimus concentration and the following formula for orally administered drug: $Cl = [F(D/\tau)] / Css$, where Cl is tacrolimus clearance in L/h, F is the bioavailability factor for tacrolimus (F = 0.25), τ is the dosage interval in hours, and Css is the tacrolimus steady-state concentration in nanograms per milliliter which also equals micrograms per liter. If tacrolimus is administered intravenously, it is not necessary to take bioavailability into account: $Cl = k_o/Css$, where Cl is tacrolimus clearance in liters per hour, k_o is the tacrolimus infusion rate in milligrams per hour, and Css is the tacrolimus steady-state concentration in nanograms per milliliter which also equals micrograms per liter. Although this method does allow computation of tacrolimus clearance, it yields exactly the same tacrolimus dose as that supplied using linear pharmacokinetics. As a result, most clinicians prefer to directly calculate the new dose using the simpler linear pharmacokinetics method. To demonstrate this point, the patient cases used to illustrate the linear pharmacokinetics method will be used as examples for the pharmacokinetic parameter method.

Example 7 LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 5 mg every 12 hours of oral tacrolimus capsules. He has normal liver function. The current steady-state tacrolimus blood concentration equals 24 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: $Cl = [F(D/\tau)] / Css = [0.25 \cdot (5 \text{ mg}/12 \text{ h}) \cdot 1000 \text{ μg/mg}] / (24 \text{ μg/L}) = 4.3 \text{ L/h}$. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (15\ \mu g/L \cdot 4.3\ L/h \cdot 12\ h) / (0.25 \cdot 1000\ \mu g/mg) = 3.1$ mg, rounded to 3 mg every 12 hours.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Example 8 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 0.15 mg/h of intravenous tacrolimus as a continuous infusion. The current steady-state tacrolimus concentration equals 9 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: $Cl = k_o/Css = (0.15\ mg/h \cdot 1000\ \mu g/mg) / (9\ \mu g/L) = 16.7$ L/h. (Note: µg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: $k_o = Css \cdot Cl = (15\ \mu g/L \cdot 16.7\ L/h)/ 1000\ \mu g/mg = 0.25$ mg/h.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Area Under the Concentration-Time Curve Method

Some solid organ transplant centers believe that measurement or estimation of tacrolimus AUC is the best way to optimize tacrolimus therapy. While AUC can be measured using hourly postdose tacrolimus levels, studies have shown that there is a strong correlation between 3 and 4 tacrolimus concentrations and the total AUC. Based on this finding, most centers utilizing this method measure several steady-state tacrolimus concentrations and use a published regression equation determined in other patients receiving the same transplanted organ and similar drug therapy (to account for possible drug interactions) in order to convert the concentrations to an estimated AUC. Then, if necessary, adjust the tacrolimus dose using linear pharmacokinetics to achieve the target AUC: $D_{new}/AUC_{new} = D_{old}/AUC_{old}$ or $D_{new} = (AUC_{new}/AUC_{old})D_{old}$, where D is the dose,

AUC is the steady-state area under the concentration-time curve, old indicates the dose that produced the steady-state area under the concentration-time curve that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state area under the concentration-time curve.

There are many regression equations from which to choose based on the target transplant population and other concurrent therapy that may cause drug interactions with tacrolimus. The one used for the examples and problems in this book is for renal transplant patients treated with tacrolimus for at least 6 months that received other immunosuppressants (prednisone plus azathioprine).[14] In this investigation, the steady-state AUC over the dosage interval [from time 0 hours (predose) to 12 hours after the dose, $AUC_{0–12h}$] strongly correlated with four steady-state concentrations, and this relationship was used to adjust tacrolimus doses: $AUC_{0–12h}$ [in (ng · h)/mL] = 10 + (1.4 · C_{0h}) + (0.8 · C_{1h}) + (1.6 · C_{2h}) + (5.5 · C_{4h}), where C_{0h}, C_{1h}, C_{2h}, C_{4h} are steady-state tacrolimus concentrations in nanograms per milliliter obtained 0, 1, 2, and 4 hours, respectively, after a dose. The dose is then adjusted to produce a new steady-state $AUC_{0–12h}$ equal to 104 ± 33 (ng · h)/mL using linear pharmacokinetics.[13]

Example 9 DR is a 47-year-old, 78-kg (6 ft 1 in) male who has undergone renal transplantation. He is receiving 5 mg every 12 hours of oral tacrolimus. The following tacrolimus steady-state concentrations have been measured to determine an estimated $AUC_{0–12h}$: C_{0h} = 4 ng/mL, C_{1h} = 8 ng/mL, C_{2h} = 10 ng/mL, C_{3h} = 8 ng/mL. Compute a tacrolimus dose that will provide a steady-state $AUC_{0–12h}$ of 100 (ng · h)/mL.

1. *Compute pharmacokinetic parameters.*

Tacrolimus $AUC_{0–12h}$ can be estimated using the steady-state tacrolimus concentrations: $AUC_{0–12h}$ [in (ng · h)/mL] = 10 + (1.4 · C_{0h}) + (0.8 · C_{1h}) + (1.6 · C_{2h}) + (5.5 · C_{4h}) = 10 + (1.4 · 4 ng/mL) + (0.8 · 8 ng/mL) + (1.6 · 10 ng/mL) + (5.5 · 8 ng/mL) = 82 (ng · h)/mL.

2. *Compute tacrolimus dose.*

Linear pharmacokinetics is used to compute the new dose (total daily dose = 5 mg/dose · 2 doses/d = 10 mg/d): $D_{new} = (AUC_{new}/AUC_{old})D_{old}$ = {[100 (ng · h)/mL] / [82 (ng · h)/mL)]}(10 mg/d) = 12 mg/d, or 6 mg every 12 hours.

Steady-state tacrolimus serum concentrations should be measured after steady state is attained in 3–5 half-lives. Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and drug concentrations are input into the computer. The computer program has a

pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated drug concentrations at each time there are actual drug concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated drug concentrations are computed. The pharmacokinetic parameters that generated the estimated drug concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated drug concentrations that are statistically closest to the actual drug concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on drug concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include drug concentrations that are not at steady state, drug concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. When only a limited number of cyclosporine steady-state concentrations are available, Bayesian pharmacokinetic computer programs can be used to compute a complete patient pharmacokinetic profile that includes clearance, volume of distribution, and half-life. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples.[34]

Example 10 LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 5 mg every 12 hours of oral tacrolimus capsules. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL). The current steady-state tacrolimus blood concentration equals 24 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Enter patient's demographic, drug dosing, and concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 76 L, a half-life equal to 15.8 hours, and a clearance equal to 3.3 L/h.

3. *Compute dose required to achieve desired tacrolimus concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 2 mg every 12 hours will produce a steady-state tacrolimus concentration of 15 ng/mL. Using the linear pharmacokinetics and pharmacokinetic parameter methods previously described in the chapter produced a similar answer for this patient.

Example 11 FD is a 60-year-old, 85-kg (6 ft 1 in) male liver transplant patient who is receiving 0.15 mg/h of intravenous tacrolimus as a continuous infusion. He has normal liver function tests (bilirubin = 1.1 mg/dL, albumin = 3.5 g/dL). The current steady-state tacrolimus concentration equals 9 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Enter patient's demographic, drug dosing, and concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 85 L, a half-life equal to 3.6 hours, and a clearance equal to 16.3 L/h.

3. *Compute dose required to achieve desired tacrolimus concentrations.*

The one-compartment model continuous infusion equations used by the program to compute doses indicate that a dose of 0.24 mg/h will produce a steady-state tacrolimus concentration of 15 ng/mL. Using the linear pharmacokinetics and pharmacokinetic parameter methods previously described in the chapter produced a similar answer for this patient.

Example 12 YT is a 25-year-old, 55-kg (5 ft 2 in) female renal transplant recipient who received 4 mg every 12 hours of oral tacrolimus capsules for 2 doses after transplant, but because her renal function decreased, her dose was empirically changed to 2 mg every 12 hours. She has normal liver function (bilirubin = 0.9 mg/dL, albumin = 3.9 g/dL). The tacrolimus blood concentration obtained 12 hours after her first dose of the lower dosage regimen equaled 22 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 15 ng/mL.

1. *Enter patient's demographic, drug dosing, and concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 54 L, a half-life equal to 1.8 hours, and a clearance equal to 21 L/h.

3. *Compute dose required to achieve desired tacrolimus concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 1 mg every 12 hours will produce a steady-state tacrolimus concentration of 15 ng/mL.

TABLE 16-1 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics or area under the concentration-time curve (AUC) method
Computerized	Bayesian computer program	Bayesian computer program

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 16-1.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current immunosuppressive therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with tacrolimus exists.

1. VI is a 37-year-old, 85-kg (6 ft 1 in) male heart transplant patient who requires therapy with oral tacrolimus. He has normal liver function. Suggest an initial dosage regimen designed to achieve a steady-state tacrolimus concentration equal to 15 ng/mL.

2. Patient VI (please see problem 1) was prescribed 5 mg every 12 hours of tacrolimus capsules for 4 days, and the steady-state tacrolimus concentration equals 28 ng/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration of 15 ng/mL.

3. AS is a 9-year-old, 35-kg female (4 ft 6 in) hematopoietic stem cell transplantation patient who requires therapy with oral tacrolimus. She has normal liver function. Suggest an initial tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration equal to 12 ng/mL.

4. Patient AS (please see problem 3) was prescribed 3 mg every 12 hours of tacrolimus capsules for 3 days, and the steady-state tacrolimus concentration equals 9 ng/mL. The patient is assessed to be compliant with her dosage regimen. Suggest an oral tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration equal to 12 ng/mL.

5. FL is a 29-year-old, 78-kg (5 ft 11 in) male liver transplant patient who requires therapy with oral tacrolimus. He has poor liver function because of his liver disease.

Suggest an initial tacrolimus dosage regimen to be started 24 hours before transplant surgery designed to achieve a steady-state tacrolimus concentration equal to 15 ng/mL.

6. Patient FL (please see problem 5) is 10 days postsurgery for a liver transplantation. He was prescribed 4 mg every 12 hours of tacrolimus capsules since transplantation, and the steady-state tacrolimus concentration equals 33 ng/mL. The patient is assessed to be compliant with his dosage regimen. Suggest a tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration of 15 ng/mL.

7. PH is a 22-year-old, 67-kg female (5 ft 5 in) renal transplant patient who requires therapy with oral tacrolimus. She is 36 hours post transplantation procedure, and the transplanted kidney is beginning to function normally. Her liver function is normal. Suggest an initial tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration equal to 15 ng/mL.

8. Patient PH (please see problem 7) was prescribed 3 mg every 12 hours of tacrolimus capsules for 3 days, and the steady-state tacrolimus concentration equals 11 ng/mL. The patient is assessed to be compliant with her dosage regimen. Suggest a tacrolimus dosage regimen designed to achieve a steady-state tacrolimus concentration of 15 ng/mL.

9. PU is a 55-year-old, 68-kg (5 ft 8 in) male heart transplant patient who received a continuous intravenous infusion of tacrolimus (0.25 mg/h for 24 hours) and was switched to oral tacrolimus capsules 3 mg every 12 hours. He has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) function. The tacrolimus concentration equals 25 ng/mL 12 hours after the first oral dose of the drug. Compute a tacrolimus dose that will provide a steady-state concentration of 20 ng/mL.

10. LH is a 25-year-old, 60-kg (5 ft 3 in) female renal transplant patient who was given a new prescription for tacrolimus capsules 4 mg every 12 hours 2 days after transplantation surgery. She has normal liver function (bilirubin = 0.4 mg/dL, albumin = 3.7 g/dL) and is also being treated with phenytoin. The trough tacrolimus concentration before the fourth dose equals 10 ng/mL. Compute a tacrolimus dose that will provide a steady-state concentration of 20 ng/mL.

11. GY is a 36-year-old, 71-kg (5 ft 11 in) male who has undergone renal transplantation. He is receiving 8 mg every 12 hours of oral tacrolimus. The following tacrolimus steady-state concentrations have been measured to determine an estimated AUC_{0-12h}: C_{0h} = 6 ng/mL, C_{1h} = 13 ng/mL, C_{2h} = 16 ng/mL, C_{3h} = 12 ng/mL. Compute a tacrolimus dose that will provide a steady-state AUC_{0-12h} of 100 (ng · h)/mL.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for adult patients is 0.06 L/h/kg. The tacrolimus blood clearance for this patient is expected to be Cl = 0.06 L/h/kg · 85 kg · = 5.1 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral tacrolimus is D = (Css · Cl · τ) / F = (15 μg/L · 5.1 L/h · 12 h) / (0.25 · 1000 μg/mg) = 3.7 mg, rounded to 4 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 3 days of therapy (5 half-lives = 5 · 12 h = 60 h).

Literature-Based Recommended Dosing

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus oral dosage range for adult patients is 0.1–0.3 mg/kg/d. Because this is a heart transplant patient, a dose in the middle of the range (0.15 mg/kg/d) will be used in order to avoid graft rejection. The initial tacrolimus dose for this patient is Dose = 0.15 mg/kg/d · 85 kg = 12.8 mg/d, rounded to 12 mg/d or 6 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after 3 days (5 half-lives = 5 · 12 h = 60 h) of treatment.

2. *Solution to problem 2.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 5 mg/dose · 2 doses/d = 10 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15 \text{ ng/mL} / 28 \text{ ng/mL})\ 10 \text{ mg/d}$$
$$= 5.4 \text{ mg/d, rounded to } 6 \text{ mg/d}$$

The new suggested dose would be 6 mg/d or 3 mg every 12 hours of tacrolimus capsules to be started at the next scheduled dosing time.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: Cl = [F(D/τ)] / Css = [0.25 · (5 mg/12 h) · 1000 μg/mg] / (28 μg/L) = 3.7 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (15 μg/L · 3.7 L/h · 12 h) / (0.25 ·1000 μg/mg) = 2.7 mg, rounded to 3 mg every 12 hours.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

3. *Solution to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for pediatric patients is 0.138 L/h/kg. The tacrolimus blood clearance for this patient is expected to be Cl = 0.138 L/h/kg · 35 kg · = 4.8 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral tacrolimus is D = (Css · Cl · τ) / F = (12 μg/L · 4.8 L/h · 12 h) / (0.25 · 1000 μg/mg) = 2.8 mg, rounded to 3 mg every 12 hours of tacrolimus capsules.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 3 days (5 half-lives = 5 · 12 h = 60 h).

Literature-Based Recommended Dosing

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus oral dosage range is 0.1–0.3 mg/kg/d. Because this is a pediatric patient, a dose in the middle of the range (0.15 mg/kg/d) will be used in order to

avoid graft-versus-host disease. The initial tacrolimus dose for this patient is Dose = 0.15 mg/kg/d · 35 kg = 5.3 mg/d, rounded to 6 mg/d or 3 mg every 12 hours of tacrolimus capsules.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 3 days (5 half-lives = 5 · 12 h = 60 h) of treatment.

4. *Solution to problem 4.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions by the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 3 mg/dose · 2 doses/d = 6 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12 \text{ ng/mL} / 9 \text{ ng/mL})\ 6 \text{ mg/d} = 8 \text{ mg/d}$$

The new suggested dose would be 8 mg/d or 4 mg every 12 hours of tacrolimus capsules to be started at the next scheduled dosing time.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: Cl = [F(D/τ)] / Css = [0.25 · (3 mg/12 h) · 1000 μg/mg] / (9 μg/L) = 6.9 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (12 μg/L · 6.9 L/h · 12 h) / (0.25 · 1000 μg/mg) = 4 mg, given as 4 mg every 12 hours of tacrolimus capsules.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life

equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

5. *Solution to problem 5.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for adult patients with liver dysfunction is 0.04 L/h/kg. The tacrolimus blood clearance for this patient is expected to be Cl = 0.04 L/h/kg · 78 kg = 3.1 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral tacrolimus is $D = (Css \cdot Cl \cdot \tau) / F = (15\ \mu g/L \cdot 3.1\ L/h \cdot 12\ h) / (0.25 \cdot 1000\ \mu g/mg) = 2.2$ mg, rounded to 2 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 12 days of therapy (5 half-lives = 5 · 60 h = 300 h or 12.5 d). However, this patient is scheduled to receive his transplant the next day.

Literature-Based Recommended Dosing

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus oral dosage range for adult patients is 0.1–0.3 mg/kg/d. Because this patient has liver dysfunction, a dose in the lower end of the range (0.1 mg/kg/d) will be used in order to avoid graft rejection. The initial tacrolimus dose for this patient is Dose = 0.1 mg/kg/d · 78 kg = 7.8 mg/d, rounded to 8 mg/d. Because this patient has liver dysfunction, this dose should be empirically reduced by 50%: 8 mg/d · 0.5 = 4 mg/d or 2 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 12 days of therapy (5 half-lives = 5 · 60 h = 300 h or 12.5 d). However, this patient is scheduled to receive his transplant the next day.

6. *Solution to problem 6.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the third day ($5\ t_{1/2} = 5 \cdot 12\ h = 60\ h$) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 4 mg/dose · 2 doses/d = 8 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15 \text{ ng/mL} / 33 \text{ ng/mL})\ 8 \text{ mg/d} = 3.6 \text{ mg/d, rounded to 4 mg/d}$$

The new suggested dose would be 4 mg/d or 2 mg every 12 hours of tacrolimus capsules to be started at the next scheduled dosing time.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: Cl = [F(D/τ)] / Css = [0.25 · (4 mg/12 h) · 1000 μg/mg] / (33 μg/L) = 2.5 L/h. (Note: μg/L = ng/mL and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: D = (Css · Cl · τ) / F = (15 μg/L · 2.5 L/h · 12 h) / (0.25 · 1000 μg/mg) = 1.8 mg, rounded to 2 mg every 12 hours.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

7. *Solution to problem 7.*

Pharmacokinetic Dosing Method

1. *Estimate clearance according to disease states and conditions present in the patient.*

The mean tacrolimus clearance for adult patients is 0.06 L/h/kg. The tacrolimus blood clearance for this patient is expected to be Cl = 0.06 L/h/kg · 67 kg = 4.0 L/h.

2. *Compute dosage regimen.*

A 12-hour dosage interval will be used for this patient. (Note: ng/mL = μg/L and this concentration unit was substituted for Css in the calculations so that unnecessary

unit conversion was not required. Also, a conversion constant of 1000 μg/mg is used to change the dose amount to milligrams.) The dosage equation for oral tacrolimus is $D = (Css \cdot Cl \cdot \tau) / F = (15\ \mu g/L \cdot 4.0\ L/h \cdot 12\ h) / (0.25 \cdot 1000\ \mu g/mg) = 2.9$ mg, rounded to 3 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after about 3 days of therapy (5 half-lives = 5 · 12 h = 60 h).

Literature-Based Recommended Dosing

1. *Choose tacrolimus dose based on disease states and conditions present in the patient and transplant type.*

The tacrolimus oral dosage range for adult patients is 0.1–0.3 mg/kg/d. Because this is a kidney transplant patient, a dose in the lower end of the range (0.1 mg/kg/d) will be used in order to avoid nephrotoxicity. The initial tacrolimus dose for this patient is Dose = 0.1 mg/kg/d · 67 kg = 6.7 mg/d, rounded to 6 mg/d or 3 mg every 12 hours.

Tacrolimus concentrations would be obtained on a daily basis with steady state expected to occur after 3 days (5 half-lives = 5 · 12 h = 60 h) of treatment.

8. *Solution to problem 8.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired concentration.*

The patient would be expected to achieve steady-state conditions after the third day ($5\ t_{1/2} = 5 \cdot 12$ h = 60 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 3 mg/dose · 2 doses/d = 6 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (15\ ng/mL / 11\ ng/mL)\ 6\ mg/d = 8.2\ mg/d, \text{ rounded to } 8\ mg/d$$

The new suggested dose would be 8 mg/d or 4 mg every 12 hours of tacrolimus capsules to be started at the next scheduled dosing time.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the third day ($5\ t_{1/2} = 5 \cdot 12$ h = 60 h) of therapy.

Tacrolimus clearance can be computed using a steady-state tacrolimus concentration: $Cl = [F(D/\tau)] / Css = [0.25 \cdot (3\ mg/12\ h) \cdot 1000\ \mu g/mg] / (11\ \mu g/L) = 5.7\ L/h$. (Note: $\mu g/L = ng/mL$ and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute tacrolimus dose.*

Tacrolimus clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau) / F = (15\ \mu g/L \cdot 5.7\ L/h \cdot 12\ h) / (0.25 \cdot 1000\ \mu g/mg) = 4.1$ mg, rounded to 4 mg every 12 hours.

A steady-state trough tacrolimus concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the tacrolimus steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = $5 \cdot 12\ h = 60\ h$). Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

9. *Solution to problem 9.*

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 69 L, a half-life equal to 14 hours, and a clearance equal to 3.4 L/h.

3. *Compute dose required to achieve desired tacrolimus concentrations.*

The one-compartment model infusion and first-order absorption equations used by the program to compute doses indicates that a dose of 4 mg every 12 hours will produce a steady-state tacrolimus concentration of 20 ng/mL.

10. *Solution to problem 10.*

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and concentration/time data into the computer program.*

Because the patient is also being treated with phenytoin, an enzyme-induction drug interaction for tacrolimus should be entered into the program at the appropriate place.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 60 L, a half-life equal to 9 hours, and a clearance equal to 4.5 L/h.

3. *Compute dose required to achieve desired tacrolimus concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicate that a dose of 6 mg every 12 hours will produce a steady-state tacrolimus concentration of 20 ng/mL.

