

UNIT I

Introduction to Pharmacology

Pharmacokinetics

1

I. OVERVIEW

The goal of drug therapy is to prevent, cure, or control various disease states. To achieve this goal, adequate drug doses must be delivered to the target tissues so that therapeutic yet nontoxic levels are obtained. Pharmacokinetics examines the movement of a drug over time through the body. Pharmacological as well as toxicological actions of drugs are primarily related to the plasma concentrations of drugs. Thus, the clinician must recognize that the speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action are controlled by four fundamental pathways of drug movement and modification in the body (Figure 1.1). First, drug absorption from the site of administration (Absorption) permits entry of the therapeutic agent (either directly or indirectly) into plasma. Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids (Distribution). Third, the drug may be metabolized by the liver, kidney, or other tissues (Metabolism). Finally, the drug and its metabolites are removed from the body in urine, bile, or feces (Elimination). This chapter describes how knowledge of these four processes (Absorption, Distribution, Metabolism, and Elimination) influences the clinician's decision of the route of administration for a specific drug, the amount and frequency of each dose, and the dosing intervals.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization, etc.) and by the therapeutic objectives (for example, the desirability of a rapid onset of action or the need for long-term administration or restriction to a local site). There are two major routes of drug administration, enteral and parenteral. (Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration.)

A. Enteral

Enteral administration, or administering a drug by mouth, is the simplest and most common means of administering drugs. When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue, facilitating direct absorption into the bloodstream.

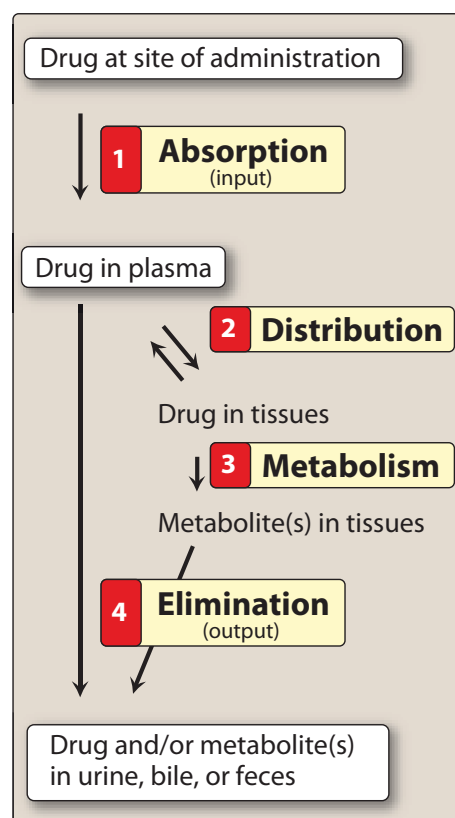


Figure 1.1

Schematic representation of drug absorption, distribution, metabolism, and elimination.

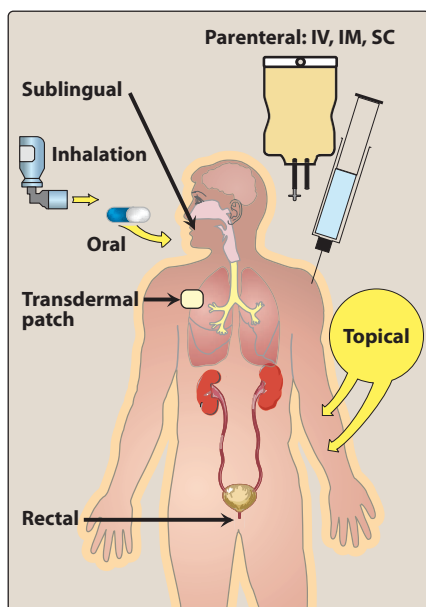


Figure 1.2

Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

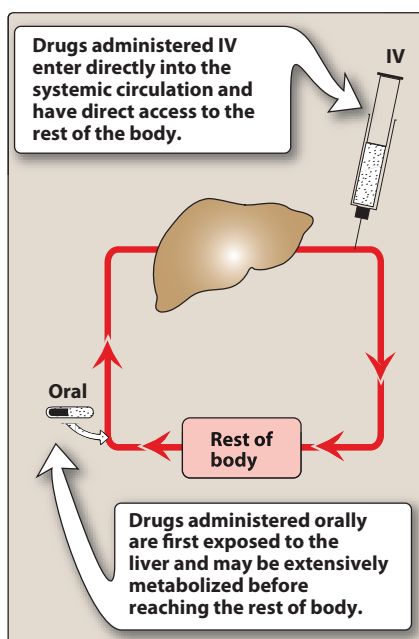


Figure 1.3

First-pass metabolism can occur with orally administered drugs. IV = intravenous.

