Principle of Pharmacokinetics

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Learning objectives:

At the end of this lecture the students should be able to:

1- Explain the pharmacokinetic processes: absorption, distribution, metabolism and excretion, and justify the importance of this process in drug therapy.
2- Describe the role of pharmacokinetic variables (bioavailability, volume of distribution and clearance …) in determination of dose and interval of drugs.
3- Define the relation between the pharmacokinetics and pharmacodynamics with respect to the desired concentration at the site of action and the calculated dose and interval.

DRUG-BODY INTERACTIONS

The interactions between a drug and the body are conveniently divided into two classes.

The actions of the drug on the body are termed **pharmacodynamic** processes. These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease.

The actions of the body on the drug are called **pharmacokinetic** processes. Pharmacokinetic processes govern the **absorption, distribution, metabolism and elimination** of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with impaired renal function. The following paragraphs provide a brief introduction to pharmacokinetics.

Pharmacokinetic Principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. Most often, a drug is administered into one body compartment, eg, the gut, and must move to its site of action in another compartment, eg, the brain in the case of an antiseizure medication. This requires that the drug be **absorbed** into the blood from its site of administration and **distributed** to its site of action, **permeating** through the various barriers that separate these compartments. Finally, after bringing about its effect, a drug should be **eliminated** at a reasonable rate by **metabolic** inactivation, by **excretion** from the body, or by a combination of these processes.

Absorption

Transfer of drugs from the site of administration into the systemic circulation is called absorption. Several mechanisms are involved in this transfer.

A. Permeation

Drug permeation proceeds by several mechanisms. **Passive diffusion** in an aqueous or lipid medium is common, but active processes play a role in the movement of many drugs, especially those whose molecules are too large to diffuse readily (Figure 1–4). Drug **vehicles** can be very important in facilitating transport and permeation.

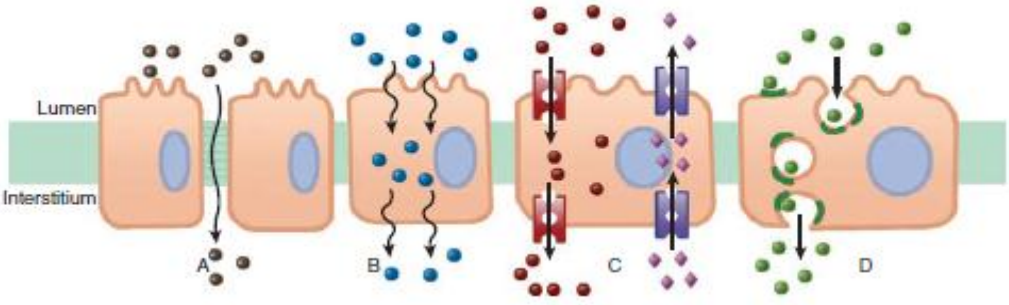


Figure 1–4 Mechanisms of drug permeation. Drugs may diffuse passively through aqueous channels in the intercellular junctions (eg, tight junctions, **A**), or through lipid cell membranes (**B**). Drugs with the appropriate characteristics may be transported by carriers into or out of cells (**C**). Very impermeant drugs may also bind to cell surface receptors (dark binding sites), be engulfed by the cell membrane (endocytosis), and then released inside the cell or expelled via the membrane-limited vesicles out of the cell into the extracellular space (exocytosis, **D**)

1. ***Aqueous diffusion*—**Aqueous diffusion occurs within thelarger aqueous compartments of the body (interstitial space,cytosol, etc) and across epithelial membrane tight junctionsand the endothelial lining of blood vessels through aqueouspores that—in some tissues—permit the passage of moleculesas large as MW 20,000–30,000
2. ***Lipid diffusion*—**Lipid diffusion is the most important limitingfactor for drug permeation because of the large number oflipid barriers that separate the compartments of the body. Because these lipid barriers separate aqueous compartments,the**lipid:aqueous partition coefficient** of a drug determineshow readily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain orlose electrical charge-bearing protons, depending on the pH),the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules attractwater molecules. The ratio of lipid-soluble form to water-solubleform for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation (described in the followingtext). See Figure 1–4B.

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = pK_a - pH$$

3. ***Special carriers*—**Special carrier molecules exist for many substancesthat are important for cell function and too large or tooinsoluble in lipid to diffuse passively through membranes, eg, peptides, amino acids, and glucose. These carriers bring aboutmovement by active transport or facilitated diffusion and,unlike passive diffusion, are selective, saturable, and inhibitable. Because many drugs are or resemble such naturally occurringpeptides, amino acids, or sugars, they can use these carriersto cross membranes. See Figure 1–4C.
4. ***Endocytosis and exocytosis*—**A few substances are so large orimpermeant that they can enter cells only by endocytosis, theprocess by which the substance is bound at a cell-surface receptor, engulfed by the cell membrane, and carried into the cell bypinching off of the newly formed vesicle inside the membrane, Figure 1–4D. The reverse process (exocytosis) is responsible for the secretionof many substances from cells.

C. Ionization of Weak Acids and Weak Bases; theHenderson-Hasselbalch Equation
The electrostatic charge of an ionized molecule attracts waterdipoles and results in a polar, relatively water-soluble and lipidinsolublecomplex. Because lipid diffusion depends on relativelyhigh lipid solubility, ionization of drugs may markedly reducetheir ability to permeate membranes. A very large percentage ofthe drugs in use are weak acids or weak bases;
For drugs, a weak acid is best defined as a neutral moleculethat can reversibly dissociate into an anion (a negativelycharged molecule) and a proton (a hydrogen ion). For example,aspirin dissociates as follows:

$$C_8H_7O_2COOH \rightleftharpoons C_8H_7O_2COO^- + H^+$$

Neutral aspirin	Aspirin anion	Proton

A weak base can be defined as a neutral molecule that can forma cation (a positively charged molecule) by combining with aproton.For example, pyrimethamine, an antimalarial drug, undergoes the following association-dissociation process:

$$C_{12}H_{11}ClN_3NH_3^+ \rightleftharpoons C_{12}H_{11}ClN_3NH_2 + H^+$$

Pyrimethamine cation	Neutral pyrimethamine	Proton

Note that the protonated form of a weak acid is the neutral,more lipid-soluble form, whereas the unprotonated form of aweak base is the neutral form. The law of mass action requires thatthese reactions move to the left in an acid environment (low pH,excess protons available) and to the right in an alkaline environment.