11. *Solution to problem 11.*

1. *Compute pharmacokinetic parameters.*

Tacrolimus $AUC_{0–12h}$ can be estimated using the steady-state tacrolimus concentrations: $AUC_{0–12h}$ [in (ng · h)/mL] = 10 + (1.4 · C_{0h}) + (0.8 · C_{1h}) + (1.6 · C_{2h}) + (5.5 · C_{4h}) = 10 + (1.4 · 6 ng/mL) + (0.8 · 13 ng/mL) + (1.6 · 16 ng/mL) + (5.5 · 12 ng/mL) = 120 (ng · h)/mL.

2. *Compute tacrolimus dose.*

Linear pharmacokinetics is used to compute the new dose (total daily dose = 8 mg/dose · 2 doses/d = 16 mg/d): $D_{new} = (AUC_{new}/AUC_{old})D_{old}$ = {[100 (ng · h)/mL] / [(120 ng · h)/mL)]}(16 mg/d) = 13.3 mg/d, rounded to 14 mg/d or 7 mg every 12 hours.

Steady-state tacrolimus serum concentrations should be measured after steady state is attained in 3–5 half-lives. Tacrolimus concentrations should also be measured if the patient experiences signs or symptoms of graft rejection, or if the patient develops potential signs or symptoms of tacrolimus toxicity.

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Part VI

OTHER DRUGS

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17

LITHIUM

INTRODUCTION

Lithium is an alkali metal that is administered as a monovalent cation (Li^+) for the treatment of bipolar disorder. In the United States, orally administered carbonate and citrate salts of lithium are available. While lithium is still used as a primary treatment for bipolar disorders, valproic acid, lamotrigine, or carbamazepine may be used for some subsets of the disease.[1] Although this drug has been used in psychiatric medicine since the 1940s, the mechanism of action of lithium is largely unknown. Among the current theories are competition with other cations at receptor and tissue sites, dopamine-receptor supersensitivity blockage, decreased stimulation of β-receptor induced adenylate cyclase, and enhanced sensitivity to serotonin (5-HT), acetylcholine, and γ-aminobutyric acid (GABA).[1,2]

THERAPEUTIC AND TOXIC CONCENTRATIONS

The general therapeutic range for lithium is 0.6–1.5 mmol/L. Because lithium is a monovalent cation, the therapeutic range expressed in mEq/L is identical to these values (i.e., 0.6–1.5 mEq/L). However, most clinicians apply different therapeutic concentration ranges depending on the clinical situation of the patient.[3,4] For individuals with acute mania, a minimum lithium concentration of 0.8 mmol/L is usually recommended. The usual desired range for these individuals is 0.8–1 mmol/L. If patients with acute mania do not respond to these levels, it is necessary to occasionally use lithium concentrations of 1–1.2 mmol/L and in some instances concentrations as high as 1.2–1.5 mmol/L are needed. For long-term maintenance use, the usual desired range is 0.6–0.8 mmol/L. If patients do not respond to these levels during maintenance treatment, occasional use of lithium concentrations equal to 0.9–1 mmol/L is required and in some cases concentrations as high as 1–1.2 mmol/L are necessary to gain an adequate outcome.

These therapeutic ranges are based on steady-state lithium serum concentrations obtained 12 hours after a dose. The adoption of a standardized 12-hour postdose lithium

concentration to assess dose and response has been paramount in establishing the aforementioned therapeutic ranges for the agent.[5] After oral administration, lithium concentrations follow a complex concentration/time curve that is best described using multicompartment models (Figure 17-1).[5–9] There is a great deal of variability among patients in the time needed for distribution between serum and tissues to occur, and under these conditions using a uniform time for the determination of steady-state serum concentrations is important. When lithium serum concentration monitoring is anticipated for an individual, the patient needs to understand that it is important to take their medication as instructed for 2–3 days before the blood sample is obtained, to have the blood sample withdrawn 12 ± 0.5 hours after the last dose, and to report any discrepancies in compliance and blood sampling time to their care provider.

Short-term side effects observed when starting lithium or after a dosage increase include muscle weakness, lethargy, polydipsia, polyuria, nocturia, headache, impairment of memory or concentration, confusion, impaired fine motor performance, and hand tremors.[1,2,10] Many of these adverse effects will diminish with continued dosing of lithium. However, some intervention may be needed for the tremor including a shorter dosage interval using the same total daily dose in order to decrease peak lithium concentrations, a decreased lithium dose, or concurrent treatment with a β-blocker. Long-term adverse effects include a drug-induced diabetes insipidus, renal toxicity (glomerulosclerosis, renal tubular atrophy, interstitial nephritis, urinary casts), hypothyroidism with or without goiter formation, electrocardiographic abnormalities, leukocytosis, weight gain, and dermatologic changes.[1,2,10]

At lithium serum concentrations within the upper end of the therapeutic range (1.2–1.5 mmol/L), the following adverse effects can be noted in patients: decreased memory and concentration, drowsiness, fine hand tremor, weakness, lack of coordination, nausea,

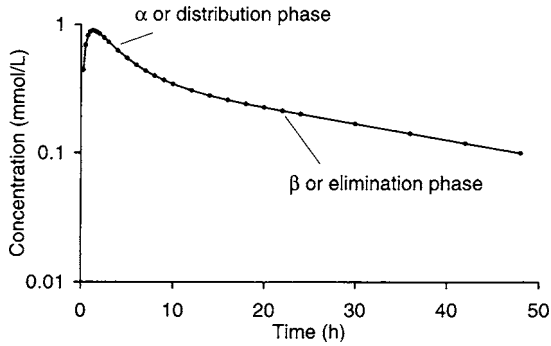

FIGURE 17-1 Lithium ion serum concentration/time curve after a single 900-mg oral dose of lithium carbonate (24.4 mmol or mEq of lithium ion) rapid-release capsules. Maximum serum concentrations occur 2–3 hours after the dose is given. After the peak concentration is achieved, the distribution phase lasts for 6–10 hours, followed by the elimination phase. In patients with good renal function (creatinine clearance >80 mL/min), the average elimination half-life for lithium is 24 hours. Because of the long distribution phase, lithium serum concentrations used for dosage adjustment purposes should be obtained no sooner than 12 hours after dosage administration.

diarrhea, vomiting, or fatigue.[1,2,10] At concentrations just above the therapeutic range (1.5–3 mmol/L), confusion, giddiness, agitation, slurred speech, lethargy, blackouts, ataxia, dysarthria, nystagmus, blurred vision, tinnitus, vertigo, hyperreflexia, hypertonia, coarse hand tremors, and muscle fasciculations may occur in patients. If concentrations exceed 3 mmol/L, severe toxicity occurs with choreoathetosis, seizures, irreversible brain damage, arrhythmias, hypotension, respiratory and cardiovascular complications, stupor, coma, and death. At toxic lithium concentrations, lithium can cause a nonspecific decrease in glomerular filtration which, in turn, decreases lithium clearance. The decrease in lithium clearance will cause a further increase in the lithium serum concentration. This phenomenon can cause a viscous circle of decreased clearance leading to increased lithium serum concentration, which leads to additional decreases in lithium clearance and so on. Because of this and the severe toxic side effects, lithium concentrations above 3.5–4 mmol/L may require hemodialysis to remove the drug as quickly as possible.[1,4,10]

CLINICAL MONITORING PARAMETERS

The signs and symptoms of bipolar disease include both those of depression (depressed affect, sad mood, decreased interest and pleasure in normal activities, decreased appetite and weight loss, insomnia or hypersomnia, psychomotor retardation or agitation, decreased energy or fatigue, feelings of worthlessness or guilt, impaired decision making and concentration, suicidal ideation or attempts) and mania (abnormal and persistently elevated mood, grandiosity, decreased need for sleep, pressure of speech, flight of ideas, distractible with poor attention span, increased activity or agitation, excessive involvement in high-risk activities).[11] Generally, onset of action for lithium is 1–2 weeks, and a 4- to 6-week treatment period is required to assess complete therapeutic response to the drug.[10,11]

Before initiating lithium therapy, patients should undergo a complete physical exam, and a general serum chemistry panel (including serum electrolytes and serum creatinine), complete blood cell count with differential, thyroid function tests, urinalysis (including osmolality and specific gravity) and urine toxicology screen for substances of abuse should be obtained. For patients with renal dysfunction (measured 24-hour creatinine clearance) or baseline cardiac disease (electrocardiogram), additional testing is recommended. Clinicians should consider ordering a pregnancy test for females of child-bearing age. Follow-up testing in the following areas should be conducted every 6–12 months: serum electrolytes, serum creatinine (measured 24-hour creatinine clearance in patients with renal dysfunction), thyroid function tests, complete blood cell count with differential. If urine output exceeds 3 L/d, a urinalysis with osmolality and specific gravity should also be measured.

Lithium serum concentrations should be measured in every patient receiving the drug. As previously discussed, dosage schedules should be arranged so that serum samples for lithium measurement are obtained 12 ± 0.5 hours after a dose.[5] Usually this requires administration of the drug every 12 hours for twice daily dosing. For three times a day dosing, it is necessary to give the drug so that there is a 12-hour time period overnight. Examples of two common dosage schemes are 0900 H, 1500 H, and 2100 H or 0800 H, 1400 H, and 2000 H. Obviously, the choice should be individualized based upon the patient's lifestyle. Upon initiation of therapy, serum concentrations can be measured

every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal. Otherwise, lithium concentrations may accumulate to toxic levels due to the decrease in lithium clearance. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations. If lithium dosage alterations are needed, or therapy with another drug known to interact with lithium is added, lithium serum concentrations should be measured within 1–2 weeks after the change.

After patients have been stabilized on a multiple dose per day regimen, it is possible to consider once daily administration of lithium for those receiving a total dose of 1800 mg/d or less.[4] However, the change in dosage interval will alter the 12-hour lithium concentration, and further dosage titration may be needed to reestablish desired levels.[4]

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Lithium is eliminated almost completely (>95%) unchanged in the urine.[9] The ion is filtered freely at the glomerulus, and subsequently 60–80% of the amount filtered is reabsorbed by the proximal tubule of the nephron. Lithium eliminated in the saliva, sweat, and feces accounts for less than 5% of the administered dose.[10] On average, lithium clearance is approximately 20% of the patient's creatinine clearance.[10,12,13] Lithium is administered orally as carbonate or citrate salts. Lithium carbonate capsules (150, 300, 600 mg) and tablets (rapid release: 300 mg; sustained release: 300, 450 mg) are available. There are 8.12 mmol (or 8.12 mEq) of lithium in 300 mg of lithium carbonate. Lithium citrate syrup (8 mmol or mEq/5 mL) is another oral dosage form. Oral bioavailability is good for all lithium salts and dosage forms and equals 100%.[14,15] The peak lithium concentration occurs 15–30 minutes after a dose of lithium citrate syrup, 1–3 hours after a dose of rapid-release lithium carbonate tablets or capsules, and 4–8 hours after a dose of sustained-release lithium carbonate tablets. Lithium ion is not plasma protein bound. The typical dose of lithium carbonate is 900–2400 mg/d in adult patients with normal renal function.

EFFECTS OF DISEASE STATES AND CONDITIONS ON LITHIUM PHARMACOKINETICS

Adults with normal renal function (creatinine clearance >80 mL/min) have an average elimination half-life of 24 hours, volume of distribution equal to 0.9 L/kg, and clearance of 20 mL/min for lithium.[5–9] During an acute manic phase, lithium clearance can increase by as much as 50%, which produces a half-life that is about $^1/_2$ the normal value.[16] In children 9–12 years of age, average elimination half-life equals 18 hours, volume of distribution is 0.9 L/kg, and clearance equals 40 mL/min for the ion.[17] Because glomerular filtration and

creatinine clearance decrease with age, lithium clearance can be decreased in elderly patients, producing half-lives up to 36 hours.[12,13] Because of the circadian rhythm of glomerular filtration, lithium clearance is about 30% higher during daytime hours.[18]

Because lithium is eliminated almost exclusively by the kidney, renal dysfunction is the most important disease state that affects lithium pharmacokinetics. Lithium clearance rate decreases in proportion to creatinine clearance. In adults, the lithium clearance/creatinine clearance ratio is 20%, but during a manic phase increases to about 30%.[12,13,16] This relationship between renal function and lithium clearance will form the basis for initial dosage computation later in this chapter. Because of the decrease in clearance, the average lithium half-life is 40–50 hours in renal failure patients.

The renal clearance of lithium for a patient is influenced by the state of sodium balance and fluid hydration in that individual. Lithium is reabsorbed in the proximal tubule of the nephron via the same mechanisms used to maintain sodium balance.[5] Thus, when a patient is in negative sodium balance, the kidney increases sodium reabsorption as a compensatory maneuver and lithium reabsorption increases as a result. The kidney also increases sodium reabsorption when a patient becomes dehydrated, and, again, lithium reabsorption increases. In both cases, increased lithium reabsorption leads to decreased lithium clearance. Some common things that cause sodium depletion and/or dehydration include sodium-restricted diets for the treatment of other conditions; vomiting, diarrhea, or fever that might be due to viral or other illnesses; heavy or intense exercise; excessive sweating; use of saunas or hot tubs; and hot weather. Overuse of coffee, tea, soft drinks, or other caffeine-containing liquids and ethanol should be avoided by patients taking lithium. Patients should be advised to maintain adequate fluid intake at all times (2.5–3 L/d) and to increase fluid intake as needed.[11]

During periods of acute mania, lithium clearance can be increased by as much as 50%.[16] Lithium is generally not used in the first trimester due to possible teratogenic effects on the fetus.[10,11] Due to increased glomerular filtration, lithium clearance may be increased in pregnant women, especially during the third trimester. Lithium crosses the placenta, and human milk concentrations are 30–100% that of concurrent serum concentrations.[19]

Lithium is removed from the body by hemodialysis, peritoneal dialysis, and arteriovenous hemodiafiltration with clearance values of 30–50 mL/min, 13–15 mL/min and 21 mL/min, respectively.[10,20,21] The sieving coefficient for lithium during hemofiltration is 0.90.[22,23] Replacement doses of lithium during dialysis or hemofiltration should be determined using serum concentration monitoring.

DRUG INTERACTIONS

Many diuretics have drug interactions with lithium.[24] Thiazide diuretics cause sodium and water depletion, which leads to increased sodium reabsorption in the proximal tubule of the kidney as a compensatory mechanism. Since lithium is reabsorbed by the same mechanisms as sodium, lithium reabsorption increases and lithium clearance decreases by 40–50% during treatment with thiazide diuretics. Other diuretics that work at the site of the distal tubule of the kidney may cause a similar interaction with lithium (chlorthalidone, metolazone). Although there are case reports of loop diuretics causing a similar interaction, there are also reports of no drug interaction between lithium and these agents.

Because of this, many clinicians favor the use of a loop diuretic, with careful monitoring of adverse effects and lithium serum concentrations, in patients taking lithium. Amiloride has also been reported to have minimal effects on lithium clearance.

Nonsteroidal antiinflammatory agents (NSAIDs) also decrease lithium clearance and increase lithium concentrations. The probable mechanism is a NSAID-induced decrease in renal blood flow via inhibition of prostaglandins. Of these agents, sulindac and aspirin appear to have little or no drug interaction with lithium.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been reported to inhibit the elimination of lithium by an undefined mechanism. Of the two classes of drugs, more documentation exists for the ACEIs where lithium serum concentrations have increased by as much as 200–300% from pretreatment levels.

Some serotonin-specific reuptake inhibitors (SSRIs) have been reported to cause a serotonergic hyperarousal syndrome when taken in conjunction with lithium. Case reports of this problem are currently available for fluoxetine, sertraline, and fluvoxamine. In addition to elevated lithium concentrations, patients have developed stiffness of arms and legs, course tremors, dizziness, ataxia, dysarthric speech, and seizures when taking these SSRI agents with lithium. Although there are also literature reports of these combinations used safely, caution should be exercised when concurrent treatment with SSRIs and lithium is indicated.

Theophylline increases the lithium clearance/creatinine clearance ratio by as much as 58% resulting in an average decrease of 21% in steady-state lithium concentrations. A rare, but severe, drug interaction between lithium and antipsychotic drugs has been reported where patients are more susceptible to the development of extrapyramidal symptoms or irreversible brain damage. Again, although there are reports of using antipsychotic agents and lithium together successfully, patients requiring this combination therapy should be closely monitored for adverse drug reactions.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate lithium therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. However, it is computationally intensive. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of lithium. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient. *Test dose methods* use concentrations measured after one or more lithium test doses to rapidly individualize lithium therapy.

Pharmacokinetic Dosing Method

The goal of initial dosing of lithium is to compute the best dose possible for the patient given their set of disease states and conditions that influence lithium pharmacokinetics and the type and severity of their bipolar disease. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

CLEARANCE ESTIMATE

Lithium ion is almost totally eliminated unchanged in the urine, and there is a consistent relationship between lithium clearance and creatinine clearance with a ratio of 20% between the two (lithium clearance/creatinine clearance).[10,12,13] This relationship allows the estimation of lithium clearance for a patient, which can be used to compute an initial dose of the drug. Mathematically, the equation for the straight line shown in Figure 17-2 is Cl = 0.2(CrCl), where Cl is lithium clearance in milliliters per minute and CrCl is creatinine clearance in milliliters per minute. For dosing purposes, it is more useful to have lithium clearance expressed in liters per day. The equation converted to these units is Cl = 0.288(CrCl), where Cl is lithium clearance in liters per day and CrCl is creatinine clearance in milliliters per minute. For patients with acute mania, lithium clearance is increased by about 50%, and the corresponding equation for these individuals is Cl = 0.432(CrCl), where Cl is lithium clearance in liters per day and CrCl is creatinine clearance in milliliters per minute.[16]

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATION

When given orally, lithium follows a two-compartment model (Figure 17-1).[5–9] After the peak concentration is achieved, serum concentrations drop rapidly because of distribution of drug from blood to tissues (α or distribution phase). By 6–10 hours after administration of the drug, lithium concentrations decline more slowly, and the elimination rate constant for this segment of the concentration/time curve is the one that varies with renal function (β or elimination phase). While this model is the most correct from a strict pharmacokinetic viewpoint, it cannot easily be used clinically because of its mathematical complexity. During the elimination phase of the concentration/time curve, lithium serum concentrations drop very slowly due to the long elimination half-life (24 hours with normal renal function, up to 50 hours with end-stage renal disease). Because of this, a very simple pharmacokinetic equation that computes the average lithium steady-state serum concentration (Css in mmol/L = mEq/L) is widely used and allows maintenance dosage calculation: $Css = [F(D/\tau)] / Cl$ or $D/\tau = (Css \cdot Cl) / F$, where F is the bioavailability fraction for the oral dosage form (F = 1 for oral lithium), D is the lithium dose in

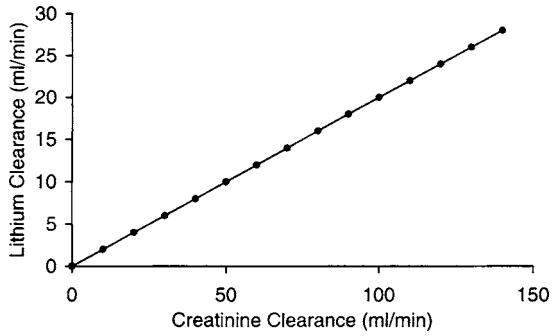

FIGURE 17-2 The ratio between lithium clearance and creatinine clearance is 0.2 for patients requiring maintenance therapy with lithium. This relationship is used to estimate lithium clearance for patients requiring initial dosing with the drug.

millimoles, τ is the dosage interval in days, and Cl is lithium clearance in liters per day. Because this equation computes lithium ion requirement and lithium carbonate doses are prescribed in milligrams, the ratio of lithium ion content to lithium carbonate salt (8.12 mmol Li^+/300 mg lithium carbonate) is used to convert the result from this equation into a lithium carbonate dose. Total daily amounts of lithium are usually given as almost equally divided doses two or three times a day, and single doses above 1200 mg/d of lithium carbonate are usually not given in order to avoid gastrointestinal upset.

STEADY-STATE CONCENTRATION SELECTION

Lithium serum concentrations are selected based on the presence or absence of acute mania and titrated to response.[3] For individuals with acute mania, a minimum lithium concentration of 0.8 mmol/L is usually recommended. The usual desired range for these individuals is 0.8–1 mmol/L. If patients with acute mania do not respond to these levels, it is necessary to occasionally use lithium concentrations of 1–1.2 mmol/L and in some instances concentrations as high as 1.2–1.5 mmol/L are needed. For long-term maintenance use, the usual desired range is 0.6–0.8 mmol/L. If patients do not respond to these levels during maintenance treatment, occasional use of lithium concentrations equal to 0.9–1 mmol/L is required and in some cases concentrations as high as 1–1.2 mmol/L are necessary to gain an adequate outcome.

