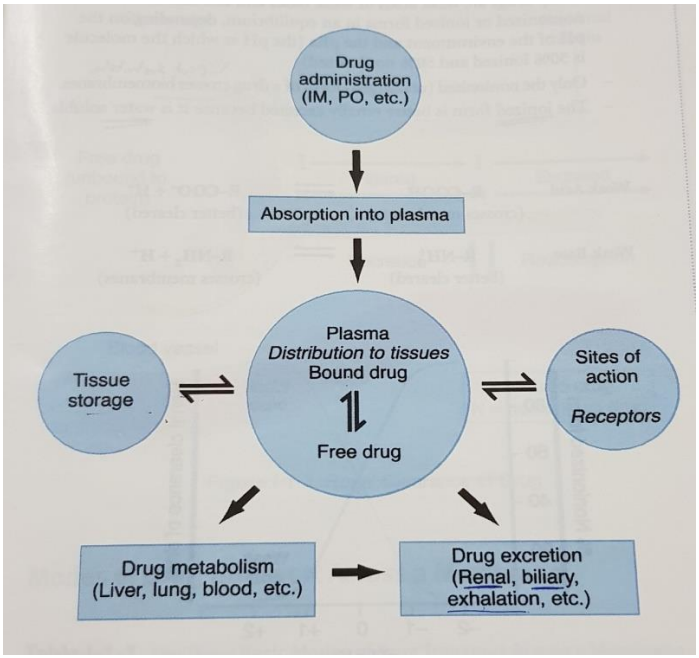
Lec.2

Pharmacokinetics

Pharmacokinetic: Are the effects of the body on drugs.

Several physiologic process (body size, maturation of organ function in infants) and pathologic processes (heart failure, renal failure) dictate dosage adjustment in individual patients. These processes modify specific pharmacokinetic parameters.



The major processes involved in pharmacokinetics are:

1- Absorption: is the transfer of drug from the site of administration to the blood stream.

The rate and extent of absorption depend on the:

Environment where the drug absorbed(e.g.PH of GIT: weak acid drug in stomach absorbed in highly acidic stomach, weak base drug absorbed in intestine with alkaline ph 7.5)

Nature formulation of drug (particle size, enteric coating)

Drugs dosage form (syrup absorbed faster than tablet)

Blood flow at site of a absorption ↑ → ↑absorption

Route of administration (which influences bioavailability),route of administration other than intravenous may result in partial absorption & lower bioavailability.

Bioavailability (F) of the drug: is the fraction (F) of administered dose that reaches the systemic circulation e.g./ if 100 mg if drug is administered orally and 70 mg is absorbed unchanged, bioavailability is 0.7 or 70%.

Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

- Bioavailability of intravenous routes of administration 100%

- Other routes bioavailability reduced by incomplete absorption, first pass metabolism, that occurs before the drug enters the systemic circulation.

2- Distribution: the process of distribution of drug from systemic circulation to organs and tissue.The blood, body water, extracellular, lymphatic cerebrospinal fluids are involved in movement of drug through the body.

Depending upon its (drug)chemical and physical properties, drug bounding to plasma protein or dissolved in body tissue fat, delaying its progress to its site of action, metabolism or excretion.

Volume of distribution (Vd): the ratio of the amount of drug in the body to the drug concentration in the plasma.

$$Vd = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}}$$

Units = Volume(Liter)

- Vd is low when a high percentage of a drug is bound to plasma proteins.
- Vd is high when high percentage of drug is being sequestered in tissues.