The Henderson-Hasselbalch equation relates the ratio of protonated to unprotonated weak acid or weak base to the molecule'spKa and the pH of the medium as follows:

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = pK_a - pH$$

This equation applies to both acidic and basic drugs. Inspectionconfirms that the lower the pH relative to the pKa, the greater willbe the fraction of drug in the protonated form. Because the uncharged form is the more lipid-soluble, more of a weak acid willbe in the lipid-soluble form at acid pH, whereas more of a basicdrug will be in the lipid-soluble form at alkaline pH. Application of this principle is made in the absorption of acidic and basic drugs from stomach (acidic pH) and intestine (alkaline pH).

Distribution

The movement of drugs from blood to interstitial fluid and, in some cases, into cells is called distribution and is estimated by volume of distribution,

Apparent Volume of Distribution

Volume of distribution (V) relates the amount of drug in the bodyto the concentration of drug (C) in blood or plasma:

$$V = \frac{\text{Amount of drug in body}}{C} \qquad (1)$$

Volume of distribution, volume *apparently* necessary to contain the amount of drug ***homogeneously***at the concentration found in the blood, plasma, orwater. Drugs with very high volumes of distribution have muchhigher concentrations in extravascular tissue than in the vascularcompartment, ie, they are ***not***homogeneously distributed.Drugsthat are completely retained within the vascular compartment, onthe other hand, would have a minimum possible volume of distributionequal to the blood component in which they are distributed,eg, 0.04 L/kg body weight or 2.8 L/70 kg for adrug that is restricted to the plasma compartment.

Metabolism

In general, lipophilicxenobiotics are transformed to more polar and hence more readily excreted products. The role that metabolism plays in the inactivationof lipid-soluble drugs can be quite dramatic. For example,lipophilic barbiturates such as thiopental and pentobarbital would have extremely long half-lives if it were not for their metabolicconversion to more water-soluble compounds.Metabolic products are often less pharmacodynamically activethan the parent drug and may even be inactive. However, somebiotransformation products have *enhanced* activity or toxic properties.It is noteworthy that the synthesis of endogenous substrates such as steroid hormones, cholesterol, active vitamin D congeners,and bile acids involves many pathways catalyzed by enzymes associatedwith the metabolism of xenobiotics. Finally, drug-metabolizingenzymes have been exploited in the design of pharmacologicallyinactive prodrugs that are converted to active molecules in the body.

In general, all of these reactions can be assigned toone of two major categories called **phase I** and **phase II reactions.** Phase I includes oxidation , reduction and hydrolysis. Phase II includes conjugation.

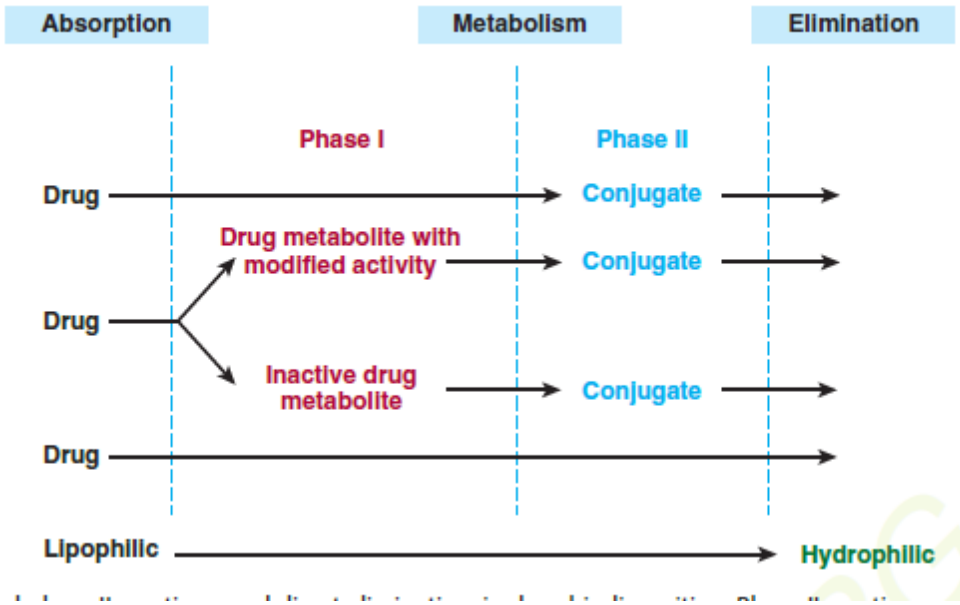


FIGURE 4–1 Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I
reactions.

If phase I metabolites are sufficiently polar, they may be readilyexcreted. However, many phase I products are not eliminatedrapidly and undergo a subsequent reaction in which an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, oran amino acid combines with the newly incorporated functionalgroup to form a highly polar conjugate. Such conjugation or syntheticreactions are the hallmarks of phase II metabolism.