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Compute an oral lithium dose for this patient for maintenance therapy.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$
$$CrCl_{est} = 97\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the lithium clearance for this patient:

$$Cl = 0.288(CrCl) = 0.288(97\ mL/min) = 27.9\ L/d$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F = (0.6\ mmol/L \cdot 27.9\ L/d) / 1 = 16.7\ mmol/d$$

D/τ = (300-mg lithium carbonate/8.12 mmol Li^+) 16.7 mmol/d = 617 mg/d, rounded to 600 mg/d of lithium carbonate. This dose would be given as 300 mg of lithium carbonate every 12 hours.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Example 2 Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 3.5\ mg/dL)$$
$$CrCl_{est} = 25\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the lithium clearance for this patient:

$$Cl = 0.288(CrCl) = 0.288(25\ mL/min) = 7.2\ L/d$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring maintenance therapy for bipolar disease, the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F = (0.6\ mmol/L \cdot 7.2\ L/d)/1 = 4.3\ mmol/d$$

D/τ = (300 mg lithium carbonate/8.12 mmol Li^+) 4.3 mmol/d = 159 mg/d, rounded to 150 mg/d of lithium carbonate. This dose would be given as 150 mg of lithium carbonate daily.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Example 3 Same patient profile as in example 1, but serum creatinine is 0.9 mg/dL, and the patient is being treated for acute mania. Compute an oral lithium carbonate dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$
$$CrCl_{est} = 97\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the lithium clearance for this patient:

$$Cl = 0.432\ (CrCl) = 0.432\ (97\ mL/min) = 41.9\ L/d$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring therapy for the acute manic phase of bipolar disease, the desired lithium concentration would be 0.8 mmol/L. Oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F = (0.8\ mmol/L \cdot 41.9\ L/d) / 1 = 33.5\ mmol/d$$

D/τ = (300 mg lithium carbonate/8.12 mmol Li^+) 33.5 mmol/d = 1238 mg/d, rounded to 1200 mg/d of lithium carbonate. This dose would be given as 600 mg of lithium carbonate every 12 hours.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

Literature-Based Recommended Dosing

Because of the large amount of variability in lithium pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard lithium doses for various situations are warranted. The original computation of these doses was based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. For the treatment of acute mania, initial doses are usually 900–1200 mg/d of lithium carbonate.[10,11] If the drug is being used for bipolar disease prophylaxis, an initial dose of 600 mg/d lithium carbonate is recommended.[10,11] In both cases, the total daily dose is given in 2–3 divided daily doses. To avoid adverse side effects, lithium doses are slowly increased by 300–600 mg/d every 2–3 days according to clinical response and lithium serum concentrations. Renal dysfunction is the major condition that alters lithium pharmacokinetics and dosage.[25–28] If creatinine clearance is 10–50 mL/min, the prescribed initial dose is 50–75% of that recommended for patients with normal renal function. For creatinine clearance values below 10 mL/min, the prescribed dose should be 25–50% of the usual dose in patients with good renal function. Recommended doses for children and adolescents with normal renal function are 15–60 mg/kg/d and 600–1800 mg/d, respectively, with doses administered three to four times daily.[29]

Zetin and associates have developed a multiple regression equation that computes lithium carbonate doses for patients based on hospitalization status, age, gender, and weight of the patient as well as the presence or absence of concurrent tricyclic use by the patient.[30,31] However, since renal function was not assessed as an independent parameter in their study population, this dosage method is not presented.

To illustrate the similarities and differences between this method of initial dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 4 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Recommend an oral lithium dose for this patient for maintenance therapy.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$
$$CrCl_{est} = 97\ mL/min$$

2. *Choose lithium dose based on disease states and conditions present in the patient.*

The patient requires prophylactic lithium therapy for bipolar disease, and has good renal function. A lithium carbonate dose of 600 mg/d, given as 300 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

Example 5 Same patient profile as in example 4, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 3.5\ mg/dL)$$
$$CrCl_{est} = 25\ mL/min$$

2. *Choose lithium dose based on disease states and conditions present in the patient.*

The patient requires prophylactic lithium therapy for bipolar disease, and has moderate renal function. With an estimated creatinine clearance of 25 mL/min, lithium carbonate doses should be 50–75% of the usual amount. A lithium carbonate dose of 300 mg/d, given as 150 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 150–300 mg/d every 5–7 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

Example 6 Same patient profile as in example 4, but serum creatinine is 0.9 mg/dL, and the patient is being treated for the acute mania phase of bipolar disease. Compute an oral lithium carbonate dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg]/(72 \cdot 0.9\ mg/dL)$$
$$CrCl_{est} = 97\ mL/min$$

2. *Choose lithium dose based on disease states and conditions present in the patient.*

The patient requires lithium therapy for acute mania, and has good renal function. A lithium carbonate dose of 900 mg/d, given as 300 mg at 0800 H, 1400 H, and 2000 H, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

Test Dose Methods to Assess Initial Lithium Dosage Requirements

Several methods to assess initial lithium dosage requirement using one or most lithium test doses and one or more lithium serum concentrations are available for clinical use.

COOPER NOMOGRAM

The Cooper nomogram of lithium maintenance dosage assessment requires the administration of a single test dose of 600-mg lithium carbonate and a single lithium serum concentration measured 24 hours later.[32,33] The 24-hour lithium serum concentration is compared to a table that converts the observed concentration into the lithium carbonate dose required to produced a steady-state lithium concentration between 0.6–1.2 mmol/L (Table 17-1). The theoretical basis for this dosage approach lies in the relationship between the serum concentration of a drug obtained about one half-life after dosage and the elimination rate constant for the drug in a patient. This nomogram can also be expressed as an equation for the total

TABLE 17-1 Cooper Nomogram for Lithium Dosing[32,33]

Lithium carbonate dosage required to produce steady-state lithium serum concentrations between 0.6–1.2 mmol/L*

LITHIUM SERUM CONCENTRATION 24 HOURS AFTER THE TEST DOSE (mmol/L)	LITHIUM CARBONATE DOSAGE REQUIREMENT†
<0.05	1200 mg three times daily (3600 mg/d)‡
0.05–0.09	900 mg three times daily (2700 mg/d)
0.10–0.14	600 mg three times daily (1800 mg/d)
0.15–0.19	300 mg four times daily (1200 mg/d)
0.20–0.23	300 mg three times daily (900 mg/d)
0.24–0.30	300 mg twice daily (600 mg/d)
>0.30	300 mg twice daily§ (600 mg/d)

*Lithium dosage requirements should be reassessed with changes in clinical status (mania versus maintenance treatment), renal function or other factors that alter lithium pharmacokinetics.
†Dosage schedule determined to provide minimum fluctuation in lithium serum concentration and maximum patient compliance. A change in dosage interval can be made by the prescribing clinician, but the total daily dose should remain the same.
‡Use extreme caution. Patient appears to have an increased clearance and short half-life for lithium, which would require large lithium carbonate maintenance doses. However, this large of a maintenance dose requires careful patient monitoring for response and adverse side effects.
§Use extreme caution. Patient appears to have a reduced clearance and long half-life for lithium, and may accumulate steady-state lithium concentrations above the therapeutic range.

daily lithium dosage requirement (D in mmol/d): $D = e^{(4.80-7.5C_{test})}$, where C_{test} is the 24-hour postdose lithium concentration for a 600-mg lithium carbonate dose.[10] Perry and associates have suggested a similar nomogram that employs a larger test dose of 1200-mg lithium carbonate.[4,34,35] An important requirement for these methods is an accurate lithium assay that can reproducibly measure the lithium concentrations that occur after a single dose of the drug. Additionally, at the time the lithium carbonate test dose is given, the lithium serum concentration in the patient must equal zero.

Example 7 LK is a 47-year-old, 65-kg (5 ft 5 in) female with bipolar disease. She is not currently experiencing an episode of acute mania. Her serum creatinine is 0.9 mg/dL. Compute an oral lithium dose for this patient during maintenance therapy using the Cooper nomogram.

1. *Administer 600-mg lithium carbonate test dose and measure 24-hour postdose lithium concentration. Use nomogram to recommend lithium carbonate maintenance dose.*

After the test dose was given, the 24-hour lithium concentration was 0.12 mmol/L. The recommended lithium carbonate maintenance dose is 600 mg three times daily. The doses would be given at 0900 H, 1500 H, and 2100 H to allow a 12-hour window after the evening dose so that lithium serum concentration measurements can be made.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

PERRY METHOD

This technique conducts a small pharmacokinetic experiment in a patient after the administration of a lithium carbonate test dose.[36] First, a test dose (600–1500 mg) of lithium carbonate is given to the patient. Then, lithium serum concentrations are measured 12 and 36 hours after the test dose was given. The two lithium concentrations are used to compute the elimination rate constant for the individual: $k_e = (\ln C_{12h} - \ln C_{36h})/\Delta t$, where k_e is the elimination rate constant in h^{-1} for lithium, C_{12h} and C_{36h} are the lithium concentrations in mmol/L (or mEq/L) at 12 and 36 hours, respectively, after the test dose was given and Δt is the difference between times (24 hours) that the two serum concentrations were obtained. With knowledge of the elimination rate constant (k_e), the accumulation ratio (R) can be computed for any dosage interval: $R = 1/(1 - e^{-k_e\tau})$, where τ is the dosage interval in hours. The accumulation ratio (R) is also equal to the ratio of the concentration at any time, t, after a single dose ($C_{SD,t}$ in mmol/L) and the steady-state concentration at that same time after the dose during multiple dosing ($C_{ss,t}$ in mmol/L): $R = C_{ss,t}/C_{SD,t}$ or $C_{ss,t} = R \cdot C_{SD,t}$. Once a steady-state concentration can be computed for a dosage regimen, linear pharmacokinetic principles can be used to compute the dose required to achieve a target lithium steady-state serum concentration: $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired

steady-state concentration. As with the Cooper nomogram, the lithium serum concentration must be zero before the test dose is administered.

Example 8 HG is a 32-year-old, 58-kg (5 ft 1 in) female with bipolar disease. She is not currently experiencing an episode of acute mania. Her serum creatinine is 0.9 mg/dL. A single test dose of lithium (1200 mg) was given to the patient, and lithium concentrations were measured as 0.6 mmol/L and 0.3 mmol/L at 12 hours and 36 hours, respectively, after the drug was given. Compute an oral lithium dose for this patient, which will produce a steady-state serum concentration of 0.8 mmol/L using the Perry method.

1. *Administer lithium carbonate test dose and measure 12 and 36 hours postdose lithium concentrations. Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = (\ln C_{12h} - \ln C_{36h})/\Delta t = [\ln (0.6 \text{ mmol/L}) - \ln (0.3 \text{ mmol/L})]/24 \text{ h} = 0.0289 \text{ h}^{-1}$. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0289\text{h}^{-1})(12\text{h})}] = 3.4$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady-state lithium concentration for 1200 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 3.4 \cdot 0.6 \text{ mmol/L} = 2.0 \text{ mmol/L}$. Linear pharmacokinetic principles can be used to compute the dose required to achieve the target lithium steady-state serum concentration: $D_{new} = (0.8 \text{ mmol/L} / 2 \text{ mmol/L})1200 \text{ mg} = 480 \text{ mg}$, rounded to 450 mg every 12 hours of lithium carbonate.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

REPEATED ONE-POINT OR RITSCHEL METHOD

The method to individualize lithium dose proposed by Ritschel and associates utilizes another way to compute the elimination rate constant for a patient.[37,38] In this case, two equal lithium doses are administered apart from each other by the desired dosage interval (usually 12 hours). A single serum concentration is obtained before the second test dose is given and another is gathered after the second dose is given at a time equaling the anticipated dosage interval. These are used to compute the elimination rate constant (k_e in h^{-1}) for the patient: $k_e = \{\ln [C_1/(C_2 - C_1)]\} / \tau$, where C_1 is the lithium concentration in mmol/L obtained after the first test dose, C_2 is the lithium concentration in mmol/L obtained after the second test dose, and τ is the expected dosage interval in hours for lithium dosing and is also the postdose time at which the lithium concentrations were obtained.

With knowledge of the elimination rate constant (k_e), the accumulation ratio (R) can be computed for the dosage interval: $R = 1/(1 - e^{-k_e\tau})$, where τ is the dosage interval in hours.

The accumulation ratio (R) is also equal to the ratio of the concentration at any time, t, after a single dose ($C_{SD,t}$ in mmol/L) and the steady-state concentration at that same time after the dose is administered as multiple doses ($C_{ss,t}$ in mmol/L): $R = C_{ss,t}/C_{SD,t}$ or $C_{ss,t} = R \cdot C_{SD,t}$. Once a steady-state concentration can be computed for a dosage regimen, linear pharmacokinetic principles can be used to compute the dose required to achieve a target lithium steady-state serum concentration: $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state peak or trough concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. As with the Cooper and Perry methods, the lithium serum concentration must be zero before the test dose is administered.

Example 9 CB is a 27-year-old, 75-kg (6 ft 2 in) male with bipolar disease. He is currently experiencing an episode of acute mania. His serum creatinine is 1.0 mg/dL. Two test doses of lithium (600 mg each, 12 hours apart) were given to the patient, and lithium concentrations were measured as 0.3 mmol/L and 0.5 mmol/L 12 hours after the first and second doses, respectively. Compute an oral lithium dose for this patient to produce a steady-state serum concentration of 1.2 mmol/L using the Ritschel repeated one-point method.

1. *Administer lithium carbonate test doses and measure lithium concentrations. Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = \{\ln [C_1/(C_2 - C_1)]\} / \tau, = \ln [(0.3 \text{ mmol/L}) / (0.5 \text{ mmol/L} - 0.3 \text{ mmol/L})] / 12 \text{ h} = 0.0338 \text{ h}^{-1}$. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0338\text{h}^{-1})(12\text{h})}] = 3.0$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady-state lithium concentration for 600 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 3.0 \cdot 0.3 \text{ mmol/L} = 0.9 \text{ mmol/L}$. Linear pharmacokinetic principles can be used to compute the dose required to achieve the target lithium steady-state serum concentration: $D_{new} = (1.2 \text{ mmol/L} / 0.9 \text{ mmol/L})600 \text{ mg} = 800 \text{ mg}$, rounded to 900 mg every 12 hours of lithium carbonate.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

USE OF LITHIUM SERUM CONCENTRATIONS TO ALTER DOSAGES

Because of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce lithium serum concentrations that are expected. Because of this, lithium serum concentrations are measured in all

patients to ensure that therapeutic, nontoxic levels are present. Additionally, important patient parameters should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When lithium serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change lithium doses since this drug follows *linear pharmacokinetics*.

Also, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult cases where renal function is changing, serum concentrations are obtained at suboptimal times, or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because lithium follows linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state peak or trough concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The principle disadvantage is steady-state concentrations are required.

Example 10 YC is a 37-year-old, 55-kg (5 ft 1 in) female with bipolar disease. She is currently not experiencing an episode of acute mania and requires prophylactic treatment with lithium. Her serum creatinine is 0.6 mg/dL. The patient is receiving 900 mg of lithium carbonate at 0800 H, 1400 H, and 2000 H, and her 12-hour postdose steady-state lithium serum concentration equals 1.1 mmol/L. Compute a new lithium dose to achieve a steady-state concentration of 0.6 mmol/L.

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose (2700 mg/d) that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (0.6 \text{ mmol/L} / 1.1 \text{ mmol/L})\ 2700 \text{ mg/d}$$
$$= 1473 \text{ mg/d, round to } 1500 \text{ mg/d}$$

The patient would be administered 600 mg of lithium carbonate at 0800 H and 2000 H, and 300 mg of lithium carbonate at 1400 H.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients.[16] The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, renal function, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall.[39]

For comparison purposes, three cases presented previously using other dosage methods are managed using a Bayesian pharmacokinetic computer program.

Example 11 YC is a 37-year-old, 55-kg (5 ft 1 in) female with bipolar disease. She is currently not experiencing an episode of acute mania and requires prophylactic treatment with lithium. Her serum creatinine is 0.6 mg/dL. The patient is receiving 900 mg of lithium carbonate at 0800 H, 1400 H, and 2000 H, and her steady-state lithium serum concentration equals 1.1 mmol/L. Compute a new lithium dose to achieve a steady-state concentration of 0.6 mmol/L.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. 900 mg of lithium carbonate provides 24.4 mmol of lithium ion: 900 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 24.4 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 38 L, a half-life equal to 17.9 hours, and a clearance equal to 1.48 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 13 mmol Li^+ every 12 hours will produce a steady-state concentration of 0.6 mmol/L. This dose is equivalent to 480 mg of lithium carbonate [13 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 480 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 450 mg of lithium carbonate would be given every 12 hours.

Example 12 LK is a 47-year-old, 65-kg (5 ft 5 in) female with bipolar disease. She is not currently experiencing an episode of acute mania. Her serum creatinine is 0.9 mg/dL. After the test dose of 600 mg lithium carbonate was given, the 24 h lithium concentration was 0.12 mmol/L. Compute an oral lithium dose for this patient for maintenance therapy that would achieve a steady-state concentration equal to 0.6 mmol/L.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. 600 mg of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 16.2 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 77 L, a half-life equal to 38 hours, and a clearance equal to 1.42 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 10 mmol Li^+ every 8 hours will produce a steady-state concentration of 0.8 mmol/L. This dose is equivalent to 369 mg of lithium carbonate [10 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 369 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 300 mg of lithium carbonate would be given three times daily at 0800 H, 1400 H, and 2000 H to provide a 12-hour window for serum concentration monitoring after the evening dose.

Example 13 CB is a 27-year-old, 75-kg (6 ft 2 in) male with bipolar disease. He is currently experiencing an episode of acute mania. His serum creatinine is 1.0 mg/dL.

Two test doses of lithium (600 mg each) were given to the patient at 0800 H and 2000 H, and lithium concentrations were measured as 0.3 mmol/L and 0.5 mmol/L 12 hours after the first and second doses, respectively. Compute an oral lithium dose for this patient to produce a steady-state serum concentration of 1.2 mmol/L.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. 600 mg of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 16.2 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 38 L, a half-life equal to 19.2 hours, and a clearance equal to 1.37 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 22 mmol Li^+ every 12 hours will produce a steady-state concentration of 1.2 mmol/L. This dose is equivalent to 813 mg of lithium carbonate [22 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 813 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 900 mg of lithium carbonate would be given every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 17-2.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current therapy is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with lithium exists.

TABLE 17-2 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/equations	Pharmacokinetic dosing method	Linear pharmacokinetics method
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics method
Test dose	Cooper nomogram or Perry method or Repeated one-point method	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

1. PG is a 67-year-old, 72-kg (6 ft 1 in, serum creatinine = 1.2 mg/dL) male with bipolar disease requiring maintenance therapy with oral lithium. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state lithium concentration equal to 0.6 mmol/L.

2. Patient PG (please see problem 1) was prescribed lithium carbonate 900 mg orally every 12 hours. The current 12-hour postdose steady-state lithium concentration equals 1.0 mmol/L. Compute a new lithium carbonate dose that will provide a steady-state concentration of 0.6 mmol/L.

3. DU is a 21-year-old, 70-kg (5 ft 9 in, serum creatinine = 0.8 mg/dL) female with bipolar disease who requires therapy with lithium. She is currently experiencing an episode of acute mania. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state lithium concentration equal to 0.8 mmol/L.

4. Patient DU (please see problem 3) was prescribed lithium carbonate 600 mg orally at 0800 H, 1400 H, and 2000 H. The current 12-hour postdose steady-state lithium concentration equals 0.6 mmol/L. Compute a new oral lithium dose that will provide a steady-state concentration of 1 mmol/L.

5. JH is a 35-year-old, 60-kg (5 ft 2 in, serum creatinine = 0.8 mg/dL) female with bipolar disease requiring maintenance treatment with lithium. She was administered a test dose of lithium carbonate 600 mg, and the 24-hour postdose lithium concentration is 0.07 mmol/L. Suggest an initial lithium dosage regimen designed to achieve a steady-state concentration equal to 0.8 mmol/L.

6. Patient JH (please see problem 5) was prescribed lithium carbonate 600 mg orally every 12 hours starting 12 hours after the concentration for the test dose was measured. A lithium serum concentration was obtained just before the tenth dose of this regimen and equaled 0.4 mmol/L. Compute a new oral lithium carbonate dose that will provide a steady-state concentration of 0.6 mmol/L.

7. PZ is a 24-year-old, 80-kg (5 ft 11 in, serum creatinine = 1.1 mg/dL) male in the acute manic phase of bipolar disease who requires therapy with oral lithium. He was

administered a test dose of lithium carbonate 600 mg at 0800 H, and the 24-hour postdose lithium concentration is 0.21 mmol/L. Suggest an initial lithium dosage regimen designed to achieve a steady-state concentration equal to 0.8 mmol/L.

8. Patient PZ (please see problem 7) was prescribed lithium carbonate 600 mg orally at 0800 H, 1400 H, and 2000 H (first dose at 1400 H on the same day the lithium test dose concentration was obtained.) A lithium serum concentration was obtained just before the twelfth dose of this regimen and equaled 1.5 mmol/L. Compute a new lithium carbonate dose that will provide a steady-state concentration of 1 mmol/L.

9. WG is a 41-year-old, 130-kg (5 ft 11 in, serum creatinine = 1.2 mg/dL) male in the acute phase of bipolar disease that requires treatment with lithium carbonate. He was given a test dose of lithium carbonate 1200 mg at 0800 H, and lithium concentrations were obtained 12- and 36-hour postdose. The lithium concentrations were 0.42 mmol/L and 0.28 mmol/L. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state concentration equal to 1 mmol/L.

10. FY is a 32-year-old, 68-kg (5 ft 4 in, serum creatinine = 0.9 mg/dL) female with bipolar disease that requires maintenance treatment with lithium carbonate. She was given a test dose of lithium carbonate 900 mg at 0800 H, and lithium concentrations were obtained 12 and 36 hours postdose. The lithium concentrations were 0.3 mmol/L and 0.11 mmol/L. Suggest an initial lithium carbonate dosage regimen designed to achieve a steady-state concentration equal to 1.0 mmol/L.

11. MW is a 22-year-old, 81-kg (6 ft 2 in) male with bipolar disease. He is currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Two test doses of lithium (900 mg each, 12 hours apart) were given to the patient, and lithium concentrations were measured as 0.19 mmol/L and 0.31 mmol/L 12 hours after the first and second doses, respectively. Compute an oral lithium dose for this patient, which will produce a steady-state serum concentration of 1 mmol/L.

12. YT is a 42-year-old, 66-kg (5 ft 0 in) female with bipolar disease. She requires prophylactic treatment for bipolar disease. Her serum creatinine is 1.4 mg/dL. Two test doses of lithium (300 mg each, 12 hours apart) were given to the patient, and lithium concentrations were measured as 0.11 mmol/L and 0.2 mmol/L 12 hours after the first and second doses, respectively. Compute an oral lithium dose for this patient, which will produce a steady-state serum concentration of 0.6 mmol/L.