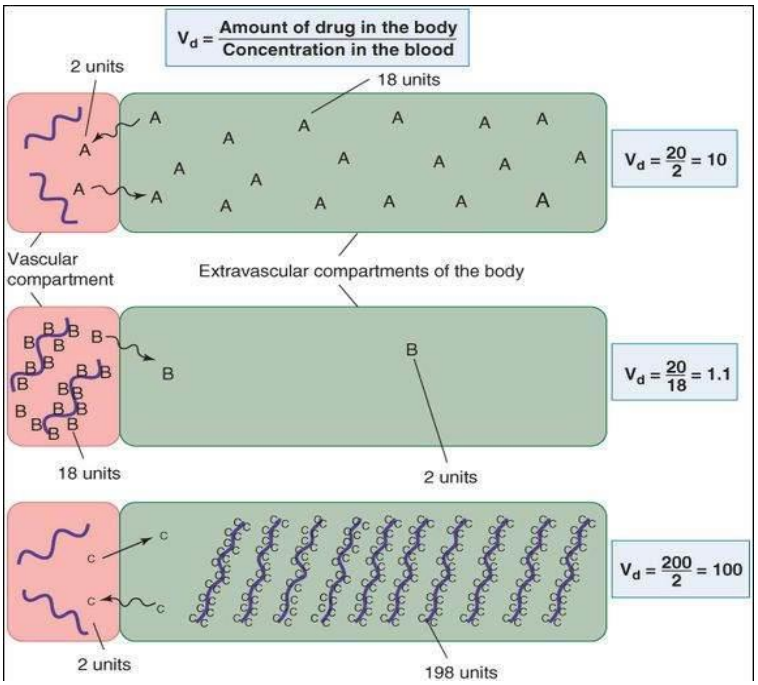


Fig.2: Effect of drug binding on volume of distribution. Drug A diffuse freely between the 2 compartments and does not bind to macromolecules (heavy wavy lines) in the vascular (volume 1 L) or the extravascular compartments(volume 5 L)of the hypothetical organism in the diagram. With 20 units of the drug in the body, the steady -state distribution leaves a blood concentration of 2 units/L. Drug B, on the other hand, binds avidly to proteins in the blood. At equilibrium, only 2 units of the total are present in the extravascular volume , leaving 18 units still in the blood . In each case, the total amount of drug in the body is the same (20 units), but the apparent volumes of distribution are very different. Drug C is avidly bound to molecules in peripheral tissues, so that a larger total dose (200 units) is required to achieve measurable plasma concentrations. At equilibrium, 198 units are found in the peripheral tissues and only 2 units in the plasma , so that the calculated volume of distribution is greater than physical volume of the system.

3- Metabolism:

All organisms are exposed to foreign chemical compounds (Xenobiotics) in air, water and food. To ensure elimination of pharmacologically active xenobiotics as well as to terminate the action of many endogenous substances, evolution has resulted in metabolic pathways that alter their activity and their susceptibility to excretion.

* The most important organ for drug metabolism is the liver. The kidneys play an important role in the metabolism of some drugs, a few drugs (e.g. esters) are metabolized in many tissues (liver, blood, intestinal wall) because of the broad distribution of their enzymes.

* Kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in distal convoluted tubules. Therefore lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general phase I and phase II reactions.

Phase I: involve reduction, oxidation, hydrolysis.

Phase II: consist of conjugation reactions. If the metabolite from phase I is sufficiently polar it can be excreted by kidney, many phase I metabolites are still too lipophilic to be excreted as subsequent conjugation reaction with an endogenous substrate as glucuronic acid, sulfuric acid, acetic acid or amino acid result in polar, more water soluble.

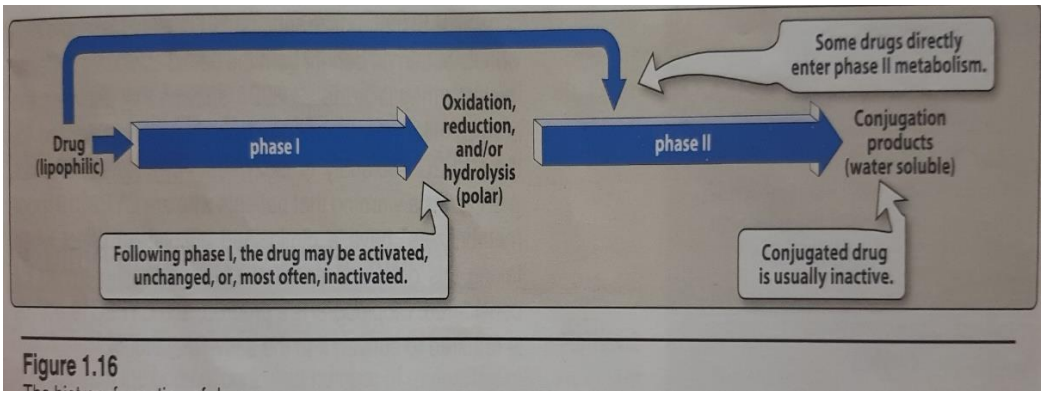


Figure 1.16

• **CYP450:** cytochrome P450 system is important for drug metabolism and endogenous compounds (steroid, lipids). Located in most cells, but primarily in the liver and GI tract.

• Phase I reactions most frequently involved in drug metabolism are catalyzed by CYP450.