MICROSOMAL MIXED FUNCTION OXIDASE SYSTEM & PHASE I REACTIONS

Many drug-metabolizing enzymes are located in the lipophilicendoplasmic reticulum membranes of the liver and other tissues. In particular, they contain theimportant class of enzymes known as the **mixed function oxidases**(MFOs), or **monooxygenases.**This system contains **NADPH,aflavoprotein**, **cytochrome P450**and **molecular oxygen**

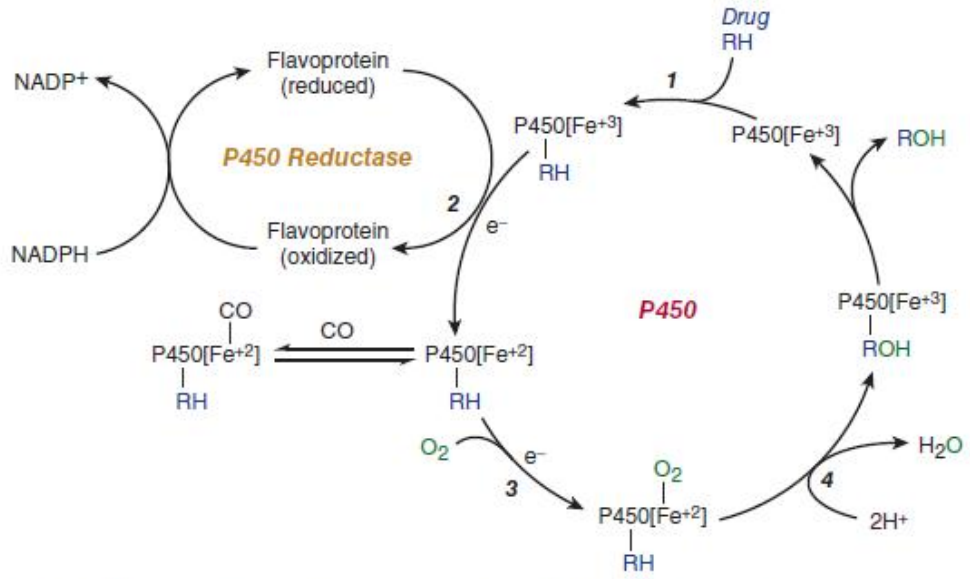


FIGURE 4–3 Cytochrome P450 cycle in drug oxidations. RH, parent drug; ROH, oxidized metabolite; e^-, electron.

Enzyme Induction

Some of drugs, onrepeated administration, induceP450 expression by enhancing the rate of its synthesis or reducing its rate of degradation (Table 4–2). Induction results in accelerated substrate metabolism and usually in a decrease in the pharmacologic action of the inducer and also of co-administered drugs. Environmental chemicals and pollutants are also capable of inducing P450 enzymes. Exposure to benzo[a]pyrenewhich are present in tobacco smoke, is known to induce CYP1A enzymes and to alter the rates of drug metabolism.

Enzyme Inhibition

Certain drug substrates inhibit cytochrome P450 enzyme activity. Imidazole-containing drugs such as cimetidine andketoconazole bind tightly to the P450 heme iron and effectively reduce the metabolism of endogenous substrates (eg, testosterone)or other co-administered drugs through competitive inhibition.

FACTORS AFFECTING DRUG METABOLISM

Genetic Factors

Genetic factors that influence enzyme levels account for some ofthese differences, giving rise to "genetic polymorphisms" in drugmetabolism (see also Chapter 5). The first examples of drugs foundto be subject to genetic polymorphisms were the muscle relaxantsuccinylcholine, the antituberculosis drug isoniazid, and theanticoagulantwarfarin. A true genetic polymorphism is defined as theoccurrence of a variant allele of a gene at a population frequency of≥ 1%, resulting in altered expression or functional activity of thegene product, or both. Well-defined and clinically relevant geneticpolymorphisms in both phase I and phase II drug-metabolizing enzymes exist that result in altered efficacy of drug therapy oradverse drug reactions **(ADRs).**

Commensal Gut Microbiota

It is increasingly recognized that the human gut microbiome canalso significantly influence drug responses. More than 1000 species of intestinal microorganismshave been identified. Their biotransformation extending from predominantlyreductive and hydrolytic reactions to decarboxylation, dehydroxylation,dealkylation, dehalogenation, and deamination. Notably, such bacterially mediated reduction of the cardiac drug digoxinsignificantly contributes to its metabolism and elimination.Co-treatment with antibiotics such as erythromycin or tetracycline increases digoxin serum levels twofold, increasing the risk of cardiotoxicity.

Diet & Environmental Factors

Diet and environmental factors contribute to individual variationsin drug metabolism. Charcoal-broiled foods and cruciferousvegetables are known to induce CYP1A enzymes, whereas grapefruitjuice is known to inhibit the CYP3A metabolism of coadministereddrug substrates.

Age

Increased susceptibility to the pharmacologic or toxic activity ofdrugs has been reported in very young and very old patients comparedwith young adults.Differences in drug metabolism play a role. Slower metabolismcould be due to reduced activity of metabolic enzymes or reduced availability of essential endogenous cofactors.

Diseases Affecting Drug Metabolism

Liver disease

Acute or chronic diseases that affect liver architecture or functionmarkedly affect hepatic metabolism of some drugs. Such conditionsinclude alcoholic hepatitis, active or inactive alcoholic cirrhosis,hemochromatosis, chronic active hepatitis, biliary cirrhosis,and acute viral or drug-induced hepatitis. Depending on theirseverity, these conditions may significantly impair hepatic drugmetabolizingenzymes, particularly microsomal oxidases, andthereby markedly affect drug elimination.

Cardiac disease

Cardiac disease, by limiting blood flow to the liver, mayimpair disposition of those drugs whose metabolism is flow-limited. These drugs are so readily metabolized by theliver that hepatic clearance is essentially equal to liver blood flow.