ANSWERS TO PROBLEMS

1. *Solution to problem 1.*

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 67\ y)72\ kg] / (72 \cdot 1.2\ mg/dL)$$
$$CrCl_{est} = 61\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the lithium clearance for this patient:

$$Cl = 0.288(CrCl) = 0.288(61\ mL/min) = 17.6\ L/d$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L. A serum concentration equal to 0.6 mmol/L will be chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F = (0.6\ mmol/L \cdot 17.6\ L/d) / 1 = 10.6\ mmol/d$$

D/τ = (300 mg lithium carbonate/8.12 mmol Li^+) 10.6 mmol/d = 392 mg/d, rounded to 450 mg/d of lithium carbonate. This dose would be given as 150 mg of lithium carbonate in the morning and 300 mg of lithium carbonate in the evening.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Literature-Based Recommended Dosing

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW]/(72 \cdot S_{Cr}) = [(140 - 67\ y)72\ kg]/(72 \cdot 1.2\ mg/dL)$$
$$CrCl_{est} = 61\ mL/min$$

2. *Choose lithium dose based on disease states and conditions present in the patient.*

The patient requires prophylactic lithium therapy for bipolar disease, and has good renal function. A lithium carbonate dose of 600 mg/d, given as 300 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

2. *Solution to problem 2.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose (1800 mg/d) that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (0.6\ mmol/L / 1.0\ mmol/L)\ 1800\ mg/d$$
$$= 1080\ mg/d, \text{ round to } 900\ mg/d$$

The patient would be administered 450 mg of lithium carbonate every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

3. *Solution to problem 3.*

Pharmacokinetic Dosing Method

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW]/(72 \cdot S_{Cr})\} \cdot 0.85 \\ &= \{[(140 - 21\ y)70\ kg]/(72 \cdot 0.8\ mg/dL)\} \cdot 0.85 \\ CrCl_{est} &= 123\ mL/min \end{aligned}$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship for a patient with acute mania is used to estimate the lithium clearance for this patient:

$$Cl = 0.432(CrCl) = 0.432(123\ mL/min) = 53.1\ L/d$$

3. *Use average steady-state concentration equation to compute lithium maintenance dose.*

For a patient requiring therapy for the acute mania phase of bipolar disease the desired lithium concentration would be 0.8–1 mmol/L. A serum concentration equal to 0.8 mmol/L was chosen for this patient, and oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+/300 mg of lithium carbonate).

$$D/\tau = (Css \cdot Cl) / F = (0.8\ mmol/L \cdot 53.1\ L/d) / 1 = 42.5\ mmol/d$$

D/τ = (300 mg lithium carbonate/8.12 mmol Li^+) 42.5 mmol/d = 1570 mg/d, rounded to 1500 mg/d of lithium carbonate. This dose would be given as 600 mg of lithium carbonate at 0800 H and 2000 H and 300 mg of lithium carbonate at 1400 H.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Literature-Based Recommended Dosing

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$\begin{aligned} CrCl_{est} &= \{[(140 - age)BW]/(72 \cdot S_{Cr})\} \cdot 0.85 \\ &= \{[(140 - 21\ y)70\ kg]/(72 \cdot 0.8\ mg/dL)\} \cdot 0.85 \\ CrCl_{est} &= 123\ mL/min \end{aligned}$$

2. *Choose lithium dose based on disease states and conditions present in the patient.*

The patient requires acute lithium therapy for the treatment of the acute manic phase of bipolar disease, and has good renal function. A lithium carbonate dose of 1200 mg/d, given as 600 mg every 12 hours, is recommended as the initial amount. The dosage rate will be increased 300–600 mg/d every 2–3 days as needed to provide adequate therapeutic effect, avoid adverse effects, and produce therapeutic lithium steady-state concentrations.

4. *Solution to problem 4.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose (1800 mg/d) that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (1 \text{ mmol/L} / 0.6 \text{ mmol/L})\ 1800 \text{ mg/d}$$
$$= 3000 \text{ mg/d, round to } 2700 \text{ mg/d}$$

The patient would be administered 900 mg of lithium carbonate at 0800 H, 1400 H, and 2000 H.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

5. *Solution to problem 5.*

Cooper Nomogram

1. *Administer 600-mg lithium carbonate test dose and measure 24-hour postdose lithium concentration. Use Cooper nomogram to recommend lithium carbonate maintenance dose.*

After the test dose was given, the 24-hour postdose lithium concentration was 0.07 mmol/L. The recommended lithium carbonate maintenance dose is 900 mg three times daily. The doses would be given at 0900 H, 1500 H, and 2100 H to allow a 12-hour window after the evening dose so that lithium serum concentration measurements can be made.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Six hundred milligrams of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/ 300 mg lithium carbonate) = 16.2 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 99 L, a half-life equal to 27 hours, and a clearance equal to 2.53 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 34 mmol Li^+ every 12 hours will produce a steady-state concentration of 0.8 mmol/L. This dose is equivalent to 1256 mg of lithium carbonate [34 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 1256 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 1200 mg of lithium carbonate would be given every 12 hours.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

6. *Solution to problem 6.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose (1200 mg/d) that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (0.6 \text{ mmol/L} / 0.4 \text{ mmol/L})\ 1200 \text{ mg/d} = 1800 \text{ mg/d}$$

The patient would be administered 900 mg of lithium carbonate every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Six hundred milligrams of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 16.2 mmol Li^+. In this case, the concentration

after the test dose (problem 5) as well as the concentration just before the 10th dose can be used in the program.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 112 L, a half-life equal to 35 hours, and a clearance equal to 2.22 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 21 mmol Li^+ every 12 hours will produce a steady-state concentration of 0.8 mmol/L. This dose is equivalent to 776 mg of lithium carbonate [21 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 776 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 750 mg of lithium carbonate would be given every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

7. *Solution to problem 7.*

Cooper Nomogram

1. *Administer 600-mg lithium carbonate test dose and measure 24-hour postdose lithium concentration. Use Cooper nomogram to recommend lithium carbonate maintenance dose.*

After the test dose was given, the 24-hour lithium concentration was 0.21 mmol/L. The recommended lithium carbonate maintenance dose is 300 mg three times daily. The doses would be given at 0900 H, 1500 H, and 2100 H to allow a 12-hour window after the evening dose so that lithium serum concentration measurements can be made.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Six hundred milligrams of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 16.2 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 44 L, a half-life equal to 25 hours, and a clearance equal to 1.2 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 8 mmol Li^+ every 8 hours will produce a steady-state concentration of 0.8 mmol/L. This dose is equivalent to 296 mg of lithium carbonate [8 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 296 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 300 mg of lithium carbonate would be given at 0900 H, 1500 H, and 2100 H to allow a 12 hours window after the evening dose so that lithium serum concentration measurements can be made.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

8. *Solution to problem 8.*

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose (1800 mg/d) that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (1 \text{ mmol/L} / 1.5 \text{ mmol/L})\ 1800 \text{ mg/d} = 1200 \text{ mg/d}$$

The patient would be administered 600 mg of lithium carbonate every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Six hundred milligrams of lithium carbonate provides 16.2 mmol of lithium ion: 600 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 16.2 mmol Li^+. In this case, the concentration after the test dose (problem 7) as well as the concentration just before the twelfth dose can be used in the program.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 44 L, a half-life equal to 25 hours, and a clearance equal to 1.2 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 16 mmol Li^+ every 12 hours will produce a steady-state concentration of 1 mmol/L. This dose is equivalent to 591 mg of lithium carbonate [16 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 591 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 600 mg of lithium carbonate would be given every 12 hours.

When lithium dosage alterations are needed, lithium serum concentrations should be measured within 1–2 weeks after the change. During lithium maintenance therapy, steady-state lithium serum concentrations should be repeated every 3–6 months. This time period should be altered to every 6–12 months for patients whose mood is stable or every 1–2 months for patients with frequent mood alterations.

9. *Solution to problem 9.*

Perry Method

1. *Administer lithium carbonate test dose and measure 12 and 36 hours postdose lithium concentrations. Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = (\ln C_{12h} - \ln C_{36h})/\Delta t = [\ln (0.42 \text{ mmol/L}) - \ln (0.28 \text{ mmol/L})]/24 \text{ h} = 0.0169 \text{ h}^{-1}$. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0169\text{h}^{-1})(12\text{h})}] = 5.4$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady-state lithium concentration for 1200 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 5.4 \cdot 0.42 \text{ mmol/L} = 2.3 \text{ mmol/L}$. Linear pharmacokinetic principles can be used to compute the dose required to achieve the target lithium steady-state serum concentration: $D_{new} = (1 \text{ mmol/L} / 2.3 \text{ mmol/L})1200 \text{ mg} = 522 \text{ mg}$, rounded to 600 mg every 12 hours of lithium carbonate.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Twelve hundred milligrams of lithium carbonate provides 32.5 mmol of lithium ion: 1200 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 32.5 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 67 L, a half-life equal to 41 hours, and a clearance equal to 1.13 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 14 mmol Li^+ every 12 hours will produce a steady-state concentration of 1 mmol/L. This dose is equivalent to 517 mg of lithium carbonate [14 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 517 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 600 mg of lithium carbonate would be given every 12 hours.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

10. *Solution to problem 10.*

Perry Method

1. *Administer lithium carbonate test dose and measure 12 and 36 hours postdose lithium concentrations. Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = (\ln C_{12h} - \ln C_{36h})/\Delta t = [\ln (0.3 \text{ mmol/L}) - \ln (0.11 \text{ mmol/L})] / 24 \text{ h} = 0.0418 \text{ h}^{-1}$. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0418\text{h}^{-1})(12\text{h})}] = 2.5$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady state lithium concentration for 900 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 2.5 \cdot 0.3$ mmol/L = 0.75 mmol/L. Linear pharmacokinetic principles can be used to compute the dose required to achieve the target lithium steady-state serum concentration: D_{new} = (1 mmol/L / 0.75 mmol/L)900 mg = 1200 mg every 12 hours of lithium carbonate.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Nine hundred milligrams of lithium carbonate provides 24.4 mmol of lithium ion: 900 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 24.4 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 47 L, a half-life equal to 17 hours, and a clearance equal to 1.94 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 31-mmol Li^+ every 12 hours will produce a steady-state concentration of 1 mmol/L. This dose is equivalent to 1145 mg of lithium carbonate [31 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 1145 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 1200 mg of lithium carbonate would be given every 12 hours.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

11. *Solution to problem 11.*

Ritschel Method

1. *Administer lithium carbonate test doses and measure lithium concentrations . Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = \{\ln [C_1/(C_2 - C_1)]\}/\tau$, $= \ln [(0.19 \text{ mmol/L})/(0.31 \text{ mmol/L} - 0.19 \text{ mmol/L})]/12 \text{ h} = 0.0383 \text{ h}^{-1}$. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0383\text{h}^{-1})(12\text{h})}] = 2.7$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady-state lithium concentration for 900 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 2.7 \cdot 0.19$ mmol/L = 0.5 mmol/L. Linear pharmacokinetic principles can be used to compute the dose required to achieve the target lithium steady-state serum concentration: D_{new} = (1 mmol/L / 0.5 mmol/L) 900 mg = 1800 mg every 12 hours of lithium carbonate. Because the dose exceeds 1200 mg per administration time, the total daily dose of 3600 mg/d would be split into 3 equal doses of 1200 mg and given at 0900 H, 1500 H, and 2100 H.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Nine hundred milligrams of lithium carbonate provides 24.4 mmol of lithium ion: 900 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 24.4 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 79 L, a half-life equal to 19 hours, and a clearance equal to 2.89 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 27 mmol Li^+ every 8 hours will produce a steady-state concentration of 1 mmol/L. This dose is equivalent to 998 mg of lithium carbonate [27 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 998 mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 900 mg of lithium carbonate would be given at 0900 H, 1500 H, and 2100 H.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

12. *Solution to problem 12.*

Ritschel Method

1. *Administer lithium carbonate test doses and measure lithium concentrations. Compute the lithium elimination rate constant and accumulation ratio for the patient.*

The lithium elimination rate constant is computed using the two serum concentrations: $k_e = \{\ln [C_1/(C_2 - C_1)]\} / \tau$, = ln [(0.11 mmol/L)/(0.2 mmol/L – 0.11 mmol/L)] / 12 h = 0.0167 h^{-1}. The lithium accumulation ratio is computed using the elimination rate constant and desired lithium dosage interval of 12 h: $R = 1/(1 - e^{-k_e\tau}) = 1/[1 - e^{-(0.0167h^{-1})(12h)}] = 5.5$.

2. *Compute the estimated lithium concentration at steady state for the test dose that was given. Use this relationship to compute the dosage regimen for the patient.*

Using the lithium concentration at 12 hours, the steady-state lithium concentration for 300 mg every 12 hours can be computed: $C_{ss,t} = R \cdot C_{SD,t} = 5.5 \cdot 0.11$ mmol/L = 0.6 mmol/L. This is the desired steady-state concentration, so 300 mg every 12 hours of lithium carbonate would be prescribed.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized. Because patients with acute mania can have increased lithium clearance, lithium concentrations should be remeasured in these patients once the manic episode is over and clearance returns to normal.

Bayesian Pharmacokinetic Computer Program

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

Lithium doses must be entered into DrugCalc as millimoles of lithium ion. Three hundred milligrams of lithium carbonate provides 8.12 mmol of lithium ion: 300 mg (8.12 mmol Li^+/300 mg lithium carbonate) = 8.12 mmol Li^+.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 61 L, a half-life equal to 65 hours, and a clearance equal to 0.65 L/h.

3. *Compute dose required to achieve desired lithium serum concentrations.*

The one-compartment first-order absorption equations used by the program to compute doses indicates that a dose of 5 mmol Li^+ every 12 hours will produce a steady-state concentration of 0.6 mmol/L. This dose is equivalent to 185 mg of lithium carbonate [5 mmol (300 mg lithium carbonate/8.12 mmol Li^+) = 185-mg lithium carbonate]. Rounding this dose to an amount available as an oral dosage form, 150 mg of lithium carbonate would be given every 12 hours. Because of the long lithium half-life for this patient, a dose of 300 mg every day could also be prescribed.

Upon initiation of therapy, serum concentrations can be measured every 2–3 days for safety reasons in patients that are predisposed to lithium toxicity even though steady state has not yet been achieved. Once the desired steady-state lithium concentration has been achieved, lithium concentrations should be rechecked every 1–2 weeks for approximately 2 months or until concentrations have stabilized.

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18

THEOPHYLLINE

INTRODUCTION

Theophylline is a methylxanthine compound that is used for the treatment of asthma, chronic obstructive pulmonary disease (COPD; chronic bronchitis and emphysema), and premature apnea. The bronchodilatory effects of theophylline are useful primarily for patients with asthma because bronchospasm is a key component of that disease state.[1] The use of theophylline in patients with chronic obstructive pulmonary disease is more controversial because these diseases have different pathophysiologic profiles, although some patients do exhibit a mixed disease profile with a limited reversible airway component. Even COPD patients without significant bronchospasm demonstrate clinical improvement when taking theophylline.[2–4] Theophylline is also a central nervous system stimulant which explains its usefulness in the treatment of premature apnea.

In the chronic management of asthma or chronic obstructive pulmonary disease patients, theophylline is now considered to be adjunctive therapy.[5–8] Asthma is now recognized as an inflammatory disease, and inhaled corticosteroids are considered the mainstay of therapy.[8] Inhaled selective β_2-agonists are used as bronchodilators in asthmatic patients. Other drugs that are useful in patients with asthma are cromolyn, nedocromil, oral corticosteroids, inhaled anticholinergics, and leukotriene modifiers. Inhaled bronchodilators are the preferred treatment for COPD patients with selective β_2-agonists or anticholinergics considered first line agents.[6] Theophylline is considered for use in asthmatic patients and chronic obstructive pulmonary disease patients after their respective therapies have commenced. Theophylline is also useful in these patients when they are unable or unwilling to use multiple metered dose inhaler (MDI) devices or if an intravenous drug is needed. For the treatment of premature apnea, most clinicians prefer to use caffeine, a related methylxanthine agent, instead of theophylline because of smoother apnea control and reduced adverse effects.

The bronchodilatory response via smooth muscle relaxation in the lung to theophylline is postulated to occur by several mechanisms.[9] Of these, the two predominate mechanisms of action are inhibition of cyclic nucleotide phosphodiesterases which increases intracellular

cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and antagonism of adenosine receptors. In addition to bronchodilation, theophylline increases diaphragmatic contractility, increases mucociliary clearance, and exerts some antiinflammatory effects. Theophylline is a general central nervous system stimulant and specifically stimulates the medullary respiratory center. These are the reasons why it is a useful agent in the treatment of premature apnea.

THERAPEUTIC AND TOXIC CONCENTRATIONS

The generally accepted therapeutic ranges for theophylline are 10–20 μg/mL for the treatment of asthma or COPD, or 6–13 μg/mL for the treatment of premature apnea. Clinical guidelines suggest that for initial treatment of pulmonary disease, clinical response to theophylline concentrations between 5–15 μg/mL should be assessed before higher concentrations are used.[5,7] Many patients requiring chronic theophylline therapy will derive sufficient bronchodilatory response with a low likelihood of adverse effects at concentrations of 8–12 μg/mL. However, theophylline therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

In the upper end of the therapeutic range (>15 μg/mL) some patients will experience minor caffeine-like side effects owing to theophylline treatment.[1] These adverse effects include nausea, vomiting, dyspepsia, insomnia, nervousness, and headache. Theophylline concentrations exceeding 20–30 μg/mL can cause various tachyarrhythmias including sinus tachycardia. At theophylline concentrations above 40 μg/mL, serious life-threatening adverse effects including ventricular arrhythmias (premature ventricular contractions, ventricular tachycardia or fibrillation) or seizures can occur. Theophylline-induced seizures are an ominous sign as they respond poorly to antiepileptic therapy and can result in post-seizure neurologic sequelae or death. Unfortunately, minor side effects do not always occur before severe, life-threatening adverse effects are manifested. Also, seizures caused by theophylline therapy have been reported to occur in patients at theophylline concentrations as low as 25 μg/mL. Because of these reasons, serum concentration monitoring is mandatory for patients receiving theophylline. Clinicians should understand that all patients with "toxic" theophylline serum concentrations in the listed ranges will not exhibit signs or symptoms of theophylline toxicity. Rather, theophylline concentrations in the ranges given increase the likelihood that an adverse effect will occur.

CLINICAL MONITORING PARAMETERS

Measurement of pulmonary function tests are an important component of assessing response to bronchodilator therapy in patients with asthma or chronic obstructive pulmonary disease.[6,8] Forced expiratory volume over 1 second (FEV_1) should be measured on a regular basis for asthmatic patients, and peak-flow meter monitoring can be routinely performed by these individuals at home. Successful bronchodilator therapy will increase both of these values. In addition to the use of FEV_1 to monitor bronchodilator drug effect, other spirometric tests useful for patients with COPD include vital capacity (VC), total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory

flow over the middle 50% of the expiratory curve ($FEF_{25-75\%}$ or $FEF_{50\%}$). Patients should also be monitored for clinical signs and symptoms of their disease states including frequency and severity of following events: dyspnea, coughing, wheezing, impairment of normal activity. During acute exacerbations or in severe cases of either pulmonary disease state, arterial blood gases may be determined and used as a monitoring parameter. When theophylline is used to treat premature infants with apnea, the frequency of apneic events is monitored as a measure of therapeutic effect.

Theophylline serum concentration monitoring is mandatory in patients receiving the drug. If a patient is experiencing clinical signs or symptoms that could be due to a theophylline adverse effect, a theophylline serum concentration should be obtained at that time to rule out drug-induced toxicity. For dose adjustment purposes, theophylline serum concentrations should be measured at steady state after the patient has received a consistent dosage regimen for 3–5 drug half-lives. Theophylline half-life varies from 3 to 5 hours in children and tobacco-smoking individuals to 50 hours or more in patients with severe heart or liver failure. If the theophylline is given as a continuous intravenous infusion, it can take a considerable amount of time for some patients to achieve effective concentrations so an intravenous loading dose is commonly administered to patients (Figure 18-1). The ideal situation is to administer an intravenous loading dose that will achieve the desired concentration immediately, then start an intravenous continuous infusion that will maintain that concentration (Figure 18-1). In order to derive this perfect situation, the theophylline volume of distribution (V in liters) would have to be known to compute the loading dose (LD in milligrams): $LD = Css \cdot V$, where Css is the desired theophylline concentration in milligrams per liter. However, this pharmacokinetic parameter is rarely, if ever, known for a patient, so a loading dose based on a population average volume of distribution is used to calculate the amount of theophylline needed. Since the patient's own, unique volume of distribution will most likely be greater (resulting in too low of a loading dose) or less (resulting in too large of a loading dose) than the population average volume of distribution used to compute the loading dose, the desired steady-state theophylline concentration will not be achieved. Because of this, it will still take 3–5 half-lives for the patient to reach steady-state conditions while receiving a constant intravenous

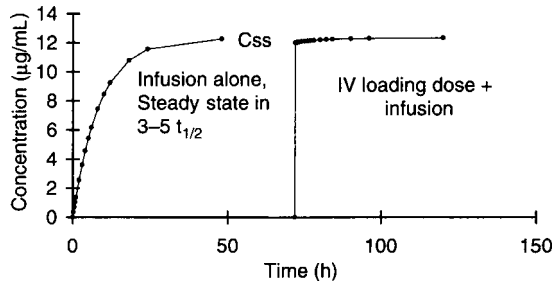

FIGURE 18-1 When intravenous theophylline or aminophylline is administered to a patient as a continuous infusion, it will take 3–5 half-lives for serum theophylline concentrations to reach steady-state levels. Because of this, maximal drug response will take time to achieve. To hasten onset of drug action, loading doses are given to attain effective theophylline concentrations immediately.