Drug -drug interactions:-

1) Enzyme induction: increase synthesis of cytochrome P450 enzymes in the liver that cause increase metabolism of drugs. Many drugs cause this induction of enzyme: phenobarbital, phenytoin, and rifampin. Several days are required to reach maximum induction, similar amount of time required to regress after withdrawal of inducer.

2) Enzyme inhibition:

The most likely inhibitors of drug metabolism are amiodarone, cimetidine, furanocoumarin present in grapefruit juice, erythromycin, ketoconazole.

• Inhibition of drug metabolism can lead to significant increase plasma drug concentration and adverse effects or toxicity.

• Metabolism may also be decreased by reduction in blood flow to metabolizing organ (e.g. propranolol reduces hepatic blood flow).

Toxic metabolism: some drugs are converted to active product by metabolism , acetaminophen when taken in large overdose.

- Acetaminophen is conjugated to harmless glucuronide and sulfate metabolites in case of taken in recommended dose.

-If large overdose is taken however a P450 dependent system converts some of the drug to reactive intermediate (N-acetyl-p-benzoquinone imine) this intermediate is conjugated with glutathione to a third harmless product.

- If glutathione stores are adequate. If glutathione stores are exhausted, however, the reactive intermediate combines with sulfhydryl groups on essential hepatic cell proteins, resulting in cell death.

- Prompt administration of other sulfhydryl donors (e.g. acetylcysteine) may be lifesaving after overdose.

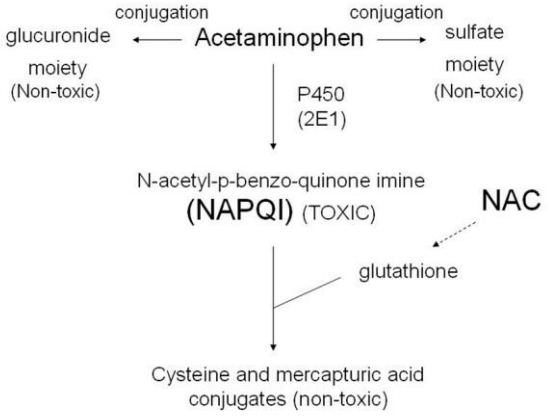


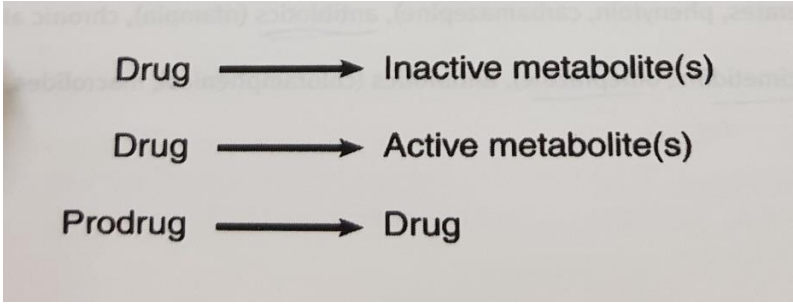
fig. Acetaminophen metabolism

• **Drug metabolism as mechanism of drug activation:**

Prodrug: are inactive as administered and must be metabolized in the body to become active as (levodopa).

- Many drugs active as administered and have active metabolites as well (some benzodiazepines).

- Some drugs (lithium) are not modified by the body they continue to act until they are excreted.



First pass metabolism:

Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation a drug can be metabolized in the gut wall (CYP3A4) enzyme system, but most commonly in liver. Any of these sites can contribute to this reduction in bioavailability. (Fig.I.1.6)

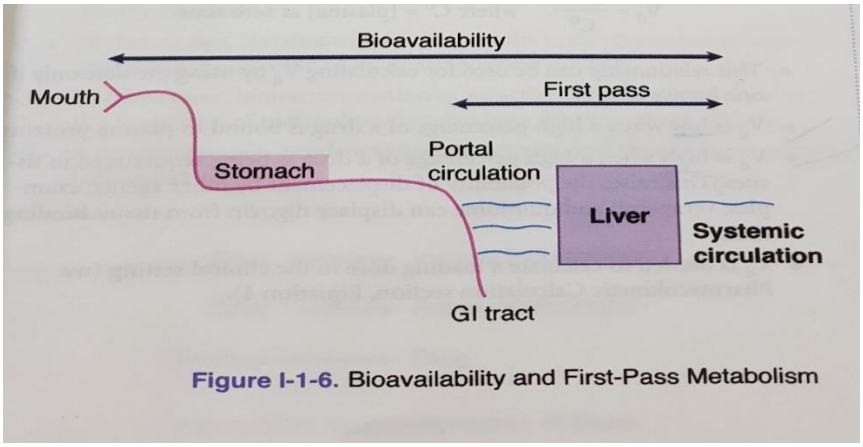


Figure I-1-6. Bioavailability and First-Pass Metabolism

4- Excretion: the kidney is the most important organ for excretion of drugs, Biliary elimination. The lungs and sweat usually play a minor role.

