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

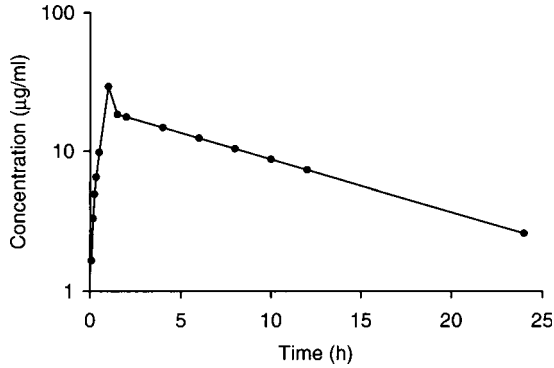

FIGURE 5-1 Concentration/time plot for vancomycin 1000 mg given as a 1-hour infusion *(circles with dashed line)*. When given as a 1-hour infusion, end of infusion concentrations are higher because the serum and tissues are not in equilibrium. A $^1/_2$- to 1-hour waiting time for vancomycin distribution 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

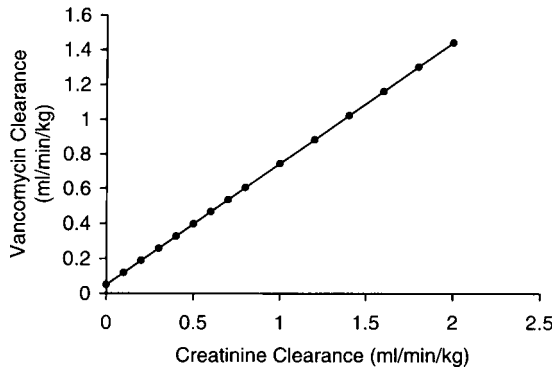

FIGURE 5-2 The clearance rate for vancomycin increases in proportion with creatinine clearance (CrCl). The equation for this relationship is Cl (in mL/min/kg) = 0.695(CrCl in mL/min/kg) + 0.05. This equation is used to estimate vancomycin clearance in patients for initial dosing purposes.

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).

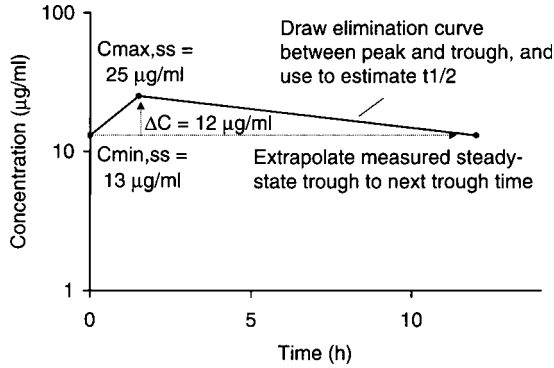

FIGURE 5-3 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough 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.

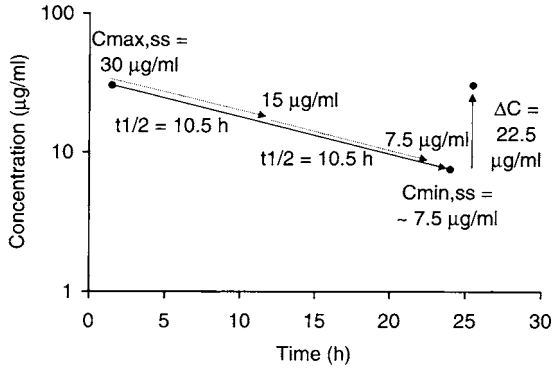

FIGURE 5-4 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

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).

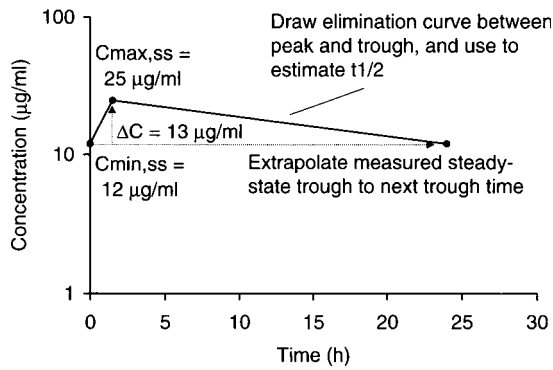

FIGURE 5-5 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough 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