Heavy metal poisoning

The impaired enzyme activity or defective formation of enzymesassociated with heavy metal poisoning or porphyria also results inreduced hepatic drug metabolism.

Pulmonary disease

Pulmonary disease may alsoaffect drug metabolism, as indicated by the impaired hydrolysis of procainamide and procaine in patients with chronic respiratoryinsufficiency and the increased half-life of antipyrine (a P450functional probe) in patients with lung cancer.

Endocrine disease

Thyroid dysfunction has been associated with alteredmetabolism of some drugs and of some endogenous compoundsas well. Hypothyroidism increases the half-life of antipyrine, digoxin, methimazole, and some □□blockers, whereas hyperthyroidismhas the opposite effect. Finally, the release of inflammatory mediators, cytokines, andnitric oxide associated with bacterial or viral infections, cancer, orinflammation are known to impair drug metabolism by inactivatingP450s and enhancing their degradation.

Excretion

Kidney is the main organ of excretion, but liver, GI tract and lung arealso important to excrete specific substances such as gases and large molecules. The general principle of water solubility is the main factor for successful excretion. The Henderson-Hasselbalch equation relates the ratio ofprotonated to unprotonated weak acid or weak base to the molecule'spKa and the pH of the medium as follows:

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = pK_a - pH$$

Application of this principle is made in the manipulation ofdrug excretion by the kidney. Almost all drugs are filtered at theglomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed bysimple passive diffusion. If the goal is to accelerate excretion ofthe drug (eg, in a case of drug overdose), it is important to preventits reabsorption from the tubule. This can often be accomplishedby adjusting urine pH to make certain that most of thedrug is in the ionized state, as shown in Figure 1–5. As a result of this partitioning effect, the drug is "trapped" in the urine. Thus,weak acids are usually excreted faster in alkaline urine; weak basesare usually excreted faster in acidic urine.

The same principle also applies to drugs when excreted from liver and entro-hepatic cycle occurs in this regards. Other minor excretion routes include sweat saliva and milk.

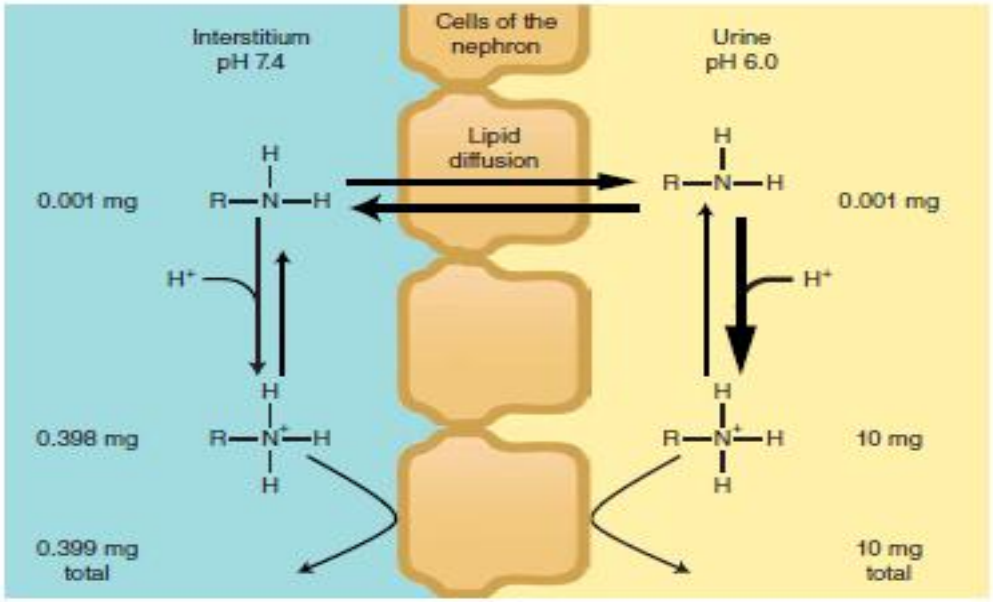


Figure 1–5 Trapping of a weak base (methamphetamine) in the urine when the urine is more acidic than the blood. In the hypotheticalcase illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane, but the total concentration (charged plusuncharged) in the urine (more than 10 mg) is 25 times higher than in the blood (0.4 mg).

CLINIAL PHARMACOKINETICS

The goal of therapeutics is to achieve a desired beneficial effect withminimal adverse effects. When a medicine has been selected for apatient, the clinician must determine the dose that most closelyachieves this goal. A rational approach to this objective combinesthe principles of pharmacokinetics with pharmacodynamics toclarify the dose-effect relationship (Figure 3–1). **Pharmacodynamics**governs the concentration-effect part of the interaction, whereas **pharmacokinetics** deals with the dose-concentration part.

The pharmacokinetic processes of absorption,distribution, and elimination determine how rapidly and for howlong the drug will appear at the target organ.Figure 3–1 illustrates a fundamental hypothesis of pharmacology,namely, that a relationship exists between a beneficial or toxiceffect of a drug and the concentration of the drug.