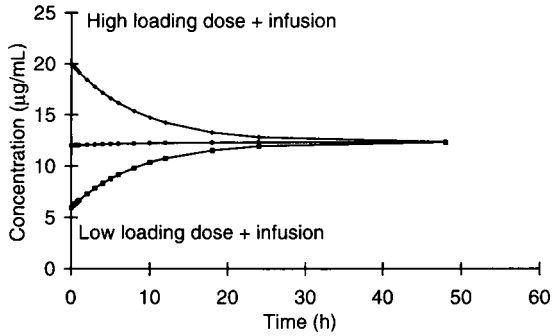

FIGURE 18-2 If the patient's own, unique theophylline volume of distribution (V) is known, the exact loading dose (LD) of intravenous theophylline or aminophylline to immediately achieve steady-state theophylline concentrations (Css) can be calculated (LD = Css · V). However, the volume of distribution for the patient is rarely known when loading doses need to be administered, and, for practical purposes, an average population volume of distribution for theophylline is used to estimate the parameter for the patient (V = 0.5 L/kg, use ideal body weight if >30% overweight). Because of this, the computed loading dose will almost always be too large or too small to reach the desired steady-state theophylline concentration, and it will still take 3–5 half-lives to attain steady-state conditions.

infusion rate (Figure 18-2). Thus, theophylline intravenous loading doses do not usually achieve steady-state serum concentrations immediately, but, hopefully, they do result in therapeutic concentrations and response sooner than simply starting an intravenous infusion alone. If oral theophylline-containing products are used to treat a patient, steady-state predose, or "trough," concentrations should be used to monitor therapy after the patient has received a stable dosage regimen for 3–5 half-lives.

After an efficacious theophylline dosage regimen has been established for a patient, theophylline serum concentrations remain fairly stable in patients receiving long-term therapy. In these cases, theophylline dosage requirements and steady-state serum concentrations should be reassessed on a yearly basis. In patients with congestive heart failure or liver cirrhosis, theophylline dosage requirements can vary greatly according to the status of the patient. For example, if a patient with compensated heart failure is receiving a stable dose of theophylline, but experiences an exacerbation of their heart disease, it is very likely that they will need to have their theophylline dosage requirements reassessed to avoid theophylline toxicity. Also, acute viral diseases, especially in children, have been associated with theophylline adverse effects in patients previously stabilized on effective, nontoxic theophylline dosage regimens.[10,11] Methods to adjust theophylline doses using serum concentrations are discussed later in this chapter.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Theophylline is primarily eliminated by hepatic metabolism (>90%). Hepatic metabolism is mainly via the CYP1A2 enzyme system with a smaller amount metabolized by CYP3A and CYP2E1. About 10% of a theophylline dose is recovered in the urine as unchanged

drug.[12,13] Strictly speaking, theophylline follows nonlinear pharmacokinetics.[14–16] However, for the purposes of clinical drug dosing in patients, linear pharmacokinetic concepts and equations can be effectively used to compute doses and estimate serum concentrations. Occasionally, theophylline serum concentrations increase in a patient more than expected after a dosage increase for an unidentifiable reason, and nonlinear pharmacokinetics may explain the observation.[14–16]

Three different forms of theophylline are available. Aminophylline is the ethylenediamine salt of theophylline, and anhydrous aminophylline contains about 85% theophylline while aminophylline dihydrate contains about 80% theophylline. Oxtriphylline is the choline salt of theophylline and contains about 65% theophylline. Theophylline and aminophylline are available for intravenous injection and oral use. Oxtriphylline is available only for oral use. The oral bioavailability of all three theophylline-based drugs is very good and generally equals 100%. However, some older sustained release oral dosage forms have been reported to exhibit incomplete bioavailability and loss of slow release characteristics under certain circumstances owing to their tablet or capsule design. Theophylline plasma protein binding is only 40%.[17,18]

The recommended dose of theophylline or one of its salt forms is based on the concurrent disease states and conditions present in the patient that can influence theophylline pharmacokinetics. Theophylline pharmacokinetic parameters used to compute doses are given in the following section for specific patient profiles.

EFFECTS OF DISEASE STATES AND CONDITIONS ON THEOPHYLLINE PHARMACOKINETICS AND DOSING

Normal adults without the disease states and conditions given later in this section with normal liver function have an average theophylline half-life of 8 hours (range: 6–12 hours) and volume of distribution of 0.5 L/kg (range: 0.4–0.6 L/kg; Table 18-1).[19–21] Most disease states and conditions that change theophylline pharmacokinetics and dosage requirements alter clearance but volume of distribution remains stable at ~0.5 L/kg in these situations. Tobacco and marijuana smoke causes induction of hepatic CYP1A2 which accelerates the clearance of theophylline.[19–24] In patients who smoke these substances, the average theophylline half-life is 5 hours. When patients stop smoking these compounds, theophylline clearance slowly approaches its baseline level for the patient over a 6- to 12-month period if the patient does not encounter "second-hand" smoke produced by other users.[25] If the patient inhales a sufficient amount of second-hand smoke, theophylline clearance for the ex-smoker may remain in the fully induced state or at some intermediate induced state.[26]

Patients with liver cirrhosis or acute hepatitis have reduced theophylline clearance which results in a prolonged average theophylline half-life of 24 hours.[20,27–29] However, the effect that liver disease has on theophylline pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with liver disease to have relatively normal or grossly abnormal theophylline clearance and half-life. For example, a liver disease patient who also smokes cigarettes could have a theophylline half-life equal to 5 hours if some liver parenchyma is present and tobacco-induced enzyme induction occurred, or 50 hours if little or no liver tissue remains. An index of liver dysfunction can

TABLE 18-1 Disease States and Conditions That Alter Theophylline Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal liver function	8 hours (range: 6–12 hours)	0.5 L/kg (range: 0.4–0.6 L/kg)	
Adult, tobacco or marijuana smoker	5 hours	0.5 L/kg	Tobacco and marijuana smoke induces CYP1A2 enzyme system and accelerates theophylline clearance.
Adult, hepatic disease (liver cirrhosis or acute hepatitis)	24 hours	0.5 L/kg	Theophylline is metabolized >90% by hepatic microsomal enzymes (primary: CYP1A2; secondary: CYP3A, CYP2E1), so loss of functional liver tissue decreases theophylline clearance. Pharmacokinetic parameters highly variable in liver disease patients.
Adult, mild heart failure (NYHA CHF classes I or II)	12 hours	0.5 L/kg	Decreased liver blood flow secondary to reduced cardiac output due to heart failure reduces theophylline clearance.
Adult, moderate-to-severe heart failure (NYHA CHF classes III or IV) or cor pulmonale	24 hours	0.5 L/kg	Moderate-to-severe heart failure reduces cardiac output even more than mild heart failure, resulting in large and variable reductions in theophylline clearance. Cardiac status must be monitored closely in heart failure patients receiving theophylline since theophylline clearance changes with acute changes in cardiac output.
Adult, obese (>30% over ideal body weight)	According to other disease states/ conditions that affect theophylline pharmacokinetics	0.5 L/kg IBW	Theophylline doses should be based on ideal body weight for patients who weigh more that 30% above IBW.

(*Continued*)

TABLE 18-1 (*Continued*)

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Children, 1–9 years, normal cardiac and hepatic function	3.5 h	0.5 L/kg	Children have increased theophylline clearance. When puberty is reached, adult doses can be used taking into account disease states and conditions that alter theophylline pharmacokinetics.
Elderly, >65 years	12 hours	0.5 L/kg	Elderly individuals with concurrent disease states/conditions known to alter theophylline clearance should be dosed using those specific recommendations.

Symbol key: IBW is ideal body weight, NYHA is New York Heart Association, CHF is congestive heart failure.

be gained by applying the Child-Pugh clinical classification system to the patient (Table 18-2). Child-Pugh scores are completely discussed in Chapter 3, but will be briefly discussed here. The Child-Pugh score consists of five laboratory tests or clinical symptoms: serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy. Each of these areas is given a score of 1 (normal) to 3 (severely abnormal; Table 18-2), and the scores for the five areas are summed. The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15. A Child-Pugh score greater than 8 is grounds for a decrease in the

TABLE 18-2 Child-Pugh Scores for Patients with Liver Disease[76]

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

initial daily drug dose for theophylline ($t_{1/2}$ = 24 hours). As in any patient with or without liver dysfunction, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Theophylline serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Heart failure causes reduced theophylline clearance because of decreased hepatic blood flow secondary to compromised cardiac output.[20,30–33] Venous stasis of blood within the liver may also contribute to the decrease in theophylline clearance found in heart failure patients. Patients with mild heart failure (New York Heart Association or NYHA Class I or II, Table 18-3) have an average theophylline half-life equal to 12 hours (range: 5–24 hours) while those with moderate to severe heart failure (NYHA class III or IV) or cor pulmonale have an average theophylline half-life of 24 hours (5–50 hours). Obviously, the effect that heart failure has on theophylline pharmacokinetics is highly variable and difficult to accurately predict. It is possible for a patient with heart failure to have relatively normal or grossly abnormal theophylline clearance and half-life. For heart failure patients, initial doses are meant as starting points for dosage titration based on patient response and avoidance of adverse effects. Theophylline serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with heart failure.

Obese patients (>30% above ideal body weight or IBW) should have volume of distribution estimates based on ideal body weight.[34–37] Theophylline half-life should be based on the concurrent disease states and conditions present in the patient. If weight-based dosage recommendations (mg/kg/d or mg/kg/h) are to be used, ideal body weight should be used to compute doses for obese individuals.

Patient age has an effect on theophylline clearance and half-life. Newborns have decreased theophylline clearance because hepatic drug–metabolizing enzymes are not yet fully developed at birth. Premature neonates have average theophylline half-lives equal to 30 hours 3–15 days after birth and 20 hours 25–57 days after birth.[38–40] Full term infants

TABLE 18-3 New York Heart Association (NYHA) Functional Classification for Heart Failure[77]

NYHA HEART FAILURE CLASS	DESCRIPTION
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitations of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

have average theophylline half-lives of 25 hours 1–2 days after birth, and 11 hours 3–30 weeks after birth.[41–43] Children between the ages of 1–9 years have accelerated theophylline clearance rates resulting in an average half-life of 3.5 hours (range: 1.5–5 hours).[44–46] As children achieve puberty, their theophylline clearance and half-life approach the values of an adult. For elderly patients over the age of 65, some studies indicate that theophylline clearance and half-life are the same as in younger adults while other investigations have found that theophylline clearance is slower and half-life is longer (average half-life = 12 hours, range: 8–16 hours).[47–51] A confounding factor found in theophylline pharmacokinetic studies conducted in older adults is the possible accidental inclusion of subjects that have subclinical or mild cases of the disease states associated with reduced theophylline clearance (heart failure, liver disease, etc.). Thus, the pharmacokinetics of theophylline in elderly individuals is somewhat controversial.

Febrile illnesses can temporarily decrease the clearance of theophylline and require an immediate dosage decrease to avoid toxicity.[10,11] The mechanism of this acute change in theophylline disposition is unclear, but probably involves decreased clearance as a result of the production of interleukins. Children seem to be at an especially high risk of theophylline adverse reactions since febrile illnesses are prevalent in this population and high theophylline doses (on a mg/kg/d basis) are prescribed.

Because only a small amount of theophylline is eliminated unchanged in the urine (<10% of a dose), dosage adjustments are not necessary in patients with renal impairment.[12,13] Theophylline is removed by hemodialysis, and, if possible, doses should be held until after the dialysis procedure is complete.[52–57] If a pulmonary exacerbation occurs owing to decreased theophylline concentrations, individualized supplemental doses of theophylline may need to be given during or after the procedure is complete. The hemoperfusion sieving coefficient for theophylline is 0.80, which indicates significant removal by these techniques.[58,59] Theophylline is not appreciably removed by peritoneal dialysis.[55]

Hypothyroid patients have decreased basal metabolic rates, and require smaller theophylline doses until a euthyroid condition is established.[60] The breast milk to serum ratio for theophylline is 0.7.[61]

DRUG INTERACTIONS

Drug interactions with theophylline are common and occur with a variety of medications.[62] Serious inhibition drug interactions are those that decrease theophylline clearance more than 30%. Clinicians should consider an arbitrary decrease in theophylline dose of 30–50% for patients receiving these agents until the actual degree of hepatic enzyme inhibition can be assessed using theophylline serum concentration monitoring. Patients should also be actively monitored for the signs and symptoms of theophylline toxicity. It should be emphasized that the magnitude of hepatic enzyme inhibition drug interactions is highly variable so some patients may require even larger theophylline dosage decreases while others will exhibit no drug interaction at all. Cimetidine given at higher doses (≥1000 mg/d) on a multiple daily dosage schedule decreases theophylline clearance by 30–50%. Other cimetidine doses (≤800 mg/d) given once or twice daily decrease theophylline clearance by 20% or less.[63,64] Ciprofloxacin and enoxacin, both quinolone antibiotics, and troleandomycin, a macrolide antibiotic, also decrease theophylline clearance by 30–50%. Estrogen and estrogen-containing

oral contraceptives, propranolol, metoprolol, mexiletine, propafenone, pentoxifylline, ticlopidine, tacrine, thiabendazole, disulfiram, nefazodone, interferon, zileuton, and fluvoxamine can also decrease theophylline clearance by this extent.

Moderate sized inhibition drug interactions are those that decrease theophylline clearance by 10–30%. For this magnitude of drug interaction, many clinicians believe that a routine decrease in theophylline dose is unnecessary for patients with steady-state theophylline concentrations below 15 μg/mL, but should be considered on a case-by-case basis for those with concentrations above this level. Should a decrease be warranted in a patient, theophylline doses can be cut by 20% to avoid adverse effects. Again, patients should be actively monitored for the signs and symptoms of theophylline toxicity. The calcium channel blockers, verapamil, and diltiazem, have been reported to cause decreases in theophylline clearance by 15–25%. Clarithromycin and erythromycin, both macrolide antibiotics, and norfloxacin, a quinolone antibiotic, can also decrease theophylline clearance by this magnitude. At doses of 600 mg/d or above, allopurinol has been reported to decrease theophylline clearance by 25%.

Theophylline elimination is also subject to induction of hepatic microsomal enzymes which increases theophylline clearance. Because hepatic microsomal enzyme induction is quite variable in patients, some individuals may require theophylline dosage increases while others will require no alteration in dosage requirements. Also, hepatic microsomal enzyme induction takes time to occur, and maximal effects may not be seen for 2–4 weeks of treatment with enzyme inducers. Patients treated with a drug that increases theophylline clearance need to be carefully monitored for the signs and symptoms of their respective disease state, and steady-state theophylline concentrations should be measured. Disease exacerbations may be caused by decreased theophylline concentrations, and a dosage increase may be warranted in some patients. Phenytoin, carbamazepine, phenobarbital, rifampin, and moricizine all increase theophylline clearance.

INITIAL DOSAGE DETERMINATION METHODS

Several methods to initiate theophylline therapy are available. The *pharmacokinetic dosing method* is the most flexible of the techniques. It allows individualized target serum concentrations to be chosen for a patient, and each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient. *Literature-based recommended dosing* is a very commonly used method to prescribe initial doses of theophylline. Doses are based on those that commonly produce steady-state concentrations in the lower end of the therapeutic range, although there is a wide variation in the actual concentrations for a specific patient.

Pharmacokinetic Dosing Method

The goal of initial dosing of theophylline is to compute the best dose possible for the patient given their set of disease states and conditions that influence theophylline pharmacokinetics and the pulmonary disorder being treated. In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.

HALF-LIFE AND ELIMINATION RATE CONSTANT ESTIMATE

Theophylline is predominately metabolized by liver. Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated. Because of this, a patient is categorized according to the disease states and conditions that are known to change theophylline half-life, and the half-life previously measured in these studies is used as an estimate of the current patient's half-life. For example, for a patient with COPD who currently smokes tobacco-containing cigarettes, theophylline half-life would be assumed to equal 5 hours. Alternatively, for a patient with moderate heart failure (NYHA CHF class III), theophylline half-life would be assumed to equal 24 hours, while a patient with severe liver disease (Child-Pugh score = 12) would be assigned an estimated half-life of 24 hours. To produce the most conservative theophylline doses in patients with multiple concurrent disease states or conditions that affect theophylline pharmacokinetics, the disease state or condition with the longest half-life should be used to compute doses. This approach will avoid accidental overdosage as much as currently possible. For instance, for a patient with asthma who currently smokes tobacco-containing cigarettes and has severe liver disease, an estimated theophylline half-life of 24 hours would be used to compute initial dosage requirements. Once the correct half-life is identified for the patient, it can be converted into the theophylline elimination rate constant (k) using the following equation: $k = 0.693/t_{1/2}$.

VOLUME OF DISTRIBUTION ESTIMATE

Theophylline volume of distribution is relatively stable in patients regardless of the disease states and conditions that are present. Volume of distribution is assumed to equal 0.5 L/kg for nonobese patients. For obese patients (>30% above ideal body weight), ideal body weight is used to compute theophylline volume of distribution. Thus, for an 80-kg patient, the estimated theophylline volume of distribution would be 40 L: $V = 0.5\ L/kg \cdot 80\ kg = 40\ L$. For a 150-kg obese patient with an ideal body weight of 60 kg, the estimated theophylline volume of distribution is 30 L: $V = 0.5\ L/kg \cdot 60\ kg = 30\ L$.

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

When given by continuous intravenous infusion or orally, theophylline follows a one-compartment pharmacokinetic model (Figures 18-1, 18-3, 18-4). When oral therapy is required, most clinicians utilize a sustained-release dosage form that has good bioavailability ($F = 1$), supplies a continuous release of theophylline into the gastrointestinal tract, and provides a smooth theophylline serum concentration/time curve that emulates an intravenous infusion after once or twice daily dosing. Because of this, a very simple pharmcokinetic equation that computes the average theophylline steady-state serum concentration (Css in μg/mL = mg/L) is widely used and allows maintenance dosage calculation: $Css = [F \cdot S\ (D/\tau)]/Cl$ or $D = (Css \cdot Cl \cdot \tau)/(F \cdot S)$, where F is the bioavailability fraction for the oral dosage form ($F = 1$ for most oral theophylline sustained-release products), S is the fraction of the theophylline salt form that is active theophylline ($S = 1$ for theophylline, $S = 0.85$ for anhydrous aminophylline, $S = 0.80$ for aminophylline dihydrate, $S = 0.65$ for oxtriphylline), D is the dose of theophylline salt in milligrams, and τ is the dosage interval in hours. Cl is theophylline clearance in liters per hour and is computed

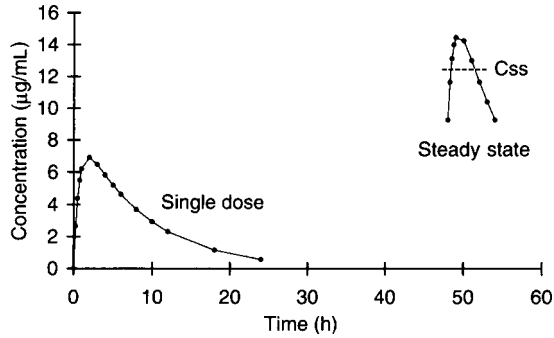

FIGURE 18-3 Serum concentration/time profile for rapid-release theophylline or aminophylline oral dosage forms after a single dose and at steady state (given every 6 hours). The curves shown would be typical for an adult cigarette smoker receiving theophylline 300 mg. The steady-state serum concentration (Css) expected from an equivalent theophylline or aminophylline continuous infusion is shown by the *dotted line* in the steady-state concentrations.

using estimates of theophylline elimination rate constant (k) and volume of distribution: Cl = kV. For example, for a patient with an estimated elimination rate constant equal to 0.139 h^{-1} and an estimated volume of distribution equal to 35 L, the estimated clearance would equal 4.87 L/h: $Cl = 0.139h^{-1} \cdot 35\ L = 4.87$ L/h.

When intravenous therapy is required, a similar pharmacokinetic equation that computes the theophylline steady-state serum concentration (Css in µg/mL = mg/L) is widely used and allows dosage calculation for a continuous infusion: $Css = [S \cdot k_0]/Cl$ or $k_0 = (Css \cdot Cl)/S$, where S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate) and k_0 is the dose of theophylline salt in milligrams. Cl is theophylline clearance in liters per hour and is computed using estimates of theophylline elimination rate constant (k) and volume of distribution: Cl = kV.

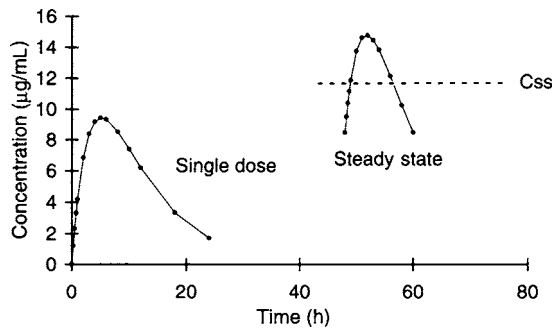

FIGURE 18-4 Serum concentration/time profile for sustained-release theophylline or aminophylline oral dosage forms after a single dose and at steady state (given every 12 hours). The curves shown would be typical for an adult cigarette smoker receiving theophylline 600 mg. The steady-state serum concentration (Css) expected from an equivalent theophylline or aminophylline continuous infusion is shown by the *dotted line* in the steady-state concentrations.

The equation used to calculate an intravenous loading dose (LD in milligrams) is based on a simple one-compartment model: $LD = (Css \cdot V)/S$, where Css is the desired theophylline steady-state concentration in micrograms per milliliter which is equivalent to milligrams per liter, V is the theophylline volume of distribution, and S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate). Intravenous theophylline loading doses should be infusions over at least 20–30 minutes.