1. Oral: Giving a drug by mouth provides many advantages to the patient; oral drugs are easily self-administered and limit the number of systemic infections that could complicate treatment. Moreover, toxicities or overdose by the oral route may be overcome with antidotes such as activated charcoal. On the other hand, the pathways involved in drug absorption are the most complicated, and the drug is exposed to harsh gastrointestinal (GI) environments that may limit its absorption. Some drugs are absorbed from the stomach; however, the duodenum is a major site of entry to the systemic circulation because of its larger absorptive surface. Most drugs absorbed from the GI tract enter the portal circulation and encounter the liver before they are distributed into the general circulation. These drugs undergo first-pass metabolism in the liver, where they may be extensively metabolized before entering the systemic circulation (Figure 1.3). [Note: First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than ninety percent of *nitroglycerin* is cleared during a single passage through the liver, which is the primary reason why this agent is not administered orally.] Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target organ. Ingestion of drugs with food, or in combination with other drugs, can influence absorption. The presence of food in the stomach delays gastric emptying, so drugs that are destroyed by acid (for example, *penicillin*) become unavailable for absorption (see p. 364). [Note: Enteric coating of a drug protects it from the acidic environment; the coating may prevent gastric irritation, and depending on the formulation, the release of the drug may be prolonged, producing a sustained-release effect.]

2. Sublingual: Placement under the tongue allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly. Administration of an agent, sublingually, has several advantages including rapid absorption, convenience of administration, low incidence of infection, avoidance of the harsh GI environment, and avoidance of first-pass metabolism.

B. Parenteral

The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation or other vascular tissue. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example *heparin*) and for agents that are unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for treatment of unconscious patients and under circumstances that require a rapid onset of action. In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these routes are irreversible and may cause pain, fear, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each route has advantages and drawbacks.

1. Intravenous (IV): Injection is the most common parenteral route. For drugs that are not absorbed orally, such as the neuromuscular blocker *atracurium*, there is often no other choice. With IV adminis-

tration, the drug avoids the GI tract and therefore, first-pass metabolism by the liver. Intravenous delivery permits a rapid effect and a maximal degree of control over the circulating levels of the drug. However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies such as emesis or by binding to activated charcoal. Intravenous injection may inadvertently introduce bacteria through contamination at the site of injection. IV injection may also induce hemolysis or cause other adverse reactions by the too-rapid delivery of high concentrations of drug to the plasma and tissues. Therefore, the rate of infusion must be carefully controlled. Similar concerns apply to intra-arterially injected drugs.

2. **Intramuscular (IM):** Drugs administered IM can be aqueous solutions or specialized depot preparations—often a suspension of drug in a nonaqueous vehicle such as polyethylene glycol. Absorption of drugs in an aqueous solution is fast, whereas that from depot preparations is slow. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. An example is sustained-release *haloperidol decanoate* (see p. 155), which slowly diffuses from the muscle and produces an extended neuroleptic effect.
3. **Subcutaneous (SC):** This route of administration, like that of IM injection, requires absorption and is somewhat slower than the IV route. Subcutaneous injection minimizes the risks associated with intravascular injection. [Note: Minute amounts of *epinephrine* are sometimes combined with a drug to restrict its area of action. *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.] Other examples of drugs utilizing SC administration include solids, such as a single rod containing the contraceptive *etonogestrel* that is implanted for long-term activity (see p. 306), and also programmable mechanical pumps that can be implanted to deliver *insulin* in diabetic patients.

C. Other

1. **Inhalation:** Inhalation provides the rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as with IV injection. This route of administration is used for drugs that are gases (for example, some anesthetics) or those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with respiratory complaints (such as asthma, or chronic obstructive pulmonary disease) because the drug is delivered directly to the site of action and systemic side effects are minimized. Examples of drugs administered via this route include *albuterol*, and corticosteroids, such as *fluticasone*.
2. **Intranasal:** This route involves administration of drugs directly into the nose. Agents include nasal decongestants such as the anti-inflammatory corticosteroid *mometasone furoate*. *Desmopressin* is administered intranasally in the treatment of diabetes insipidus; salmon *calcitonin*, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray. The abused drug, *cocaine*, is generally taken by intranasal sniffing.