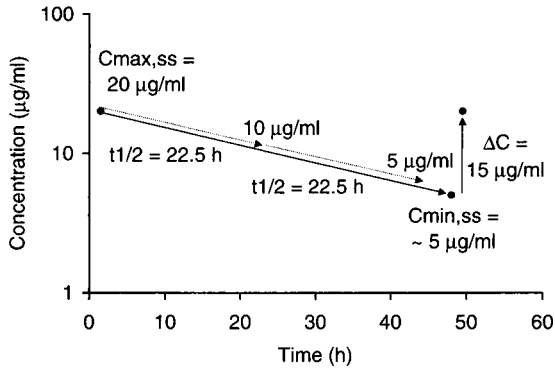

FIGURE 5-6 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

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

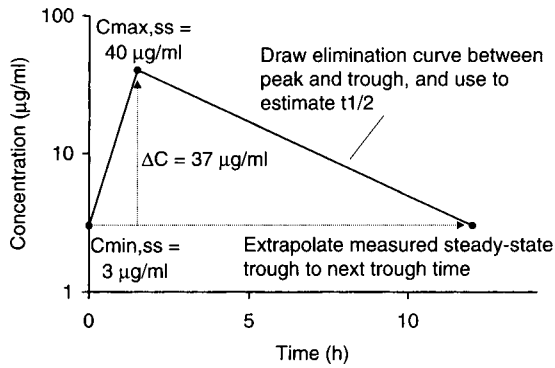

FIGURE 5-7 Graphical representation of the pharmacokinetic concepts method where a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair is used to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough 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.

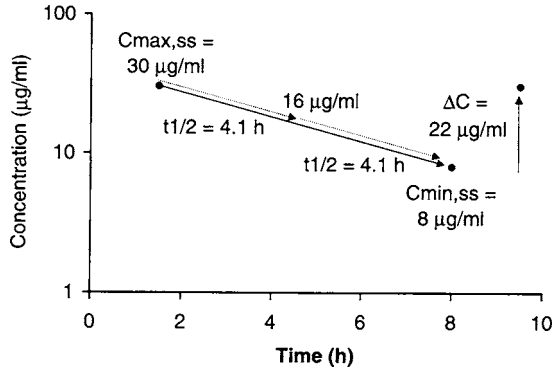

FIGURE 5-8 The pharmacokinetic concepts method uses the estimated half-life to graphically compute the new dosage interval and the change in concentration to calculate the dose for a patient.

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

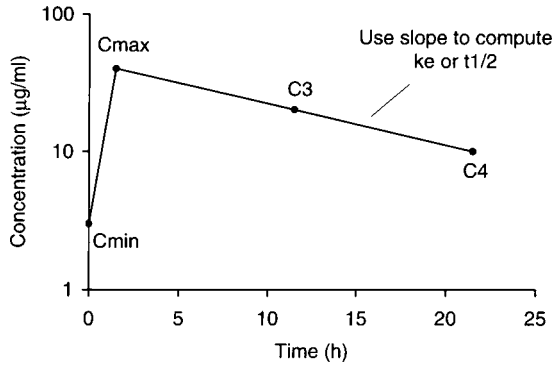

FIGURE 5-9 The one-compartment model parameter method for individualization of vancomycin doses uses a trough (C_{min}), peak (C_{max}), and 1–2 additional postdose concentrations (C_3, C_4) to compute a patient's own, unique pharmacokinetic parameters. This version of the one-compartment model parameter 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.

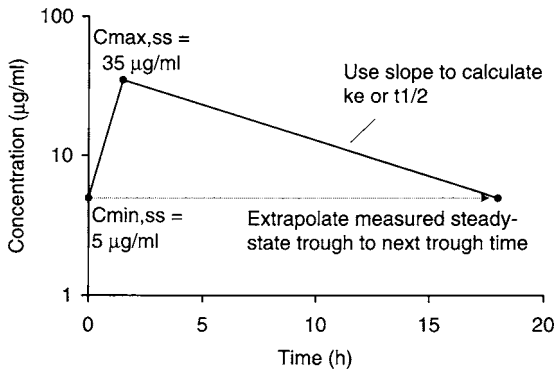

FIGURE 5-10 The steady-state version of the one-compartment model parameter method uses a steady-state peak (Css_{max}) and trough (Css_{min}) concentration pair to individualize vancomycin therapy. Because the patient is at steady state, consecutive trough concentrations will be identical, so the trough 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.