STEADY-STATE CONCENTRATION SELECTION

The generally accepted therapeutic ranges for theophylline are 10–20 μg/mL for the treatment of asthma or chronic obstructive pulmonary disease, or 6–13 μg/mL for the treatment of premature apnea. Recent guidelines suggest that for initial treatment of pulmonary disease, clinical response to theophylline concentrations between 5–15 μg/mL should be assessed before higher concentrations are used.[7] Many patients requiring chronic theophylline therapy will derive sufficient bronchodilatory response with a low likelihood of adverse effects at concentrations of 8–12 μg/mL. However, theophylline therapy must be individualized for each patient in order to achieve optimal responses and minimal side effects.

Example 1 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with oral theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 75\ kg = 38\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.139\ h^{-1} \cdot 38\ L = 5.28\ L/h$.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). Because the patient has a rapid theophylline clearance and short half-life, the initial dosage interval (τ) will be set to 8 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is: $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (8\ mg/L \cdot 5.28\ L/h \cdot 8h)/(1 \cdot 1) = 338\ mg$, rounded to 300 every 8 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to

5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 2 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with oral theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where hepatic drug–metabolizing enzymes are contained, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: V = 0.5 L/kg · 85 kg = 43 L. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.029\ h^{-1} \cdot 43\ L = 1.25$ L/h.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (10\ mg/L \cdot 1.25\ L/h \cdot 12\ h) / (1 \cdot 1) = 150$ mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

To illustrate the differences and similarities between oral and intravenous theophylline dosage regimen design, the same cases will be used to compute intravenous theophylline loading doses and continuous infusions.

Example 3 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with intravenous theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial intravenous aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 75\ kg = 38\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.139\ h^{-1} \cdot 38\ L = 5.28\ L/h$.

3. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) Therapy will be started by administering an intravenous loading dose of aminophylline to the patient: $LD = (Css \cdot V)/S = (10\ mg/L \cdot 38\ L) / 0.8 = 475\ mg$, rounded to 500 mg intravenously over 20–30 minutes.

An aminophylline continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous aminophylline is $k_0 = (Css \cdot Cl)/S = (10\ mg/L \cdot 5.28\ L/h) / 0.8 = 66\ mg/h$, rounded to 65 mg/h.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = $5 \cdot 5\ h = 25\ h$). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 4 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with intravenous aminophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial intravenous aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where hepatic drug–metabolizing enzymes are contained, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 85\ kg = 43\ L$. Estimated theophylline clearance

is computed by taking the product of the volume of distribution and the elimination rate constant: Cl = kV = 0.029 h^{-1} · 43 L = 1.25 L/h.

3. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) Therapy will be started by administering an intravenous loading dose of aminophylline to the patient: LD = (Css · V)/S = (10 mg/L · 43 L) / 0.8 = 538 mg, rounded to 500 mg intravenously over 20–30 minutes.

An aminophylline continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is k_0 = (Css · Cl)/S = (10 mg/L · 1.25 L/h)/0.8 = 16 mg/h, rounded to 15 mg/h.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

Because of the large amount of variability in theophylline pharmacokinetics, even when concurrent disease states and conditions are identified, many clinicians believe that the use of standard theophylline doses for various situations is warrented.[20,65,66] The original computation of these doses was based on the pharmacokinetic dosing method described in the previous section, and subsequently modified based on clinical experience. In general, the expected theophylline steady-state serum concentration used to compute these doses was 10 μg/mL. Suggested theophylline maintenance doses stratified by disease states and conditions known to alter theophylline pharmacokinetics are given in Table 18-4.[66] For obese individuals (>30% over ideal body weight), ideal body weight should be used

Table 18-4 Theophylline Dosage Rates for Patients with Various Disease States and Conditions[66]

DISEASE STATE/CONDITION	MEAN DOSE(mg/kg/h)
Children 1–9 years	0.8
Children 9–12 years or adults smokers	0.7
Adolescents 12–16 years	0.5
Adults nonsmokers	0.4
Elderly nonsmokers (>65 years)	0.3
Decompensated CHF, cor pulmonale, cirrhosis	0.2

to compute doses.[34–37] Because the doses are given in terms of theophylline, doses for other theophylline salt forms need to be adjusted accordingly (S = 0.85 for anhydrous aminophylline, S = 0.8 for aminophylline dihydrate, S = 0.65 for oxtriphylline). If theophylline is to be given orally, the dose given in Table 18-4 (in mg/kg/h) must be multiplied by the appropriate dosage interval for the dosage form being used: D = (theophylline dose · Wt · τ)/S, where Wt is patient weight, τ is the dosage interval, and S is the appropriate salt form correction factor for aminophylline or oxtriphylline. If theophylline is to be given as a continuous intravenous infusion the following equation is used to compute the infusion rate: k_0 = (theophylline dose · Wt)/S, where Wt is patient weight and S is the appropriate salt form correction factor for aminophylline. When more than one disease state or condition is present in a patient, choosing the lowest dose suggested by Table 18-4 will result in the safest, most conservative dosage recommendation. If an intravenous loading dose is necessary, theophylline 5 mg/kg or aminophylline 6 mg/kg is used; ideal body weight is used to compute loading doses for obese patients (>30% over ideal body weight).

To illustrate the similarities and differences between this method of dosage calculation and the pharmacokinetic dosing method, the same examples used in the previous section will be used.

Example 5 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with oral theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial theophylline dosage regimen for this patient.

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.7 mg/kg/h is suggested by the Table 18-4 for an adult cigarette smoker.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). Because the patient has a rapid theophylline clearance and half-life, the initial dosage interval (τ) will be set to 8 hours: D = (theophylline dose · Wt · τ)/S = (0.7 mg/kg/h · 75 kg · 8 h) / 1 = 420 mg, rounded to 400 mg every 8 hours. This dose is similar to that suggested by the pharmacokinetic dosing method of 300 mg every 8 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 6 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with oral theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial theophylline dosage regimen for this patient.

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with cirrhosis.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours: D = (theophylline dose · Wt · τ)/S = (0.2 mg/kg/h · 85 kg · 12 h)/1 = 204 mg, rounded to 200 mg every 12 hours. This dose is similar to that suggested by the pharmacokinetic dosing method of 150 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

To illustrate the differences and similarities between oral and intravenous theophylline dosage regimen design, the same cases will be used to compute intravenous theophylline loading doses and continuous infusions.

Example 7 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with intravenous theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial theophylline dosage regimen for this patient.

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.7 mg/kg/h is suggested by the Table 18-4 for an adult smoker.

2. *Compute dosage regimen.*

Theophylline will be administered as the intravenous drug (S = 1): k_0 = (theophylline dose · Wt)/S = (0.7 mg/kg/h · 75 kg) / 1 = 53 mg/h, rounded to 55 mg/h. A loading dose of theophylline 5 mg/kg will also be prescribed for the patient: LD = 5 mg/kg · 75 kg = 375 mg, rounded to 400 mg of theophylline infused over 20–30 minutes. These are similar to the doses that were suggested by the pharmacokinetic dosing method.

A theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 8 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with intravenous theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial intravenous aminophylline dosage regimen for this patient.

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with cirrhosis.

2. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8): D = (theophylline dose · Wt)/S = (0.2 mg/kg/h · 85 kg) / 0.8 = 21 mg/h, rounded to 20 mg/h. A loading dose of aminophylline 6 mg/kg will also be prescribed for the patient: LD = 6 mg/kg · 85 kg = 510 mg, rounded to 500 mg of aminophylline infused over 20–30 minutes. These doses are similar to that suggested by the pharmacokinetic dosing method of a 500 mg loading dose followed by a 15 mg/h continuous infusion.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

USE OF THEOPHYLLINE SERUM CONCENTRATIONS TO ALTER DOSES

Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce theophylline serum concentrations that are expected or desirable. Because of pharmacokinetic variability, the narrow therapeutic index of theophylline, and the severity of theophylline adverse side effects, measurement of theophylline serum concentrations is mandatory for patients to ensure that therapeutic, nontoxic levels are present. In addition to theophylline serum concentrations, important patient parameters (pulmonary function tests, clinical signs and symptoms of the pulmonary disease state, potential theophylline side effects, etc.) should be followed to confirm that the patient is responding to treatment and not developing adverse drug reactions.

When theophylline serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment. In most cases, a simple dosage ratio can be used to change theophylline doses assuming the drug follows *linear pharmacokinetics*. Although it has been clearly demonstrated in research studies that theophylline follows nonlinear pharmacokinetics,[14–16] in the clinical setting most patients' steady-state serum concentrations change proportionately to theophylline dose below and within the therapeutic range, and assuming linear pharmacokinetics is adequate for dosage adjustments in most patients.

Sometimes, it is useful to compute theophylline pharmacokinetic constants for a patient and base dosage adjustments on these. In this case, it may be possible to calculate and use *pharmacokinetic parameters* to alter the theophylline dose. In some situations, it may be necessary to compute theophylline clearance for the patient during a continuous infusion before steady-state conditions occur using the *Chiou method* and utilize this pharmacokinetic parameter to calculate the best drug dose.

Finally, computerized methods that incorporate expected population pharmacokinetic characteristics (*Bayesian pharmacokinetic computer programs*) can be used in difficult

cases where serum concentrations are obtained at suboptimal times or the patient was not at steady state when serum concentrations were measured. An additional benefit of this method is that a complete pharmacokinetic workup (determination of clearance, volume of distribution, and half-life) can be done with one or more measured concentrations that do not have to be at steady state.

Linear Pharmacokinetics Method

Because theophylline follows linear, dose-proportional pharmacokinetics in most patients with concentrations within and below the therapeutic range, steady-state serum concentrations change in proportion to dose according to the following equation: $D_{new}/C_{ss,new} = D_{old}/C_{ss,old}$ or $D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$, where D is the dose, Css is the steady-state concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration. The advantages of this method are that it is quick and simple. The disadvantages are steady-state concentrations are required, and the assumption of linear pharmacokinetics may not be valid in all patients. When steady-state serum concentrations increase more than expected after a dosage increase or decrease less than expected after a dosage decrease, nonlinear theophylline pharmacokinetics is a possible explanation for the observation. Because of this, suggested dosage increases greater than 75% using this method should be scrutinized by the prescribing clinician, and the risk versus benefit for the patient assessed before initiating large dosage increases (>75% over current dose).

Example 9 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who is receiving 300 mg every 8 hours of an oral theophylline sustained-release tablet. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. The current steady-state theophylline concentration equals 8 μg/mL. Compute a theophylline dose that will provide a steady-state concentration of 12 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 5$ h = 25 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 300 mg/dose · 3 doses/d = 900 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12\ \mu g/mL / 8\ \mu g/mL)\ 900\ mg/d = 1350\ mg/d$$

The new suggested dose would be 1350 mg/d or 450 mg every 8 hours of theophylline sustained-release tablets to be started at the next scheduled dosing time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 10 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who is receiving 200 mg every 12 hours of an oral theophylline sustained-release tablet. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. The current steady-state theophylline concentration equals 15 μg/mL, and he is experiencing some minor caffeine-type adverse effects (insomnia, jitteriness, nausea). Compute a theophylline dose that will provide a steady-state concentration of 10 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient has severe liver disease and would be expected to achieve steady-state conditions after 5 days (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 200 mg/dose · 2 doses/d = 400 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (10\ \mu g/mL / 15\ \mu g/mL)\ 400\ mg/d = 267\ mg/d$$

The new suggested dose would be 267 mg/d or 134 mg every 12 hours, rounded to 150 every 12 hours of theophylline sustained-release tablets, to be started after holding 1–2 doses and adverse effects have subsided.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

To illustrate the differences and similarities between oral and intravenous theophylline dosage regimen design, the same cases will be used to compute altered intravenous theophylline continuous infusions using steady-state serum concentrations.

Example 11 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who is receiving an aminophylline constant intravenous infusion at a rate of 50 mg/h. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. The current steady-state theophylline concentration equals 8 μg/mL. Compute an aminophylline infusion rate that will provide a steady-state concentration of 12 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Using linear pharmacokinetics, the new infusion rate to attain the desired concentration should be proportional to the old infusion rate that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12\ \mu g/mL / 8\ \mu g/mL)\ 50\ mg/h = 75\ mg/h$$

The new suggested infusion rate would be 75 mg/h of aminophylline.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to

5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 12 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who is receiving a 20 mg/h continuous infusion of theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. The current steady-state theophylline concentration equals 15 μg/mL, and he is experiencing some minor caffeine-type adverse effects (insomnia, jitteriness, nausea). Compute a theophylline dose that will provide a steady-state concentration of 10 μg/mL.

1. *Compute new dose to achieve desired serum concentration.*

The patient has severe liver disease and would be expected to achieve steady-state conditions after 5 days (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Using linear pharmacokinetics, the new infusion rate to attain the desired concentration should be proportional to the old infusion rate that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (10\ \mu g/mL / 15\ \mu g/mL)\ 20\ mg/h = 13\ mg/h, \text{ round to } 15\ mg/h$$

The new suggested dose would be 15 mg/h of theophylline as a continuous infusion. If necessary, the infusion could be temporarily stopped for 12–24 hours until theophylline adverse effects subsided.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Pharmacokinetic Parameter Method

The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired theophylline concentrations. The pharmacokinetic parameter method requires that steady state has been achieved and uses only a steady-state theophylline concentration (Css). During a continuous intravenous infusion, the following equation is used to compute theophylline clearance (Cl): $Cl = (S \cdot k_0)/Css$, where S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate) and k_0 is the dose of theophylline salt in milligrams per hour. If the patient is receiving oral theophylline therapy, theophylline clearance (Cl) can be calculated using the following formula: $Cl = [F \cdot S\ (D/\tau)] / Css$, where F is the bioavailability fraction for the oral dosage form (F = 1 for most oral theophylline sustained-release products), S is the fraction of the theophylline salt form that is active theophylline (S = 0.85 for anhydrous aminophylline, S = 1 for theophylline, S = 0.80 for aminophylline dihydrate, S = 0.65 for oxtriphylline),

D is the dose of theophylline salt in milligrams, Css is the steady-state theophylline concentration in milligrams per liter, and τ is the dosage interval in hours.

Occasionally, theophylline serum concentrations are obtained before and after an intravenous loading dose. Assuming a one-compartment model, the volume of distribution (V) is calculated using the following equation: $V = (S \cdot D)/(C_{postdose} - C_{predose})$ where S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate), D is the dose of theophylline salt in milligrams, $C_{postdose}$ is the postloading dose concentration in milligrams per liter and $C_{predose}$ is the concentration before the loading dose was administered in milligrams per liter (both concentrations should be obtained within 30–60 minutes of dosage administration). If the predose concentration was also a steady-state concentration, theophylline clearance can also be computed. If both clearance (Cl) and volume of distribution (V) have been measured using these techniques, the half-life ($t_{1/2} = (0.693 \cdot V)/Cl$) and elimination rate constant ($k = 0.693/t_{1/2} = Cl/V$) can be computed. The clearance, volume of distribution, elimination rate constant, and half-life measured using these techniques are the patient's own, unique theophylline pharmacokinetic constants and can be used in one-compartment model equations to compute the required dose to achieve any desired serum concentration. Because this method also assumes linear pharmacokinetics, theophylline doses computed using the pharmacokinetic parameter method and the linear pharmacokinetic method should be identical.

Example 13 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who is receiving 300 mg every 8 hours of an oral theophylline sustained-release tablet. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. The current steady-state theophylline concentration equals 8 μg/mL. Compute a theophylline dose that will provide a steady-state concentration of 12 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 5$ h = 25 h) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: $Cl = [F \cdot S\ (D/\tau)]\ /\ Css = [1 \cdot 1\ (300\ mg/8\ h)]/\ (8\ mg/L) = 4.69$ L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (12\ mg/L \cdot 4.69\ L/h \cdot 8h)/(1 \cdot 1) = 450$ mg every 8 hours.

The new theophylline dosage regimen would be instituted at the next dosage time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = $5 \cdot 5$ h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 14 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who is receiving 200 mg every 12 hours of an oral theophylline sustained-release tablet. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. The current steady-state theophylline concentration equals 15 μg/mL, and he is experiencing some minor caffeine-type adverse effects (insomnia, jitteriness, nausea). Compute a theophylline dose that will provide a steady-state concentration of 10 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient has severe liver disease and would be expected to achieve steady-state conditions after 5 days (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: Cl = [F · S (D/τ)] / Css = [1 · 1 (200 mg/12 h)] / (15 mg/L) = 1.11 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new dose: D = (Css · Cl · τ)/(F · S) = (10 mg/L · 1.11 L/h · 12 h) / (1 · 1) = 133 mg, rounded to 150 mg every 12 hours.

The new dose would be started after holding 1–2 doses and adverse effects have subsided.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

To illustrate the differences and similarities between oral and intravenous theophylline dosage regimen design, the same cases will be used to compute altered intravenous theophylline continuous infusions using steady-state serum concentrations.

Example 15 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who is receiving an aminophylline constant intravenous infusion at a rate of 50 mg/h. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. The current steady-state theophylline concentration equals 8 μg/mL. Compute an aminophylline infusion rate that will provide a steady-state concentration of 12 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration Cl = [S · k_0]/Css = [0.8 · 50 mg/h] / (8 mg/L) = 5 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new aminophylline infusion rate: k_0 = (Css · Cl) / S = (12 mg/L · 5 L/h)/(0.8) = 75 mg/h.

The new aminophylline infusion rate would be instituted immediately.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example16 OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who is receiving a 20 mg/h continuous infusion of theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. The current steady-state theophylline concentration equals 15 μg/mL, and he is experiencing some minor caffeine-type adverse effects (insomnia, jitteriness, nausea). Compute a theophylline dose that will provide a steady-state concentration of 10 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient has severe liver disease and would be expected to achieve steady-state conditions after 5 days (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration Cl = (S · k_0)/Css = (1 · 20 mg/h) / (15 mg/L) = 1.33 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new theophylline infusion rate: k_0 = (Css · Cl)/S = (10 mg/L· 1.33 L/h) / (1) = 13 mg/h, round to 15 mg/h.

The new suggested dose would be 15 mg/h of theophylline as a continuous infusion. If necessary, the infusion could be temporarily stopped for 12–24 hours until theophylline adverse effects subsided.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Example 17 PP is a 59-year-old, 65-kg (5 ft 8 in) male with emphysema who is receiving an aminophylline constant intravenous infusion at a rate of 15 mg/h. He currently smokes 2 packs of cigarettes daily and has normal liver function. However, he also has heart failure (NYHA CHF class IV). The current steady-state theophylline concentration equals 6 μg/mL. Compute an aminophylline infusion rate that will provide a steady-state concentration of 10 μg/mL. Additionally, in an attempt to boost theophylline concentrations as soon as possible, an aminophylline intravenous bolus of 300 mg over 30 minutes was given before the infusion rate was increased. The theophylline serum concentration after the additional bolus dose was 12 μg/mL.

1. *Compute pharmacokinetic parameters.*

The patient has severe heart failure and would be expected to achieve steady-state conditions after 5 days (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: Cl = (S · k_0)/Css = (0.8 · 15 mg/h) / (6 mg/L) = 2 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

Theophylline volume of distribution can be computed using the prebolus dose (Css = 6 μg/mL) and postbolus dose concentrations: V = (S · D)/($C_{postdose}$ − $C_{predose}$) = (0.8 · 300 mg) / (12 mg/L − 6 mg/L) = 40 L. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

Theophylline half-life ($t_{1/2}$) and elimination rate constant (k) can also be computed: $t_{1/2}$ = (0.693 · V)/Cl = (0.693 · 40 L)/(2 L/h) = 14 h; k = Cl/V = (2 L/h)/(40 L) = 0.05 h^{-1}.

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new aminophylline infusion rate: k_0 = (Css · Cl)/S = (10 mg/L · 2 L/h) / (0.8) = 25 mg/h.

The new aminophylline infusion rate would be instituted immediately after the additional loading dose was given.

A theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient has a half-life equal to 14 hours, the theophylline steady-state concentration could be obtained after 3 days of continuous dosing (5 half-lives = 5 · 14 h = 70 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

CHIOU METHOD

For some patients, it is desirable to individualize theophylline infusion rates as rapidly as possible before steady state is achieved. Examples of these cases include patients with heart failure or hepatic cirrhosis who have variable theophylline pharmacokinetic parameters and long theophylline half-lives. In this situation, two theophylline serum concentrations obtained at least 4–6 hours apart during a continuous infusion can be used to compute theophylline clearance and dosing rates.[67–69] In addition to this requirement, the only way theophylline can be entering the patient's body must be via intravenous infusion. Thus, the last dose of sustained-release theophylline must have been administered no less than 12–16 hours before this technique is used, or some residual oral theophylline will still be absorbed from the gastrointestinal tract and cause computation errors.

The following equation is used to compute theophylline clearance (Cl) using the theophylline concentrations:

$$Cl = \frac{2 \cdot S \cdot k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

where S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate), k_0 is the infusion rate of the theophylline salt, V is theophylline volume of distribution (assumed to equal 0.5 L/kg; use ideal body weight for obese patients >30% overweight), C_1 and C_2 are the first and second theophylline serum concentrations, and t_1 and t_2 are the times that C_1 and C_2 were obtained. Once theophylline clearance (Cl) is determined, it can be used to adjust the theophylline salt infusion rate (k_0) using the following relationship: $k_0 = (Css \cdot Cl)/S$, where S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate).

Example 18 JB is a 50-year-old, 60-kg (5 ft 7 in) male with heart failure (NYHA CHF class III) started on a 50 mg/h aminophylline infusion after being administered an intravenous loading dose. The theophylline concentration was 15.6 µg/mL at 1000 H and 18.3 µg/mL at 1400 H. What aminophylline infusion rate is needed to achieve Css = 15 µg/mL?