Clearance:

Clearance (CL) relates the rate of elimination to the plasma concentration.

$$CL = \frac{\text{Rate of elimination of drug}}{\text{Plasma concentration of drug}} \qquad \text{Unit= (Volume per unit time)}$$

For drugs eliminated with first-order kinetic, clearance is a constant; that is, the ratio of rate of elimination to plasma concentration is the same regardless of plasma concentration. Note that for drugs eliminated with zero-order kinetics, clearance is not constant.

A) First-order elimination:

The term first order elimination indicates that the rate of elimination is proportional to the concentration (i.e., the higher the concentration, the greater the amount of drug eliminated per unit time). The result is that the drug's concentration in plasma decrease exponentially with time.

Drugs with first-order elimination have a characteristic half-life of elimination that is constant regardless of the amount of drug in the body. The concentration of such a drug in blood will decrease by 50% for every half-life. Most drugs in clinical use demonstrate first-order kinetics.

B) Zero-order elimination:

The term zero-order elimination implies that the rate of elimination is constant regardless of concentration. This occurs with drugs that saturate their elimination mechanisms at concentrations of clinical interest. As a result, the concentration of these drugs in plasma decrease in a linear fashion over time. Such drugs do not have a constant half-life. This is typical of ethanol and phenytoin and aspirin at high therapeutic or toxic concentration.

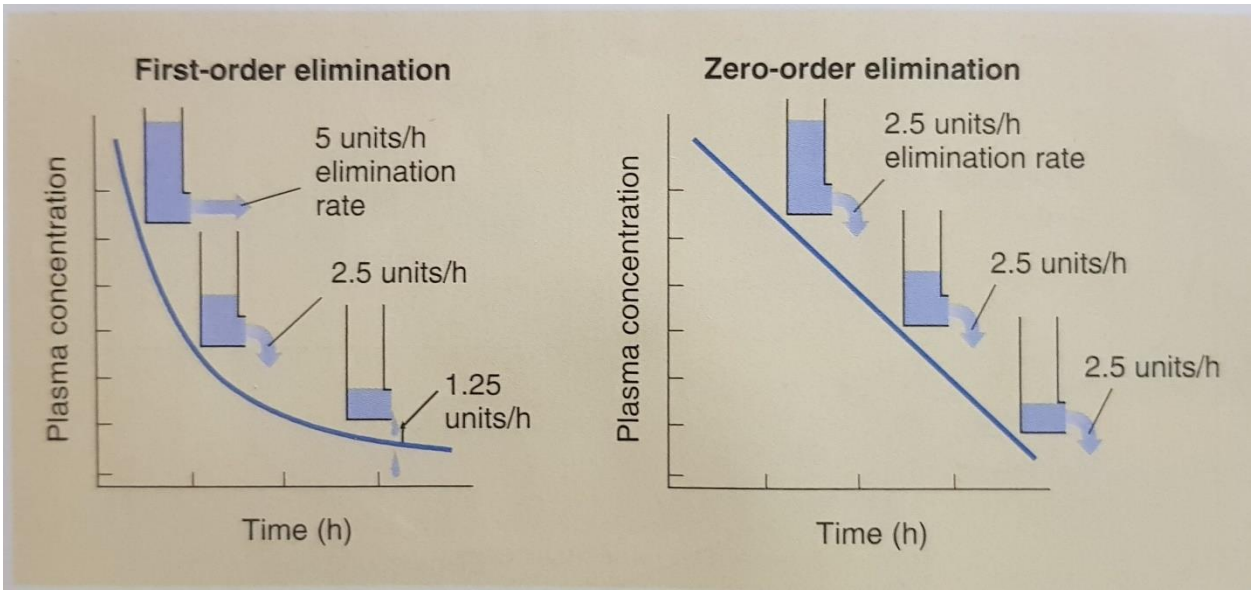


Fig 1-3: comparison of first- order and zero-order elimination. For drugs with first-order kinetics(left), rate of elimination (units per hour)is proportional to concentration; this is the more common process. In the case of zero-order elimination (right), the rate is constant and independent of concentration.