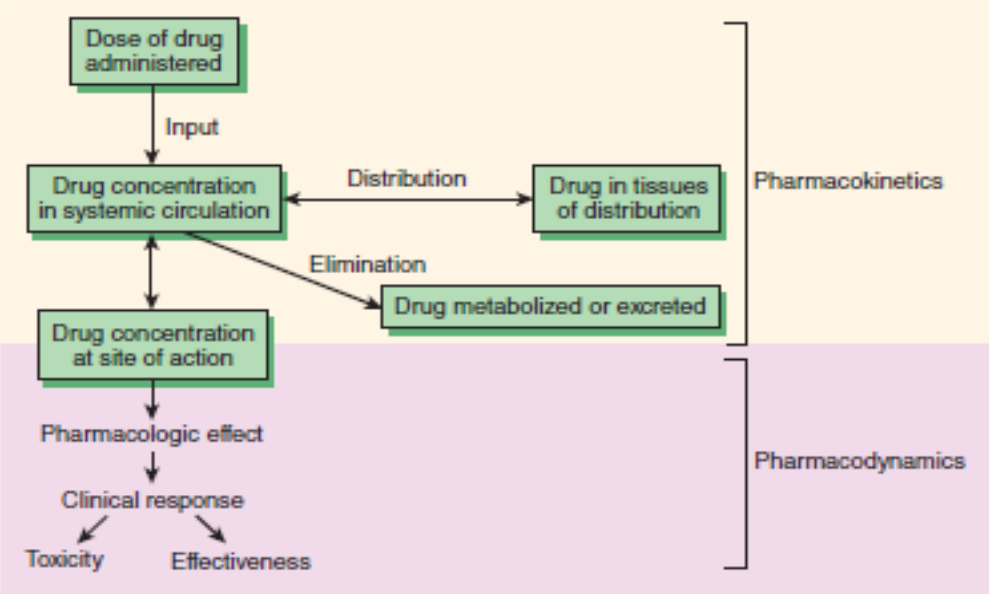


FIGURE 3–1 The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic(concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is thefocus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are input, distribution, andelimination.

The two basicparameters are **clearance,** the measure of the ability of the body to eliminate the drug; and **volume of distribution,** the measure ofthe apparent space in the body available to contain the drug.These parameters are illustrated schematically in Figure 3–2 where the volume of the beakers into which the drugs diffuse representsthe volume of distribution, and the size of the outflow "drain" inFigures 3–2B and 3–2D represents the clearance.

Clearance

Drug clearance principles are similar to the clearance concepts ofrenal physiology. Clearance of a drug is the factor that predicts therate of elimination in relation to the drug concentration (C):

$$CL = \frac{\text{Rate of elimination}}{C} \qquad (2)$$

For most drugs, clearance is constant over theconcentration range encountered in clinical settings, ie, elimination isnot saturable, and the rate of drug elimination is directly proportional to concentration (rearranging equation [2]):

$$\text{Rate of elimination} = CL \times C$$

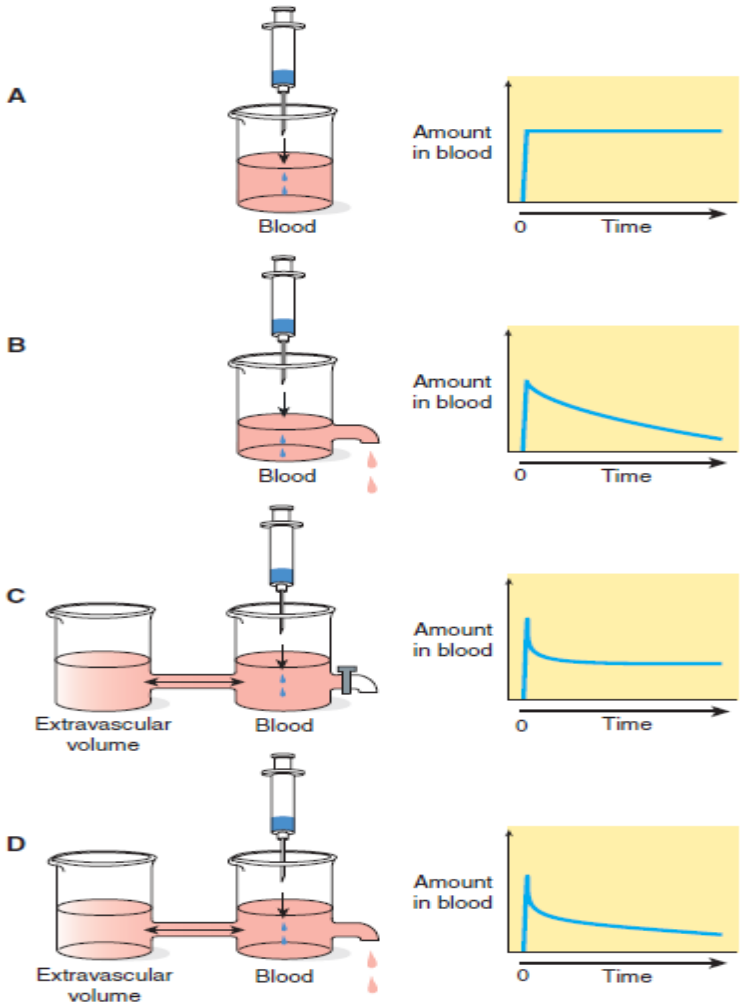


FIGURE 3–2 Models of drug distribution and elimination. The effectof adding drug to the blood by rapid intravenous injection is representedby expelling a known amount of the agent into a beaker. The time courseof the amount of drug in the beaker is shown in the graphs at the right. Inthe first example (**A**), there is no movement of drug out of the beaker, sothe graph shows only a steep rise to a maximum followed by a plateau. Inthe second example (**B**), a route of elimination is present, and the graphshows a slow decay after a sharp rise to a maximum. Because the level ofmaterial in the beaker falls, the "pressure" driving the elimination process also falls, and the slope of the curve decreases. This is an exponential decaycurve. In the third model (**C**), drug placed in the first compartment("blood") equilibrates rapidly with the second compartment ("extravascularvolume") and the amount of drug in "blood" declines exponentially to anew steady state. The fourth model (**D**) illustrates a more realistic combinationof elimination mechanism and extravascular equilibration. The resultinggraph shows an early distribution phase followed by the slowerelimination phase.