1. *Compute theophylline clearance and dose.*

$$Cl = \frac{2 \cdot S \cdot k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2[0.8(50\ mg/h)]}{15.6\ mg/L + 18.3\ mg/L} + \frac{2(0.5\ L/kg \cdot 60Kg)(15.6\ mg/L - 18.3\ mg/L)}{(15.6\ mg/L + 18.3\ mg/L)\ 4\ h} = 1.17\ L/h$$

(Note: µg/mL = mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1 was determined and placed directly in the calculation.)

$k_0 = (Css \cdot Cl)/S = (15\ mg/L \cdot 1.17\ L/h)/0.8 = 22\ mg/h$, round to 20 mg/h of aminophylline

Example 19 YU is a 64-year-old, 80-kg (5 ft 9 in) male with COPD who smokes $1^1/_2$ packs of cigarettes per day. He is started on a 40-mg/h theophylline infusion after being administered an intravenous loading dose at 0900 H. The theophylline concentration was 11.6 µg/mL at 1000 H and 8.1 µg/mL at 1600 H. What theophylline infusion rate is needed to achieve Css = 10 µg/mL?

1. *Compute theophylline clearance and dose.*

$$Cl = \frac{2 \cdot S \cdot k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2[1(40\ mg/h)]}{11.6\ mg/L + 8.1\ mg/L} + \frac{2(0.5\ L/kg \cdot 80\ Kg)(11.6\ mg/L - 8.1\ mg/L)}{(11.6\ mg/L + 8.1\ mg/L)\ 6\ h}$$
$$= 6.43\ L/h$$

(Note: µg/mL = mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1 was determined and placed directly in the calculation.)

$k_0 = (Css \cdot Cl)/S = (10\ mg/L \cdot 6.43\ L/h)\ /\ 1 = 64\ mg/h$, round to 65 mg/h of theophylline

BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

Computer programs are available that can assist in the computation of pharmacokinetic parameters for patients. The most reliable computer programs use a nonlinear regression algorithm that incorporates components of Bayes' theorem. Nonlinear regression is a statistical technique that uses an iterative process to compute the best pharmacokinetic parameters for a concentration/time data set. Briefly, the patient's drug dosage schedule and serum concentrations are input into the computer. The computer program has a pharmacokinetic equation preprogrammed for the drug and administration method (oral, intravenous bolus, intravenous infusion, etc.). Typically, a one-compartment model is used, although some programs allow the user to choose among several different equations. Using population estimates based on demographic information for the patient (age, weight, gender, liver function, cardiac status, etc.) supplied by the user, the computer program then computes estimated serum concentrations at each time there are actual serum concentrations. Kinetic parameters are then changed by the computer program, and a new set of estimated serum concentrations are computed. The pharmacokinetic parameters that generated the estimated serum concentrations closest to the actual values are remembered by the computer program, and the process is repeated until the set of pharmacokinetic parameters that result in estimated serum concentrations that are statistically closest to the actual serum concentrations are generated. These pharmacokinetic parameters can then be used to compute improved dosing schedules for patients. Bayes' theorem is used in the computer algorithm to balance the results of the computations between values based solely on the patient's serum drug concentrations and those based only on patient population parameters. Results from studies that compare various methods of dosage adjustment have consistently found that these types of computer dosing programs perform at least as well as experienced clinical pharmacokineticists and clinicians and better than inexperienced clinicians.

Some clinicians use Bayesian pharmacokinetic computer programs exclusively to alter drug doses based on serum concentrations. An advantage of this approach is that consistent dosage recommendations are made when several different practitioners are involved in therapeutic drug monitoring programs. However, since simpler dosing methods work just as well for patients with stable pharmacokinetic parameters and steady-state drug concentrations, many clinicians reserve the use of computer programs for more difficult situations. Those situations include serum concentrations that are not at steady state, serum concentrations not obtained at the specific times needed to employ simpler methods, and unstable pharmacokinetic parameters. Many Bayesian pharmacokinetic computer programs are available to users, and most should provide answers similar to the one used in the following examples. The program used to solve problems in this book is DrugCalc written by Dr. Dennis Mungall. [70]

Example 20 LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who is receiving 300 mg every 8 hours of an oral theophylline sustained-release tablet. He currently smokes 2 packs of cigarettes daily, and has normal liver (bilirubin = 0.7 mg/dL, albumin = 4.0 g/dL) and cardiac function. The current steady-state theophylline concentration equals 8 μg/mL. Compute a theophylline dose that will provide a steady-state concentration of 12 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 37 L, a half-life equal to 5.9 hours, and a clearance equal to 4.33 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 450 mg every 8 hours will produce a steady-state theophylline concentration of 12 μg/mL. Using the linear pharmacokinetics and pharmacokinetic parameter methods previously described in this chapter produced the same answer for this patient.

Example 21 HJ is a 62-year-old, 87-kg (6 ft 1 in) male with emphysema who given a new prescription of 300 mg every 12 hours of an oral theophylline sustained-release tablet. He has liver cirrhosis (Child-Pugh score = 12, bilirubin = 3.2 mg/dL, albumin = 2.5 g/dL) and normal cardiac function. The theophylline concentration after the sixth dose equals 15 μg/mL, and he is experiencing some minor caffeine-type adverse effects (insomnia, jitteriness, nausea). Compute a theophylline dose that will provide a steady-state concentration of 10 μg/mL.

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used.

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 38 L, a half-life equal to 19 hours, and a clearance equal to 1.41 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicate that a dose of 200 mg every 12 hours will produce a steady-state concentration of 11 μg/mL.

Example 22 JB is a 50-year-old, 60-kg (5 ft 7 in) male with heart failure (NYHA CHF class III) started on a 50 mg/h aminophylline infusion after being administered an intravenous loading dose of aminophylline 500 mg at 0800 H over 20 minutes. The theophylline concentration was 15.6 μg/mL at 1000 H and 18.3 μg/mL at 1400 H. What aminophylline infusion rate is needed to achieve Css = 15 μg/mL?

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. DrugCalc requires doses to be entered in terms of

theophylline, so aminophylline doses must be converted to theophylline doses for entry into the program (LD = 500-mg aminophylline · 0.8 = 400-mg theophylline, k_0 = 50 mg/h aminophylline · 0.8 = 40 mg/h theophylline).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 29 L, a half-life equal to 21 hours, and clearance equal to 0.98 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model intravenous infusion equations used by the program to compute doses indicate that a dose of aminophylline 20 mg/h will produce a steady-state concentration of 16 μg/mL. Using the Chiou method previously described in this chapter produced a comparable answer for this patient (20 mg/h to produce a steady-state concentration of 15 μg/mL).

DOSING STRATEGIES

Initial dose and dosage adjustment techniques using serum concentrations can be used in any combination as long as the limitations of each method are observed. Some dosing schemes link together logically when considered according to their basic approaches or philosophies. Dosage strategies that follow similar pathways are given in Table 18-5.

USE OF THEOPHYLLINE BOOSTER DOSES TO IMMEDIATELY INCREASE SERUM CONCENTRATIONS

If a patient has a subtherapeutic theophylline serum concentration in an acute situation, it may be desirable to increase the theophylline concentration as quickly as possible. In this setting, it would not be acceptable to simply increase the maintenance dose and wait 3–5 half-lives for therapeutic serum concentrations to be established in the patient. A rational way to increase the serum concentrations rapidly is to administer a booster dose of theophylline, a

TABLE 18-5 Dosing Strategies

DOSING APPROACH/ PHILOSOPHY	INITIAL DOSING	USE OF SERUM CONCENTRATIONS TO ALTER DOSES
Pharmacokinetic parameter/equations	Pharmacokinetic dosing method	Pharmacokinetic parameter method or Chiou method (IV infusion before steady state)
Literature-based/concept	Literature-based recommended dosing method	Linear pharmacokinetics method
Computerized	Bayesian computer program	Bayesian computer program

process also known as "reloading" the patient with theophylline, computed using pharmacokinetic techniques. A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current theophylline concentration present in the patient: $BD = [(C_{desired} - C_{actual})V]/S$, where $C_{desired}$ is the desired theophylline concentration, C_{actual} is the actual current theophylline concentration for the patient, S is the fraction of the theophylline salt form that is active theophylline (S = 1 for theophylline, S = 0.85 for anhydrous aminophylline, S = 0.80 for aminophylline dihydrate), and V is the volume of distribution for theophylline. If the volume of distribution for theophylline is known for the patient, it can be used in the calculation. However, this value is not usually known and is assumed to equal the population average of 0.5 L/kg (ideal body weight used for patients >30% overweight).

Concurrent with the administration of the booster dose, the maintenance dose of theophylline is usually increased. Clinicians need to recognize that the administration of a booster dose does not alter the time required to achieve steady-state conditions when a new theophylline dosage rate is prescribed. It still requires 3–5 half-lives to attain steady state when the dosage rate is changed. However, usually the difference between the postbooster dose theophylline concentration and the ultimate steady-state concentration has been reduced by giving the extra dose of drug.

Example 23 BN is a 22-year-old, 50-kg (5 ft 2 in) female with asthma who is receiving therapy with intravenous theophylline. She does not smoke cigarettes and has normal liver and cardiac function. After receiving an initial loading dose of aminophylline (300 mg) and a maintenance infusion of aminophylline equal to 20 mg/h for 16 hours, her theophylline concentration is measured at 5.6 μg/mL and her pulmonary function tests are worsening. Compute a booster dose of aminophylline to achieve a theophylline concentration equal to 10 μg/mL.

1. *Estimate volume of distribution according to disease states and conditions present in the patient.*

In the case of theophylline, the population average volume of distribution equals 0.5 L/kg and this will be used to estimate the parameter for the patient. The patient is nonobese, so her actual body weight will be used in the computation: $V = 0.5\ L/kg \cdot 50\ kg = 25\ L$.

2. *Compute booster dose.*

The booster dose is computed using the following equation: $BD = [(C_{desired} - C_{actual})V]/S = [(10\ mg/L - 5.6\ mg/L)25\ L] / 0.8 = 138$ mg, rounded to 150 mg of aminophylline infused over 20–30 minutes. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) If the maintenance dose was increased, it will take an additional 3–5 estimated half-lives for new steady-state conditions to be achieved. Theophylline serum concentrations should be measured at this time.

CONVERSION OF THEOPHYLLINE DOSES FROM INTRAVENOUS TO ORAL ROUTE OF ADMINISTRATION

Occasionally there is a need to convert a patient stabilized on theophylline therapy from the oral route of administration to an equivalent continuous infusion or vice versa.[71] In general, oral theophylline dosage forms, including most sustained-release tablets and

capsules, have a bioavailability equal to one. Assuming that equal theophylline serum concentrations are desired, this makes conversion between the intravenous [$k_0 = (Css \cdot Cl)/S$] and oral [$D = (Css \cdot Cl \cdot \tau)/(F \cdot S)$] routes of administration simple since equivalent doses of drug (corrected for theophylline salt form) are prescribed: $k_0 = D_{po}/(24\ h/d \cdot S_{iv})$ or $D_{po} = S_{iv} \cdot k_0 \cdot 24\ h/d$, where k_0 is the equivalent intravenous infusion rate for the theophylline salt in milligrams per hour, D_{po} is equivalent dose of oral theophylline in milligrams per day, and S_{iv} is the fraction of the intravenously administered theophylline salt form that is active theophylline.

Example 24 JH is currently receiving oral sustained-release theophylline 600 mg every 12 hours. She is responding well to therapy, has no adverse drug effects, and has a steady-state theophylline concentration of 14.7 μg/mL. Suggest an equivalent dose of aminophylline given as an intravenous infusion for this patient.

1. *Calculate equivalent intravenous dose of aminophylline.*

The patient is currently receiving 600 mg every 12 hours or 1200 mg/d (600 mg/dose · 2 doses/d = 1200 mg/d) of theophylline. The equivalent intravenous aminophylline dose would be: $k_0 = D_{po} / (24\ h/d \cdot S_{iv}) = (1200\ mg/d) / (24\ h/d \cdot 0.8) = 62.5$ mg/h, rounded to 65 mg/h of aminophylline as a continuous intravenous infusion.

Example 25 LK is currently receiving a continuous infusion of aminophylline at the rate of 40 mg/h. He is responding well to therapy, has no adverse drug effects, and has a steady-state theophylline concentration of 11.3 μg/mL. Suggest an equivalent dose of sustained-release oral theophylline for this patient.

1. *Calculate equivalent oral dose of theophylline.*

The patient is currently receiving 40 mg/h of intravenous aminophylline as a constant infusion. The equivalent oral sustained-release theophylline dose would be: $D_{po} = S_{iv} \cdot k_0 \cdot 24h/d = 0.8 \cdot 40\ mg/h \cdot 24\ h/d = 768$ mg/d, rounded to 800 mg/d. The patient would be prescribed theophylline sustained-release tablets 400 mg orally every 12 hours.

REMOVAL OF THEOPHYLLINE BODY STORES IN MANAGEMENT OF THEOPHYLLINE OVERDOSE

In addition to supportive care, treatment of seizures with anticonvulsant agents, and treatment of cardiac arrhythmias with antiarrhythmic agents, removal of theophylline from the body should be considered in cases of acute and chronic overdoses.[65] Extracorporeal methods to remove theophylline in emergency situations include hemodialysis[52–57] and charcoal hemoperfusion[72,73]. Hemoperfusion is a technique similar to hemodialysis except the blood is passed through a column of activated charcoal instead of through an artificial kidney. Charcoal hemoperfusion is very effective in removing theophylline from the blood with an extraction ratio across the column in excess of 90%, but theophylline serum concentrations can rebound 5–10 μg/mL upon discontinuation of the procedure as theophylline in the tissues come into equilibrium with the blood.[72,73] Theophylline serum concentrations should be closely monitored when charcoal hemoperfusion is instituted. Other complications of charcoal hemoperfusion include hypotension, hypocalcemia, platelet consumption, and bleeding.

Theophylline can also be removed from the body using oral doses of activated charcoal.[74,75] This method to reduce theophylline body stores is about as effective as hemodialysis removal. Activated charcoal physically adsorbss theophylline rendering it nonabsorbable from the gastrointestinal tract. If the patient is vomiting, appropriate antiemetic therapy must be instituted so that the charcoal is retained in the stomach. Phenothiazine antiemetics should be avoided as they may decrease the seizure threshold. In an acute theophylline overdose, oral activated charcoal (0.5 g/kg up to 20 g, repeated at least once in 1–2 hours) will bind theophylline that has not yet been absorbed and hold it in the gastrointestinal tract. Oral activated charcoal will also enhance the clearance of theophylline by binding theophylline secreted in gastrointestinal juices and eliminating the drug in the stool. When used in this fashion, oral activated charcoal (0.5 g/kg up to 20 g) is given every 2 hours. In both cases, a dose of oral sorbitol should be given to hasten the removal of charcoal-bound theophylline from the intestine.

After acute and chronic theophylline overdoses, a single dose of oral activated charcoal is recommended if the theophylline serum concentration is 20–30 μg/mL. For theophylline serum concentrations >30 μg/mL, multiple doses of oral activated charcoal should be used. Patients should be monitored for signs and symptoms of theophylline toxicity and treated appropriately. Theophylline serum concentrations should be measured every 2–4 hours in order to guide further therapy.

PROBLEMS

The following problems are intended to emphasize the computation of initial and individualized doses using clinical pharmacokinetic techniques. Clinicians should always consult the patient's chart to confirm that current pulmonary therapy, including inhaled bronchodilators and steroids, is appropriate. Additionally, all other medications that the patient is taking, including prescription and nonprescription drugs, should be noted and checked to ascertain if a potential drug interaction with theophylline exists.

1. NJ is a 67-year-old, 72-kg (6 ft 1 in) male with chronic bronchitis who requires therapy with oral theophylline. He currently smokes three packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial oral theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

2. Patient NJ (please see problem 1) was prescribed theophylline sustained-release tablets 500 mg orally every 8 hours. The current steady-state theophylline concentration equals 18 μg/mL. Compute a new oral theophylline dose that will provide a steady-state concentration of 12 μg/mL.

3. GF is a 56-year-old, 81-kg (5 ft 9 in) male with emphysema who requires therapy with oral theophylline. He has liver cirrhosis (Child-Pugh score = 12) and normal cardiac function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL.

4. Patient GF (please see problem 3) was prescribed theophylline sustained-release tablets 100 mg orally every 12 hours. The current steady-state theophylline concentration

equals 8 μg/mL. Compute a new oral theophylline dose that will provide a steady-state concentration of 12 μg/mL.

5. YU is a 71-year-old, 60-kg (5 ft 2 in) female with chronic obstructive pulmonary disease who requires therapy with oral theophylline. She has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL.

6. Patient YU (please see problem 5) was prescribed theophylline sustained-release tablets 200 mg orally every 12 hours. A theophylline serum concentration was obtained just before the sixth dose of this regimen and equaled 19.5 μg/mL. Assuming the theophylline concentration was zero before the first dose, compute a new oral theophylline dose that will provide a steady-state concentration of 12 μg/mL.

7. WE is a 24-year-old, 55-kg (5 ft 5 in) female with asthma who requires therapy with oral theophylline. She does not smoke cigarettes, and has normal liver and cardiac function. Suggest an initial oral theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 12 μg/mL.

8. Patient WE (please see problem 7) was prescribed theophylline sustained-release tablets 400 mg orally every 12 hours. A theophylline serum concentration was obtained just before the third dose of this regimen and equaled 13.5 μg/mL. Assuming the theophylline concentration was zero before the first dose, compute a new oral theophylline dose that will provide a steady-state concentration of 10 μg/mL.

9. IO is a 62-year-old, 130-kg (5 ft 11 in) male with chronic obstructive pulmonary disease who requires therapy with oral theophylline. He has mild heart failure (NYHA CHF class I) and normal liver function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL.

10. Patient IO (please see problem 9) was prescribed theophylline sustained-release tablets 200 mg orally every 12 hours. A theophylline serum concentration was obtained just before the sixth dose of this regimen and equaled 6.2 μg/mL. Assuming the theophylline concentration was zero before the first dose, compute a new oral theophylline dose that will provide a steady-state concentration of 10 μg/mL.

11. LG is a 53-year-old, 69-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with intravenous theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL.

12. Patient LG (please see problem 11) was prescribed intravenous aminophylline 50 mg/h. A theophylline serum concentration was obtained after 24 hours of this regimen and equaled 7.4 μg/mL. Compute a new intravenous aminophylline infusion and an aminophylline booster dose that will provide a steady-state concentration of 11 μg/mL.

13. CV is a 69-year-old, 90-kg (6 ft 1 in) male with emphysema who requires therapy with intravenous theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal

cardiac function. Suggest an initial intravenous aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 μg/mL.

14. Patient CV (please see problem 13) was prescribed intravenous aminophylline 25 mg/h and administered a loading dose of aminophylline 400 mg over 30 minutes before the continuous infusion began. A theophylline serum concentration was obtained after 72 hours of the infusion and equaled 25.2 μg/mL. Compute a new intravenous aminophylline infusion that will provide a steady-state concentration of 15 μg/mL.

15. PE is a 61-year-old, 67-kg (5 ft 6 in) female with chronic obstructive pulmonary disease who requires therapy with intravenous theophylline. She has severe heart failure (NYHA CHF class IV) and normal liver function. Suggest an initial intravenous aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 μg/mL.

16. Patient PE (please see problem 15) was prescribed intravenous aminophylline 20 mg/h and administered a loading dose of aminophylline 350 mg over 20 minutes before the continuous infusion began. Theophylline serum concentrations were obtained 12 hours and 24 hours after the infusion began and equaled 14.2 μg/mL and 18.6 μg/mL, respectively. Compute a new intravenous aminophylline infusion that will provide a steady-state concentration of 18 μg/mL.

17. ZQ is a 7-year-old, 20-kg (4 ft 7 in) female with asthma who requires therapy with oral theophylline. She has normal liver and cardiac function. Suggest an initial oral theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 6 μg/mL.

18. Patient ZQ (please see problem 17) was prescribed theophylline sustained-release tablets 100 mg orally every 8 hours. A theophylline serum concentration was obtained after 3 days of this regimen and equaled 4 μg/mL just before the seventh dose was administered. Suggest a new oral theophylline dose that will provide a steady-state concentration of 6 μg/mL.

SOLUTIONS TO PROBLEMS

1. *Answer to problem 1.*

The initial theophylline dose for patient NJ would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 72\ kg = 36\ L$. Estimated theophylline

clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.139\ h^{-1} \cdot 36\ L = 5.0\ L/h$.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). Because the patient has a rapid theophylline clearance and half-life, the initial dosage interval (τ) will be set to 8 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (10\ mg/L \cdot 5.0\ L/h \cdot 8h)/(1 \cdot 1) = 400$ mg every 8 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.7 mg/kg/h is suggested by Table 18-4 for an adult smoker.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). Because the patient has a rapid theophylline clearance and half-life, the initial dosage interval (τ) will be set to 8 hours: $D = (\text{theophylline dose} \cdot Wt \cdot \tau)/S = (0.7\ mg/kg/h \cdot 72\ kg \cdot 8\ h)/1 = 403$ mg, rounded to 400 mg every 8 hours. This dose is identical to that suggested by the pharmacokinetic dosing method.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

2. *Answer to problem 2.*

The revised theophylline dose for patient NJ would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 5$ h = 25 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 500 mg/dose · 3 doses/d = 1500 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12\ \mu g/mL / 18\ \mu g/mL)\ 1500\ mg/d = 1000\ mg/d$$

The new suggested dose would be rounded to 900 mg/d or 300 mg every 8 hours of theophylline sustained-release tablets to be started at the next scheduled dosing time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 5$ h = 25 h) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: $Cl = [F \cdot S\ (D/\tau)] / Css = [1 \cdot 1\ (500\ mg/8\ h)] / (18\ mg/L) = 3.47$ L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (12\ mg/L \cdot 3.47\ L/h \cdot 8h) / (1 \cdot 1) = 333$ mg, rounded to 300 mg every 8 hours.