First order

1. ↑Plasma drug concentration→ ↑rate of drug metabolism.
2. Rate of metabolism is proportional to drug concentration.
3. Constant <u>proportion</u> of drug eliminated per time.
4. Clearance constant.
5. Half-life is constant(time to metabolize 50% of drug)
6. Example :most drug at most doses.
7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8 mg/l	4
1	4	2
2	2	1
3	1	0.5

Zero order

1.↑plasma drug concentration →no↑ rate of metabolism.

2.Rate of metabolism becomes independent of drug concentration. Rate of drug metabolism constant.

3.constant <u>amount</u> of the drug eliminated per time.

4.clearance not constant.

5. half-life not constant.

6.Aspirin,Phenytoin.

7.

Time(hr)	Plasma conc.	Rate of elimin.
0	8	2 mg/l/hr
1	6	2
2	4	2
3	2	2

Half-life (t ½): is the time required to change the amount of drug in the body by one-half during elimination (or during constant infusion). It is a derived parameter, completely determined by Vd and CL. Like clearance, half-life is constant for drugs that follow first-order kinetics. Half-life can be determined graphically from plot of the blood level versus time or from following relationship:

$$t_{½} = \frac{0.693 \times Vd}{CL}$$

(unit = time)

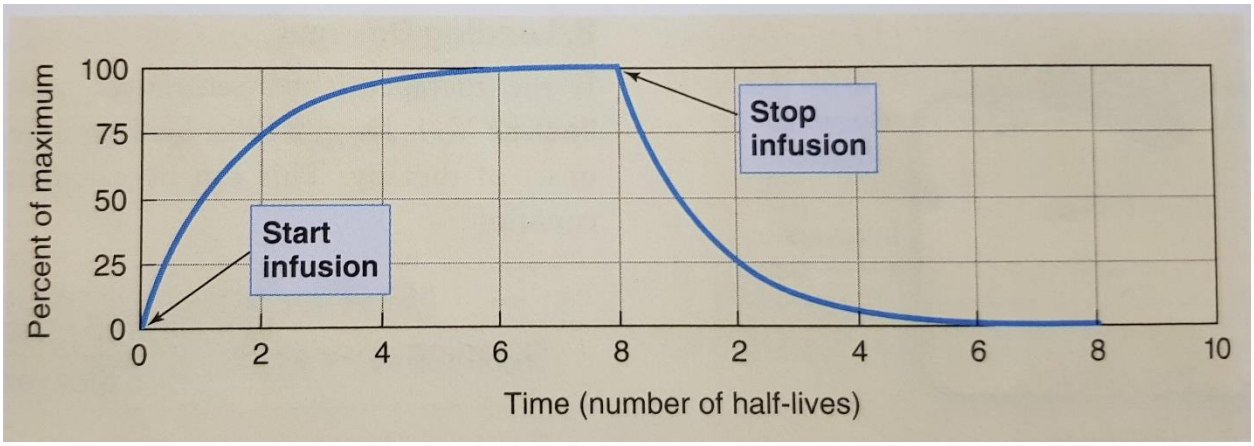


Fig 1-4: plasma conc.(plotted as percent of maximum)of adrug (t1/2 1hr)given by constant intravenous infusion for 8 half-lives and then stopped . the conc. Rises smoothly with time and always reaches 50% of steady state after 1 half-life,75% after 2half-lives, 87.5%after 3 half-lives, and so on. The decline in conc. After stopping drug administration follows the same type of curve :50%is left after 1half-life, 25%after 2 half-lives , and so on . this approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first -order kinetics

- Drugs or substances that have a shorter half-life tend to act very quickly, but their effects wear off rapidly, meaning that they usually need to be taken several times a day to have the same effect.
- Drugs with a longer half-life may take longer to start working, but their effects persist for longer, and they may only need to be dosed once a day, once a week, once a month, or even less frequently**.**
- From half-life estimate the duration of action for drug.