This is usually referred to as **first-order elimination**
In the first order elimination model, the relation between concentration of drug and time is governed by the following exponential equation:

First- order reaction

$$\frac{dc}{dt} = -KC$$

$$\ln c = \ln c_0 - kt$$

$$\log c = \log c_0 - \frac{kt}{2.303}$$

$$c = c_0 e^{-kt}$$

$$\text{Half-life } t_{1/2} = \frac{0.693}{k}$$

$$t_{1/2} = \frac{0.693 * Vd}{Cl}$$

Half-Life

Only in first-order elimination, half-life is a constant variable and independent of concentration. Half-life (*t*1/2) is the time required to change the amount of drugin the body by one-half during elimination (or during a constantinfusion). In the simplest case—and the most useful in designingdrug dosage regimens—the body may be considered as a singlecompartment (as illustrated in Figure 3–2B) of a size equal to thevolume of distribution (V). The time course of drug in the bodywill depend on both the volume of distribution and theclearance: According to the above equation, when a single dose is used it takes 4 or 5 half-lives for the body to eliminate 93-96% of drugs.

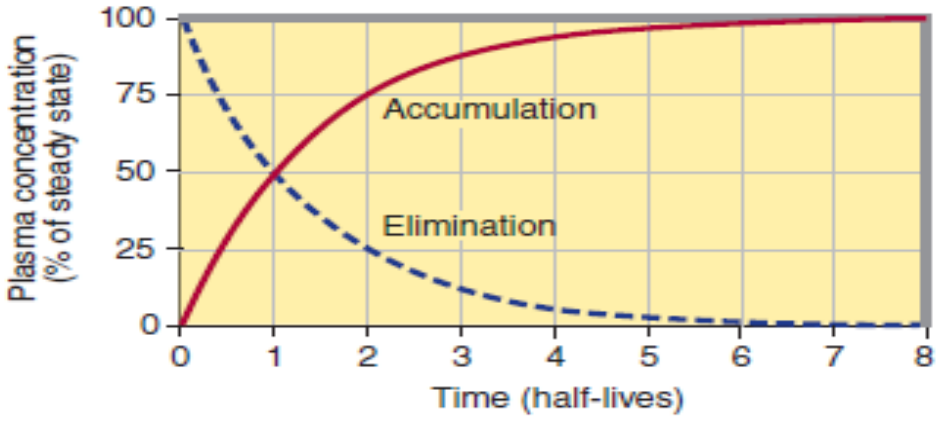


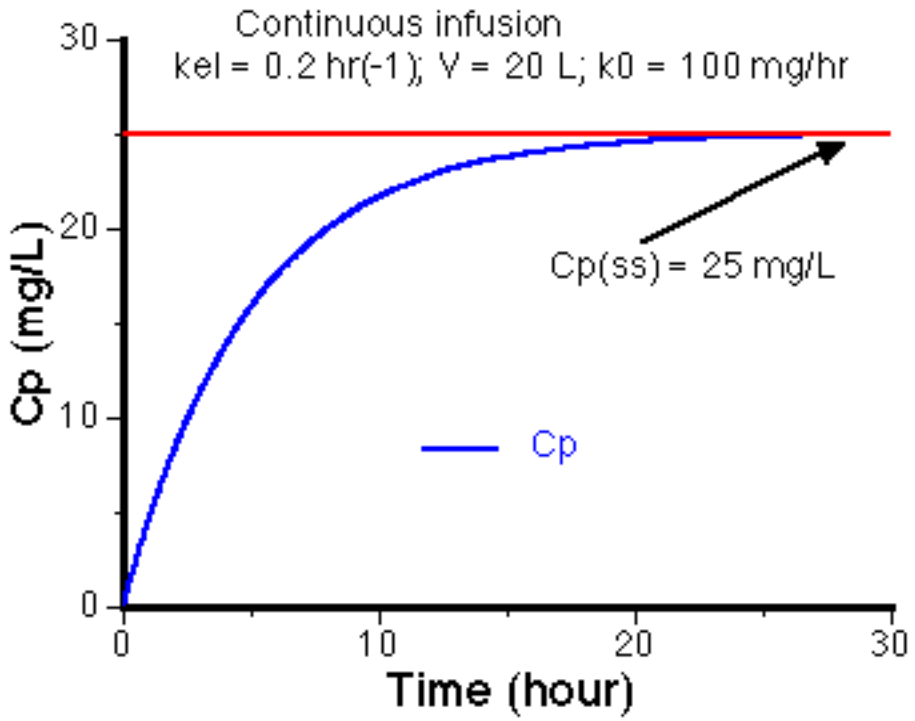
FIGURE 3–3 The time course of drug accumulation and elimination.**Solid line:** Plasma concentrations reflecting drug accumulation duringa constant-rate infusion of a drug. Fifty

percent of the steady-stateconcentration is reached after one half-life, 75% after two half-lives, andover 90% after four half-lives. **Dashed line:** Plasma concentrationsreflecting drug elimination after a constant-rate infusion of a drug hadreached steady state. Fifty percent of the drug is lost after one half-life,75% after two half-lives, etc. The "rule of thumb" that four half-lives mustelapse after starting a drug-dosing regimen before full effects will beseen is based on the approach of the accumulation curve to over 90%of the final steady-state concentration.