The new theophylline dosage regimen would be instituted at the next dosage time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

3. *Answer to problem 3.*

The initial theophylline dose for patient GF would be calculated as follows:

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where

hepatic drug–metabolizing enzymes are contained, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 81\ kg = 41\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.029\ h^{-1} \cdot 41\ L = 1.19\ L/h$.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient ($F = 1$, $S = 1$). The initial dosage interval (τ) will be set to 12 hours. (Note: $\mu g/mL = mg/L$ and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (8\ mg/L \cdot 1.19\ L/h \cdot 12\ h)/(1 \cdot 1) = 114\ mg$, rounded to 100 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = $5 \cdot 24\ h = 120\ h$ or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with cirrhosis.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient ($F = 1$, $S = 1$). The initial dosage interval (τ) will be set to 12 hours: $D = (\text{theophylline dose} \cdot Wt \cdot \tau)/S = (0.2\ mg/kg/h \cdot 81\ kg \cdot 12\ h)/1 = 194\ mg$, rounded to 200 mg every 12 hours. This dose is similar to that suggested by the pharmacokinetic dosing method of 100 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = $5 \cdot 24\ h = 120\ h$ or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

4. *Answer to problem 4.*

The revised theophylline dose for patient GF would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient has liver disease and would be expected to achieve steady-state conditions after the fifth day (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 100 mg/dose · 2 doses/d = 200 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (12\ \mu g/mL / 8\ \mu g/mL)\ 200\ mg/d = 300\ mg/d$$

The new suggested dose would be 300 mg/d or 150 mg every 12 hours of theophylline sustained-release tablets to be started at the next scheduled dosing time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient has liver disease and would be expected to achieve steady-state conditions after the fifth day (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: Cl = [F · S (D/τ)]/Css = [1 · 1 (100 mg/12 h)]/(8 mg/L) = 1.04 L/h. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new dose: D = (Css · Cl · τ)/(F · S) = (12 mg/L · 1.04 L/h · 12 h)/(1 · 1) = 150 mg every 12 hours.

The new theophylline dosage regimen would be instituted at the next dosage time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

5. *Answer to problem 5.*

The initial theophylline dose for patient YU would be calculated as follows:

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe heart failure have highly variable theophylline pharmacokinetics and dosage requirements. Heart failure patients have decreased cardiac output which leads to decreased liver blood flow, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 60\ kg = 30\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.029\ h^{-1} \cdot 30\ L = 0.87\ L/h$.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient ($F = 1$, $S = 1$). The initial dosage interval (τ) will be set to 12 hours. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (8\ mg/L \cdot 0.87\ L/h \cdot 12\ h)/(1 \cdot 1) = 84\ mg$, rounded to 100 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = $5 \cdot 24\ h = 120\ h$ or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure receiving theophylline therapy must be monitored very carefully.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with severe heart failure.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient ($F = 1$, $S = 1$). The initial dosage interval (τ) will be set to 12 hours: $D = (\text{theophylline dose} \cdot Wt \cdot \tau)/S = (0.2\ mg/kg/h \cdot 60\ kg \cdot 12\ h)/1 = 144\ mg$, rounded to 150 mg every 12 hours.

This dose is similar to that suggested by the pharmacokinetic dosing method of 100 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure receiving theophylline therapy must be monitored very carefully.

6. *Answer to problem 6.*

The revised theophylline dose for patient YU would be calculated as follows:

The patient has severe heart failure and would be expected to achieve steady-state conditions after the fifth day (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy. Because the serum theophylline serum concentration was obtained on the third day of therapy, it is unlikely that steady state has been attained, so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 24.5 L, a half-life equal to 26.6 hours, and a clearance equal to 0.64 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 100 mg every 12 hours will produce a steady-state theophylline concentration of 12.4 μg/mL.

7. *Answer to problem 7.*

The initial theophylline dose for patient WE would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected theophylline half-life ($t_{1/2}$) is 8 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/8\ h = 0.087\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: V = 0.5 L/kg · 55 kg = 28 L. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: Cl = kV = 0.087 h^{-1} · 28 L = 2.44 L/h.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1), and the initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is D = (Css · Cl · τ)/(F · S) = (12 mg/L· 2.44 L/h · 12 h) / (1 · 1) = 351 mg, rounded to 300 every 12 hours. (Note: dose rounded down because of the narrow therapeutic index for theophylline.)

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 8 hours, the theophylline steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 8 h = 40 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.4 mg/kg/h is suggested by Table 18-4 for an adult without other disease states or conditions that alter theophylline dosing.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1), and the initial dosage interval (τ) will be set to 12 hours: D = (theophylline dose · Wt · τ)/S = (0.4 mg/kg/h · 55 kg · 12 h)/1 = 264 mg, rounded to 300 mg every 12 hours. This dose is identical to that suggested by the pharmacokinetic dosing method.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 8 hours, the theophylline steady-state concentration could be obtained anytime after the second day of dosing (5 half-lives = 5 · 8 h = 40 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

8. *Answer to problem 8.*

The revised theophylline dose for patient WE would be calculated as follows:

The patient has normal cardiac and hepatic function and would be expected to achieve steady-state conditions after the second day (5 $t_{1/2}$ = 5 · 8 h = 40 h) of therapy. Because the serum theophylline serum concentration was obtained before the

third dose, it is unlikely that the serum concentration was obtained at steady state so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 24.6 L, a half-life equal to 15 hours, and a clearance equal to 1.14 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 150 mg every 12 hours will produce a steady-state theophylline concentration of 10 μg/mL.

9. *Answer to problem 9.*

The initial theophylline dose for patient IO would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with mild heart failure have highly variable theophylline pharmacokinetics and dosage requirements. Heart failure patients have decreased cardiac output which leads to decreased liver blood flow, and the expected theophylline half-life ($t_{1/2}$) is 12 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/12\ h = 0.058\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is obese [IBW_{male} (in kg) = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3 (71 in − 60) = 75 kg, patient >30% over ideal body weight], so the estimated theophylline volume of distribution will be based on ideal body weight: $V = 0.5\ L/kg \cdot 75\ kg = 38\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.058\ h^{-1} \cdot 38\ L = 2.20\ L/h$.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (8\ mg/L \cdot 2.20\ L/h \cdot 12\ h)/(1 \cdot 1) = 211$ mg, rounded to 200 mg every 12 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life

equal to 12 hours, the theophylline steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure receiving theophylline therapy must be monitored very carefully.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with heart failure. Because the patient is obese [IBW_{male} (in kg) = 50 kg + 2.3(Ht − 60) = 50 kg + 2.3(71 in − 60) = 75 kg, patient >30% over ideal body weight], ideal body weight will be used to compute doses.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1). The initial dosage interval (τ) will be set to 12 hours: D = (theophylline dose · Wt · τ)/S = (0.2 mg/kg/h · 75 kg · 12 h) / 1 = 180 mg, rounded to 200 mg every 12 hours. This dose is the same as that suggested by the pharmacokinetic dosing method.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the theophylline steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure receiving theophylline therapy must be monitored very carefully.

10. *Answer to problem 10.*

The revised theophylline dose for patient IO would be calculated as follows:

The patient has mild heart failure and would be expected to achieve steady-state conditions after the third day (5 $t_{1/2}$ = 5 · 12 h = 60 h) of therapy. Since the serum theophylline serum concentration was obtained on the third day of therapy, it is possible that the serum concentration was obtained at steady state, but half-life can vary widely in patients with heart failure. Because of this, the linear pharmacokinetics or pharmacokinetic parameter methods were not used for this patient.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 39.4 L, a half-life equal to 12.4 hours, and a clearance equal to 2.20 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model first-order absorption equations used by the program to compute doses indicates that a dose of 300 mg every 12 hours will produce a steady-state theophylline concentration of 10.2 μg/mL.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 12 hours, the theophylline steady-state concentration could be obtained anytime after the third day of dosing (5 half-lives = 5 · 12 h = 60 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure receiving theophylline therapy must be monitored very carefully.

11. *Answer to problem 11.*

The initial theophylline dose for patient LG would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline half-life ($t_{1/2}$) is 5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/5\ h = 0.139\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: V = 0.5 L/kg · 69 kg = 35 L. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.139\ h^{-1} \cdot 35\ L = 4.87$ L/h.

3. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the

calculations so that unnecessary unit conversion was not required.) Therapy will be started by administering an intravenous loading dose of aminophylline to the patient: LD = (Css · V)/S = (8 mg/L · 35 L)/0.8 = 350 mg intravenously over 20–30 minutes.

An aminophylline continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous aminophylline is k_0 = (Css · Cl)/S = (8 mg/L · 4.87 L/h) / 0.8 = 49 mg/h, rounded to 50 mg/h.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.7 mg/kg/h is suggested by Table 18-4 for an adult cigarette smoker.

2. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8): k_0 = (theophylline dose · Wt)/S = (0.7 mg/kg/h · 69 kg)/0.8 = 60 mg/h. A loading dose of aminophylline 6 mg/kg will also be prescribed for the patient: LD = 6 mg/kg · 69 kg = 414 mg, rounded to 400 mg of aminophylline infused over 20–30 minutes. Similar doses were suggested by the pharmacokinetic dosing method.

A theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

12. *Answer to problem 12.*

The revised theophylline dose for patient LG would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Using linear pharmacokinetics, the new infusion rate to attain the desired concentration should be proportional to the old infusion rate that produced the measured concentration:

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (11\ \mu g/mL / 7.4\ \mu g/mL)\ 50\ mg/h$$
$$= 74.3\ mg/h, \text{ rounded to } 75\ mg/h$$

The new suggested infusion rate would be 75 mg/h of aminophylline.

A booster dose of aminophylline would be computed using an estimated volume of distribution for the patient (0.5 L/kg · 69 kg = 35 L): $BD = [(C_{desired} - C_{actual})V]/S$ = [(11 mg/L – 7.4 mg/L) 35L]/0.8 = 157 mg, rounded to 150 mg of aminophylline over 20–30 minutes. The booster dose would be given to the patient before the infusion rate was increased to the new value.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient smokes tobacco-containing cigarettes and would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 5 h = 25 h) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration $Cl = (S \cdot k_0)/Css$ = (0.8 · 50 mg/h) / (7.4 mg/L) = 5.41 L/h. (Note: µg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new aminophylline infusion rate: $k_0 = (Css \cdot Cl)/S$ = (11 mg/L · 5.41 L/h) / (0.8) = 74 mg/h, rounded to 75 mg/h.

A booster dose of aminophylline would be computed using an estimated volume of distribution for the patient (0.5 L/kg · 69 kg = 35 L): $BD = [(C_{desired} - C_{actual})V]/S$ = [(11 mg/L – 7.4 mg/L) 35L] / 0.8 = 157 mg, rounded to 150 mg of aminophylline over 20–30 minutes. The booster dose would be given to the patient before the infusion rate was increased to the new value.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 5 h = 25 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

13. *Answer to problem 13.*

The initial theophylline dose for patient CV would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where hepatic drug–metabolizing enzymes are contained, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 90\ kg = 45\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.029\ h^{-1} \cdot 45\ L = 1.31\ L/h$.

3. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) Therapy will be started by administering an intravenous loading dose of aminophylline to the patient: $LD = (Css \cdot V)/S = (10\ mg/L \cdot 45\ L)\ /\ 0.8 = 562\ mg$, rounded to 550 mg intravenously over 20–30 minutes.

An aminophylline continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $k_0 = (Css \cdot Cl)/S = (10\ mg/L \cdot 1.31\ L/h)/0.8 = 16\ mg/h$, rounded to 15 mg/h.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with cirrhosis.

2. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8): D = (theophylline dose · Wt)/S = (0.2 mg/kg/h · 90 kg)/0.8 = 23 mg/h, rounded to 20 mg/h. A loading dose of aminophylline 6 mg/kg will also be prescribed for the patient: LD = 6 mg/kg · 90 kg = 540 mg, rounded to 550 mg of aminophylline infused over 20–30 minutes. These doses are similar to that suggested by the pharmacokinetic dosing method of a 550-mg loading dose followed by a 15 mg/h continuous infusion.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

14. *Answer to problem 14.*

The revised theophylline dose for patient CV would be calculated as follows:

The patient has liver cirrhosis and would be expected to achieve steady-state conditions after the fifth day (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy. Because the serum theophylline concentration was obtained after 72 h of therapy, it is unlikely that serum concentration is at steady state, even though a loading dose was given, so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this patient's case, it is unlikely that the patient is at steady state so the linear pharmacokinetics method cannot be used. DrugCalc requires doses to be entered in terms of theophylline, so aminophylline doses must be converted to theophylline doses for entry into the program (LD = 400 mg aminophylline · 0.8 = 320 mg theophylline, k_0 = 25 mg/h aminophylline · 0.8 = 20 mg/h theophylline).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 37 L, a half-life equal to 38 hours, and a clearance equal to 0.67 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model infusion equations used by the program to compute doses indicate that an aminophylline infusion of 13 mg/h will produce a steady-state theophylline concentration of 15 μg/mL. This dose would be started after holding the infusion for 40 hours (~1 half-life) to allow theophylline serum concentrations to decrease by 1 half.

15. *Answer to problem 15.*

The initial theophylline dose for patient PE would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

Patients with severe heart failure have highly variable theophylline pharmacokinetics and dosage requirements. Heart failure patients have decreased cardiac output which leads to decreased liver blood flow, and the expected theophylline half-life ($t_{1/2}$) is 24 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/24\ h = 0.029\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight: $V = 0.5\ L/kg \cdot 67\ kg = 34\ L$. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.029\ h^{-1} \cdot 34\ L = 0.99\ L/h$.

3. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8). (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) Therapy will be started by administering an intravenous loading dose of aminophylline to the patient: $LD = (Css \cdot V)/S = (8\ mg/L \cdot 34\ L) / 0.8 = 340\ mg$, rounded to 350 mg intravenously over 20–30 minutes.

An aminophylline continuous intravenous infusion will be started immediately after the loading dose has been administered. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for intravenous aminophylline is $k_0 = (Css \cdot Cl)/S = (8\ mg/L \cdot 0.99\ L/h) / 0.8 = 9.9\ mg/h$, rounded to 10 mg/h.

A steady-state theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 days). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure that receive theophylline therapy must be monitored very carefully.

Literature-based recommended dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.2 mg/kg/h is suggested by Table 18-4 for an adult with severe heart failure.

2. *Compute dosage regimen.*

Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8): D = (theophylline dose · Wt)/S = (0.2 mg/kg/h · 67 kg)/0.8 = 17 mg/h, rounded to 15 mg/h. A loading dose of aminophylline 6 mg/kg will also be prescribed for the patient: LD = 6 mg/kg · 67 kg = 402 mg, rounded to 400 mg of aminophylline infused over 20–30 minutes. These doses are similar to that suggested by the pharmacokinetic dosing method.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 24 hours, the theophylline steady-state concentration could be obtained anytime after the fifth day of dosing (5 half-lives = 5 · 24 h = 120 h or 5 d). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity. Theophylline pharmacokinetic parameters can change as the patient's cardiac status changes. If heart failure improves, cardiac output will increase resulting in increased liver blood flow and theophylline clearance. Alternatively, if heart failure worsens, cardiac output will decrease further resulting in decreased liver blood flow and theophylline clearance. Thus, patients with heart failure that receive theophylline therapy must be monitored very carefully.

16. *Answer to problem 16.*

The revised theophylline dose for patient PE would be calculated as follows:

The patient has severe heart failure and would be expected to achieve steady-state conditions after the fifth day (5 $t_{1/2}$ = 5 · 24 h = 120 h or 5 d) of therapy. Because the serum theophylline serum concentrations were obtained after 12 hours and 24 hours of therapy, it is unlikely that the serum concentrations were obtained at steady state even though a loading dose was given, so the linear pharmacokinetics or pharmacokinetic parameter methods cannot be used.

Chiou Method

1. *Compute theophylline clearance.*

$$Cl = \frac{2 \cdot S \cdot k_0}{C_1 + C_2} + \frac{2V(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)}$$

$$Cl = \frac{2[0.8(20\ mg/h)]}{14.2\ mg/L + 18.6\ mg/L} + \frac{2(0.5\ L/kg \cdot 67\ kg)(14.2\ mg/L - 18.6\ mg/L)}{(14.2\ mg/L + 18.6\ mg/L)\ 12\ h}$$

$$= 0.23\ L/h$$

(Note: µg/mL = mg/L and this concentration unit was substituted for concentrations so that unnecessary unit conversion was not required. Additionally, the time difference between t_2 and t_1 was determined and placed directly in the calculation.)

k_0 = (Css · Cl)/S = (18 mg/L · 0.23 L/h)/0.8 = 5 mg/h of aminophylline

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

In this case, the patient is not at steady state so the linear pharmacokinetics method cannot be used. DrugCalc requires doses to be entered in terms of theophylline, so aminophylline doses must be converted to theophylline doses for entry into the program (LD = 350 mg aminophylline · 0.8 = 280 mg theophylline, k_0 = 20 mg/h aminophylline · 0.8 = 16 mg/h theophylline).

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 26 L, a half-life equal to 31 hours, and a clearance equal to 0.59 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model infusion equations used by the program to compute doses indicate that an aminophylline infusion of 14 mg/h will produce a steady-state theophylline concentration of 18 μg/mL.

17. *Answer to problem 17.*

The initial theophylline dose for patient ZQ would be calculated as follows:

Pharmacokinetic Dosing Method

1. *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

The expected theophylline half-life ($t_{1/2}$) is 3.5 hours. The elimination rate constant is computed using the following formula: $k = 0.693/t_{1/2} = 0.693/3.5\ h = 0.198\ h^{-1}$.

2. *Estimate volume of distribution and clearance.*

The estimated theophylline volume of distribution is V = 0.5 L/kg · 20 kg = 10 L. Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant: $Cl = kV = 0.198\ h^{-1} \cdot 10\ L = 1.98$ L/h.

3. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1), and the initial dosage interval (τ) will be set to 8 hours because children have rapid clearance rates. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.) The dosage equation for oral theophylline is $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (6\ mg/L \cdot 1.98\ L/h \cdot 8\ h)/(1 \cdot 1) = 95$ mg, rounded to 100 every 8 hours.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 3.5 h = 17.5 h). Theophylline

serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Literature-Based Recommended Dosing

1. *Choose theophylline dose based on disease states and conditions present in the patient.*

A theophylline dose of 0.8 mg/kg/h is suggested by Table 18-4 for a child of this age.

2. *Compute dosage regimen.*

Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1), and the initial dosage interval (τ) will be set to 8 hours because children have rapid clearance rates: D = (theophylline dose · Wt · τ)/S = (0.8 mg/kg/h · 20 kg · 8 h)/1 = 128 mg, rounded to 100 mg every 12 hours (Note: dose rounded down to avoid potential theophylline side effects). This dose is identical to that suggested by the pharmacokinetic dosing method.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 3.5 h = 17.5 h). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

18. *Answer to problem 18.*

The revised theophylline dose for patient ZQ would be calculated as follows:

Linear Pharmacokinetics Method

1. *Compute new dose to achieve desired serum concentration.*

The patient would be expected to achieve steady-state conditions after the first day (5 $t_{1/2}$ = 5 · 3.5 h = 17.5 h) of therapy.

Using linear pharmacokinetics, the new dose to attain the desired concentration should be proportional to the old dose that produced the measured concentration (total daily dose = 100 mg/dose · 3 doses/d = 300 mg/d):

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old} = (6\ \mu g/mL / 4\ \mu g/mL)\ 300\ mg/d = 450\ mg/d$$

The new suggested dose would be 450 mg/d or 150 mg every 8 hours of theophylline sustained-release tablets to be started at the next scheduled dosing time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing (5 half-lives = 5 · 3.5 h = 17.5 h). Theophylline

serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Pharmacokinetic Parameter Method

1. *Compute pharmacokinetic parameters.*

The patient would be expected to achieve steady-state conditions after the first day ($5\ t_{1/2} = 5 \cdot 3.5\ h = 17.5\ h$) of therapy.

Theophylline clearance can be computed using a steady-state theophylline concentration: $Cl = [F \cdot S\ (D/\tau)] / Css = [1 \cdot 1\ (100\ mg/8\ h)] / (4\ mg/L) = 3.13\ L/h$. (Note: μg/mL = mg/L and this concentration unit was substituted for Css in the calculations so that unnecessary unit conversion was not required.)

2. *Compute theophylline dose.*

Theophylline clearance is used to compute the new dose: $D = (Css \cdot Cl \cdot \tau)/(F \cdot S) = (6\ mg/L \cdot 3.13\ L/h \cdot 8\ h) / (1 \cdot 1) = 150\ mg$ every 8 hours.

The new theophylline dosage regimen would be instituted at the next dosage time.

A steady-state trough theophylline serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 3.5 hours, the theophylline steady-state concentration could be obtained anytime after the first day of dosing ($5\ t_{1/2} = 5 \cdot 3.5\ h = 17.5\ h$). Theophylline serum concentrations should also be measured if the patient experiences an exacerbation of their lung disease, or if the patient develops potential signs or symptoms of theophylline toxicity.

Bayesian Pharmacokinetic Computer Programs Method

1. *Enter patient's demographic, drug dosing, and serum concentration/time data into the computer program.*

2. *Compute pharmacokinetic parameters for the patient using Bayesian pharmacokinetic computer program.*

The pharmacokinetic parameters computed by the program are a volume of distribution of 9.9 L, a half-life equal to 2.8 hours, and a clearance equal to 2.45 L/h.

3. *Compute dose required to achieve desired theophylline serum concentrations.*

The one-compartment model, first-order absorption equations used by the program to compute doses indicates that a dose of 150 mg every 8 hours will produce a steady-state theophylline concentration of 6.1 μg/mL.

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