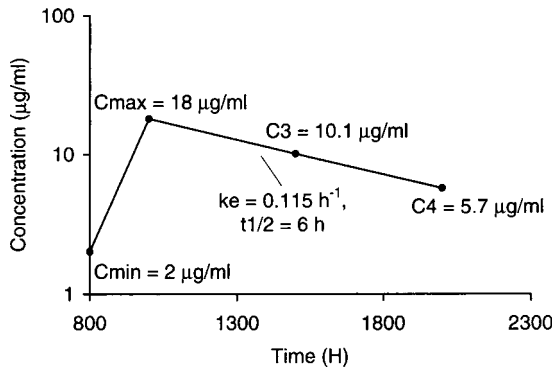

FIGURE 5-11 Graph of vancomycin serum concentrations used in one-compartment model parameter method example.

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

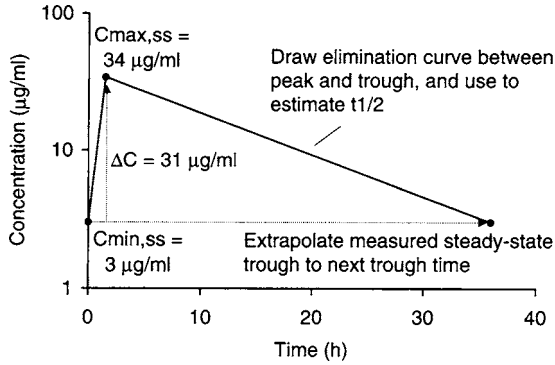

FIGURE 5-12 Solution to problem 2 using pharmacokinetic concepts method.

(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

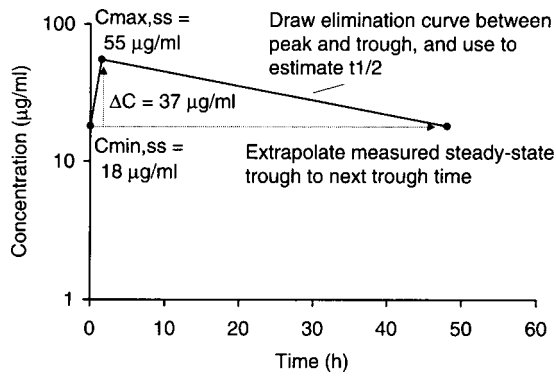

FIGURE 5-13 Solution to problem 4 using pharmacokinetic concepts method.

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

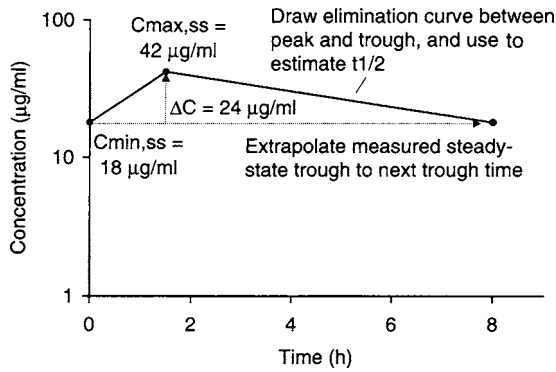

FIGURE 5-14 Solution to problem 6 using pharmacokinetic concepts method.

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

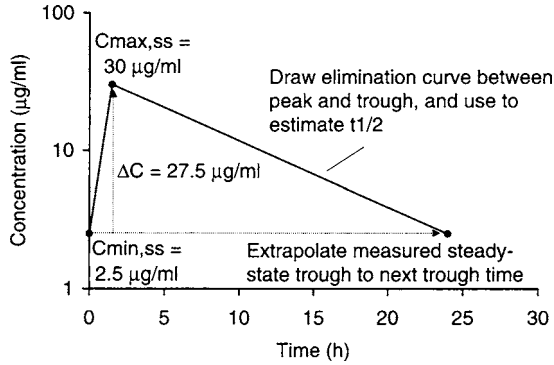

FIGURE 5-15 Solution to Problem 8 using pharmacokinetic concepts method.

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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