Drug Accumulation

Whenever drug doses are repeated, the drug will accumulate in the body until it reaches approximately the steady-state concentration (provided that the dosing interval is less than four half-lives). For convenience, if the interval is equal to half-life the accumulation pattern would be as below,

No. of $t_{1/2}$					
0	1	2	3	4	5
	0.5	0.25	0.12	0 .06	0 .03
	0.50	0.50	0.25	0.12	0.06
		0.75	0.50	0.25	0.12
			0.87	0.50	0.25
				0.93	0.50
					0.96



A. Capacity-Limited Elimination

For drugs that exhibit capacity-limited elimination (eg, phenytoin,ethanol), clearance will vary depending on the concentration of drug that is achieved. Capacity-limited eliminationis also known as mixed-order, saturable, dose- or concentrationdependent**,nonlinear, and Michaelis-Menten elimination.**Most drug elimination pathways will become saturated if thedose and therefore the concentration are high enough. Whenblood flow to an organ does not limit elimination, therelation between elimination rate and concentration (C) isexpressed mathematically in equation (5):

$$\text{Rate of elimination} = \frac{V_{max} \times C}{K_m + C}$$

The maximum elimination capacity is Vmax, and Km is the drugconcentration at which the rate of elimination is 50% of Vmax.

Bioavailability

Bioavailability is defined as the fraction of unchanged drug reachingthe systemic circulation following administration by any route.For anintravenous dose, bioavailability is assumed to be equal to unity.For a drug administered orally, bioavailability may be less than100% for two main reasons—incomplete extent of absorptionacross the gut wall and first-pass elimination by the liver (seebelow).

A. Extent of Absorption

After oral administration, a drug may be incompletely absorbed, eg,only 70% of a dose of digoxin reaches the systemic circulation. Drugs may notbe absorbed because of a reverse transporter associated withP-glycoprotein. This process actively pumps drug out of gut wall cells back into the gut lumen. Inhibition of P-glycoprotein andgut wall metabolism, eg, by grapefruit juice, may be associatedwith substantially increased drug absorption.

B. First-Pass Elimination

Following absorption across the gut wall, the portal blood deliversthe drug to the liver prior to entry into the systemic circulation. The liver is responsible for metabolism before the drug reaches the systemic circulation. The process is known asfirst-pass elimination. The systemic bioavailability of the drug (F) can be predictedfrom the extent of absorption (f) and the extraction ratio (ER):

$$F = f \times (1 - ER)$$

A drug such as morphine is almost completely absorbed (f = 1),so that loss in the gut is negligible. However, the hepatic extractionratio for morphine is morphine clearance (60 L/h/70

kg)divided by hepatic blood flow (90 L/h/70 kg) or 0.67. Its oralbioavailability (1 – ER) is therefore expected to be about 33%,which is close to the observed value (Table 3–1).

Alternative Routes of Administration & the First-Pass Effect

There are several reasons for different routes of administration used in clinical medicine (eg, oral), to maximize concentration at the site of action and minimize it elsewhere (eg, topical), to prolong the duration of drug absorption (eg, transdermal), or to avoid the first-pass effect (sublingual or rectal). The hepatic first-pass effect can be avoided to a great extent by use of sublingual tablets and transdermal preparations and to a lesser extent by use of rectal suppositories. Sublingual absorption provides direct access to systemic—not portal—veins. The transdermal route offers the same advantage. Drugs absorbed from suppositories in the lower rectum enter vessels that drain into the inferior vena cava, thus bypassing the liver. However, suppositories tend to move upward in the rectum into a region where veins that lead to the liver predominate. Thus, only about 50% of a rectal dose can be assumed to bypass the liver.

THE TARGET CONCENTRATION APPROACH TO DESIGNING A RATIONAL DOSAGE REGIMEN

A rational dosage regimen is based on the assumption that there is a **target concentration** that will produce the desired therapeutic effect. By considering the pharmacokinetic factors that determine the dose-concentration relationship, it is possible to individualize the dose regimen to achieve the target concentration. The effective concentration ranges shown in literature are a guide to the concentrations measured when patients are being effectively treated. The initial target concentration should usually be chosen from the lower end of this range.

Maintenance Dose

In most clinical situations, drugs are administered in such a way as to maintain a steady state of drug in the body, ie, just enough drug is given in each dose to replace the drug eliminated since the preceding dose. Thus, calculation of the appropriate maintenance dose is a primary goal. Clearance is the most important pharmacokinetic term to be considered in defining a rational steady-state drug dosage regimen. At steady state, the dosing rate (“rate in”) must equal the rate of elimination (“rate out”).

$$\text{Dosing rate}_{ss} = \text{Rate of elimination}_{ss}$$

$$= CL \times TC$$

Thus, if the desired target concentration is known, the clearance in that patient will determine the dosing rate. If the drug is given by a route that has a bioavailability less than 100%, then the dosing rate predicted by equation (9) must be modified. For oral dosing:

$$\text{Dosing rate}_{oral} = \frac{\text{Dosing rate}}{F_{oral}}$$

If intermittent doses are given, the maintenance dose is calculated from:

$$\text{Maintenance dose} = \text{Dosing rate} \times \text{Dosing interval}$$

Note that the steady-state concentration achieved by continuous infusion or the average concentration following intermittent dosing depends only on clearance. The volume of distribution and the half-life need not be known in order to determine the average plasma concentration expected from a given dosing rate or to predict the dosing rate for a desired target concentration. Figure 3–6 shows that at different dosing intervals, the concentration-time curves will have different maximum and minimum values even though the average concentration will always be 10 mg/L. Estimates of dosing rate and average steady-state concentrations, which may be calculated using clearance, are independent of any specific pharmacokinetic model. In contrast, the determination of maximum and minimum steady-state concentrations requires further assumptions about the pharmacokinetic model. The accumulation factor (equation [7]) assumes that the drug follows a one-compartment model (Figure 3–2B), and the peak concentration prediction assumes that the absorption rate is much faster than the elimination rate. For the calculation of estimated maximum and minimum concentrations in a clinical situation, these assumptions are usually reasonable.

$$Cp_{\infty}^{0} = Cp_{max} = \frac{Dose}{V} \bullet \left[\frac{1}{1 - e^{-kel \bullet \tau}}\right] = \frac{Dose}{V \bullet (1 - R)}$$