  6 x half-life =duration of action of the drug

Therapeutic window: is the safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug. These data are used to determine the acceptable range of plasma levels when designing a dosing regimen. e.g. therapeutic plasma conc. of theophylline 8 mg/L and toxic effect observed at 18 mg/L, Therapeutic window 8-18 mg/L. Fig.1-5

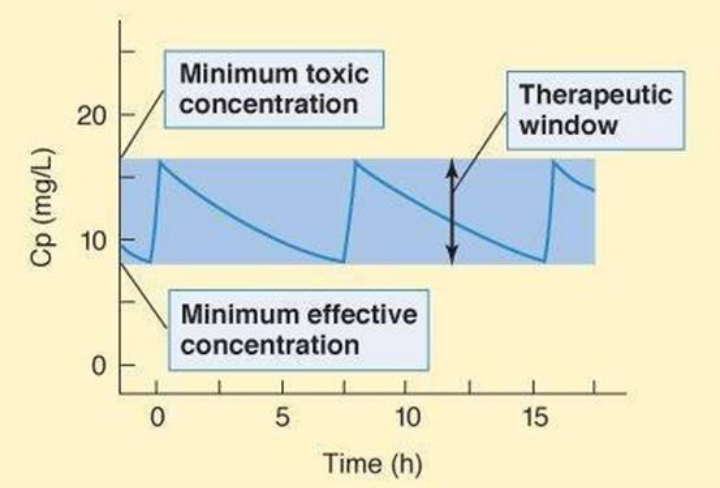


Figure 1-5: The therapeutic window for theophylline in a typical patient. The minimum effective concentration in this patient was found to be 8 mg/L; the minimum toxic concentration was found to be 16 mg/L. The therapeutic window is indicated by the blue area. To maintain the plasma concentration (Cp) within the window, this drug must be given at least once every half-life (7.5 h in this patient) because the minimum effective concentration is half the minimum toxic concentration and Cp will decay by 50% in 1 half-life. (***Note:*** This concept applies to drugs given in the ordinary, prompt-release form. Slow-release formulations can often be given at longer intervals.)

Therapeutic index (TI)

Is the ratio used to evaluate safety and usefulness of a drug for indication.

It is a ratio of the dose that produces toxicity in 50% of population (TD50) to the dose that produces a clinically effective response (ED50) in 50% of population. determined from quantal dose-response curves.

$$TI = \frac{TD50}{ED50}$$

Large value TI indicate wide margin between doses that are effective and doses that are toxic (TD50 larger than ED50).

Example:

ED50 = 3 mg

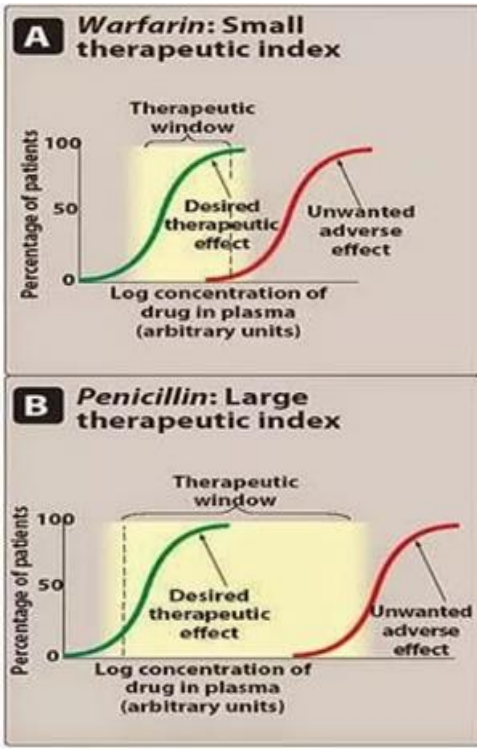
TD50 = 150 mg

TI = 150/3 = 50 in mice.

Obviously, a full range of toxic doses cannot be ethically studied in humans. Furthermore, factors such as the varying slopes of dose-response curves make this estimate a poor safety index even in animals.

The therapeutic window, a more clinically useful index of safety, describes the dosage range between the minimum effective therapeutic concentration or dose, and the minimum toxic concentration or dose.

Both therapeutic index and therapeutic window depends on the specific toxic effect used in the determination.