Cp Immediately after Many Doses

$$Cp_{\infty}^{\tau} = Cp_{min} = \frac{Dose}{V} \bullet \left[\frac{e^{-kel \bullet \tau}}{1 - e^{-kel \bullet \tau}}\right] = \frac{Dose \bullet R}{V \bullet (1 - R)}$$

Cp Immediately before Many Doses

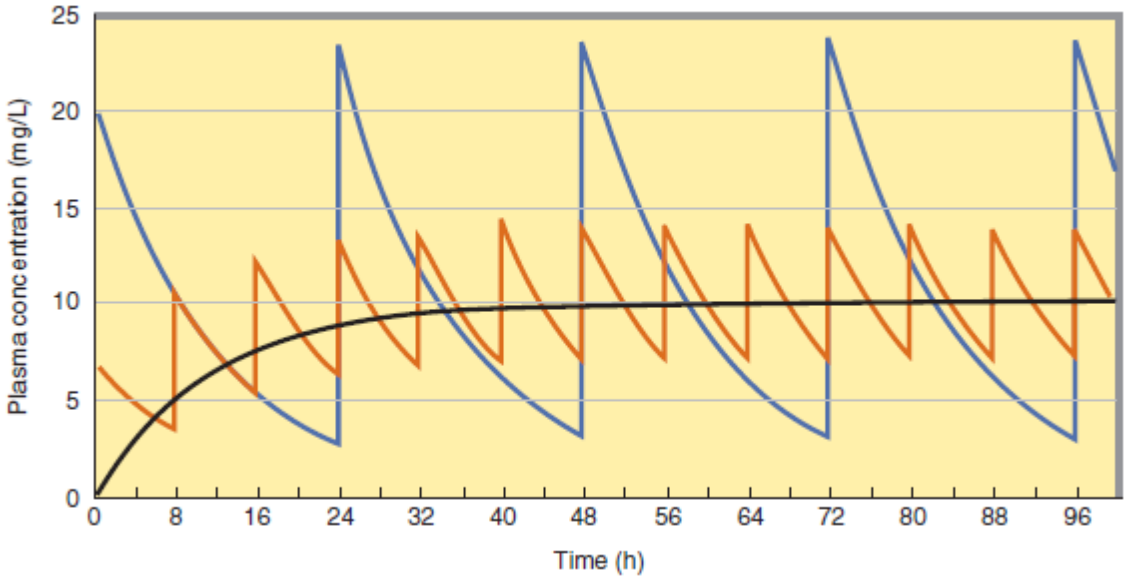


FIGURE 3–6 Relationship between frequency of dosing and maximum and minimum plasma concentrations when a steady-state theophylline plasma level of 10 mg/L is desired. The smoothly rising black line shows the plasma concentration achieved with an intravenous infusion of 28 mg/h. The doses for 8-hourly administration (orange line) are 224 mg; for 24-hourly administration (blue line), 672 mg. In each of the three cases, the mean steady-state plasma concentration is 10 mg/L.

EXAMPLE: MAINTENANCE DOSE CALCULATION

A target plasma theophylline concentration of 10 mg/L is desired to relieve acute bronchial asthma in a patient. If the patient is a nonsmoker and otherwise normal except for asthma, we may use the mean clearance given in Table 3–1, ie, 2.8 L/h/70 kg. Since the drug will be given as an intravenous infusion, F = 1.

$$\text{Dosing rate} = CL \times TC$$
$$= 2.8\ \text{L/h/70 kg} \times 10\ \text{mg/L}$$
$$= 28\ \text{mg/h/70 kg}$$

Therefore, in this patient, the infusion rate would be 28 mg/h/ 70 kg.

If the asthma attack is relieved, the clinician might want to maintain this plasma level using oral theophylline, which might be given every 12 hours using an extended-release formulation to approximate a continuous intravenous infusion. According to Table 3–1, Foral is 0.96. When the dosing interval is 12 hours, the size of each maintenance dose would be

$$\text{Maintenance dose} = \frac{\text{Dosing rate}}{F} \times \text{Dosing interval}$$
$$= \frac{28\ \text{mg/h}}{0.96} \times 12\ \text{hours}$$
$$= 350\ \text{mg}$$

A tablet or capsule size close to the ideal dose of 350 mg would then be prescribed at 12-hourly intervals. If an 8-hour dosing interval was used, the ideal dose would be 233 mg; and if the drug

was given once a day, the dose would be 700 mg. In practice, F could be omitted from the calculation since it is so close to 1.

Loading Dose

When the time to reach steady state is appreciable, as it is 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. In theory, only the amount of the loading dose need be computed—not the rate of its administration—and, to a first approximation, this is so. The volume of distribution is the proportionality factor that relates the total amount of drug in the body to the concentration; if a loading dose is to achieve the target concentration, then from equation of volume of distribution:

$$\text{Loading dose} = \begin{matrix}\text{Amount in the body}\\ \text{immediately following}\\ \text{the loading dose}\end{matrix} = V \times TC$$

For the theophylline example given in the Box, Example: Maintenance Dose Calculations, the loading dose would be 350 mg (35 L × 10 mg/L) for a 70-kg person. For most drugs, the loading dose can be given as a single dose by the chosen route of administration. Up to this point, we have ignored the fact that some drugs follow more complex multicompartment harmacokinetics, eg, the distribution process illustrated by the two-compartment model in Figure 3–2. This is justified in the great majority of cases. However, in some cases the distribution phase may not be ignored, particularly in connection with the calculation of loading doses. Thus, while the estimation of the *amount* of a loading dose may be quite correct, the *rate of administration* can sometimes be crucial in preventing excessive drug concentrations, and slow administration of an intravenous drug (over minutes rather than seconds) is almost always prudent practice.