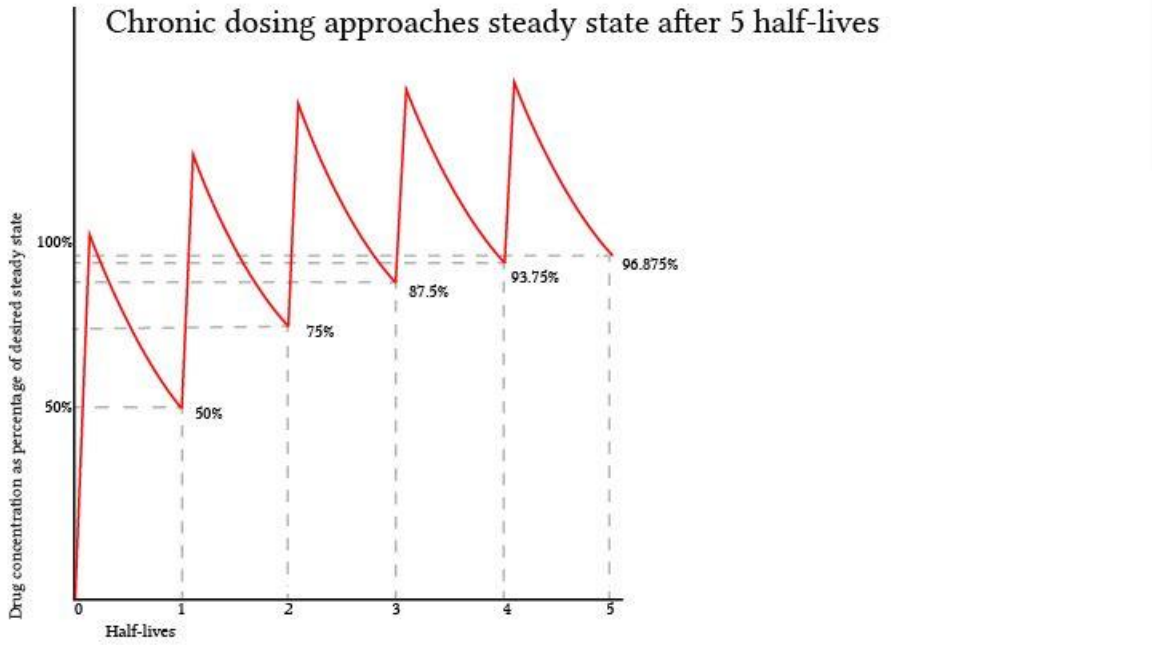


Dosage regimens: is a plan for drug administration over a period of time. An optimal dosage regimen result in the achievement of therapeutic levels of the drug in the blood without exceeding the minimum toxic concentration. To maintain the plasma concentration within a specified range over long periods of therapy, a schedule of maintenance doses is used. If it is necessary to achieve the target plasma level rapidly, a loading dose is used.

Steady state plasma concentration: when the rate of drug eliminator is equal to the rate of drug administration such plasma & tissue levels remain constant.

steady state of drug reach after 5-6 half-life =duration of action of the drug

In regular doses, drug concentration achieves a steady state in steps, but the end result is the same - the plasma drug concentration reaches a point at which the dose rate and the clearance rate are equal after about five half-lives.



Ultimately, the drug will reach close enough to the steady state after about 5 half-lives.

Maintenance dose: Drugs are generally administered to maintain a steady state plasma concentration within the therapeutic window.

Loading dose: Sometimes rapid obtainment of desired plasma levels is needed, a large loading dose may be needed at the onset of therapy.

for drugs with long half-lives, it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration

Adjustment of dosage when elimination is altered by disease:

Renal disease or reduced cardiac output often reduces the clearance of drugs that depend on renal function. Alteration of clearance by liver disease is less common but may also occur. Impairment of hepatic clearance occurs (for high extraction drugs) when liver blood flow is reduced, as I heart failure, and in severe cirrhosis and other form of liver failure. The dosage in a patient with renal impairment may be corrected .

Protein binding:

• A drug's efficiency may be affected by the degree to which it binds to the proteins within blood plasma. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Common blood proteins that drugs bind to are: Albumin, lipoprotein, glycoprotein, and α, β, and γ globulins.

• A drug in blood exists in two forms: bound and unbound:

Protein + drug ⇄ protein-drug complex.

• Unbound fraction which exhibit pharmacologic effects and may be metabolized and or excreted.

- Bound drug is have no action

Factor affecting on the plasma protein binding :-

1-displacement of one drug by another drug ex.: aspirin and warfarin →aspirin displace the warfarin due to high affinity to plasma protein→ high free active warfarin →↑ the toxicity of warfarin.

2.↓in the albumin plasma protein due to liver disease lead to ↑the free active drugs→ ↑ toxicity