3. **Intrathecal/intraventricular:** It is sometimes necessary to introduce drugs directly into the cerebrospinal fluid. For example, *amphotericin B* is used in treating cryptococcal meningitis (see p. 408).
4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* is applied as a cream directly to the skin in the treatment of dermatophytosis, and *tropicamide* or *cyclopentolate* are instilled (administered drop by drop) directly into the eye to dilate the pupil and permit measurement of refractive errors.
5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application. This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*, the antiemetic *scopolamine*, and the once-a-week contraceptive patch (Ortho Evra) that has an efficacy similar to oral birth control pills.
6. **Rectal:** Fifty percent of the drainage of the rectal region bypasses the portal circulation; thus, the biotransformation of drugs by the liver is minimized. Like the sublingual route of administration, the rectal route of administration has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents.] On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

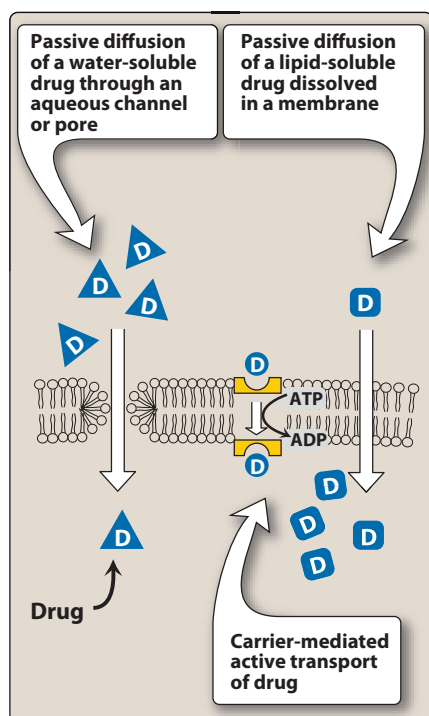


Figure 1.4

Schematic representation of drugs crossing a cell membrane of an epithelial cell of the gastrointestinal tract. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the bloodstream. The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation. Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability. For example, the oral route requires that a drug dissolve in the GI fluid and then penetrate the epithelial cells of the intestinal mucosa, yet disease states or the presence of food may affect this process.

A. Transport of a drug from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by either passive diffusion or active transport.

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments; that is, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers. Water-soluble drugs penetrate the cell membrane through aque-

ous channels or pores (Figure 1.4). Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes allowing the passage of drugs or endogenous molecules into the interior of cells, moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. This type of diffusion does not require energy, can be saturated, and may be inhibited.

2. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate (see Figure 1.4). It is capable of moving drugs against a concentration gradient—that is, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels where all the active sites are filled with substrate.¹

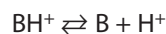
3. Endocytosis and exocytosis: This type of drug delivery transports drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. For example, vitamin B₁₂ is transported across the gut wall by endocytosis. Certain neurotransmitters (for example, norepinephrine) are stored in membrane-bound vesicles in the nerve terminal and are released by exocytosis.

B. Effect of pH on drug absorption

Most drugs are either weak acids or weak bases. Acidic drugs (HA) release an H⁺ causing a charged anion (A⁻) to form:²



Weak bases (BH⁺) can also release an H⁺. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):



1. Passage of an uncharged drug through a membrane: A drug passes through membranes more readily if it is uncharged (Figure 1.5). Thus, for a weak acid, the uncharged HA can permeate through membranes, and A⁻ cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH⁺ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the

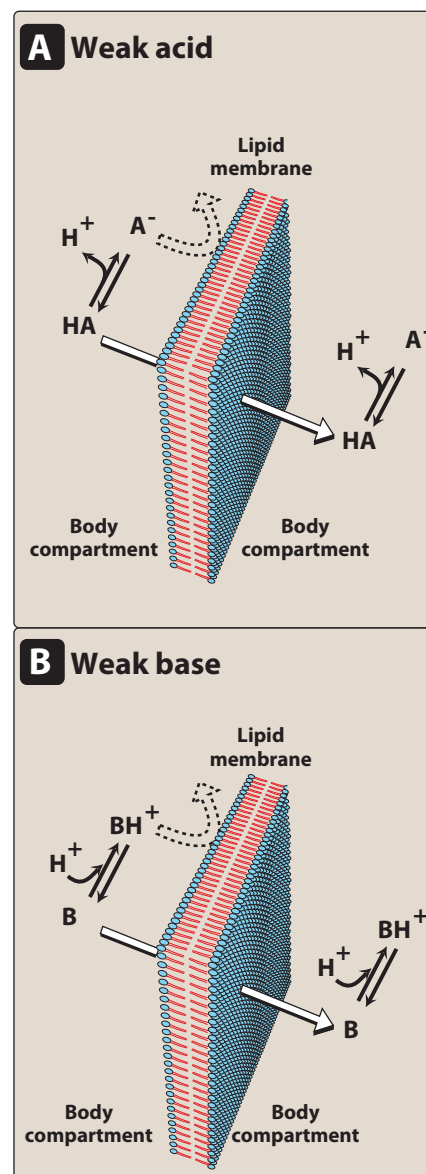


Figure 1.5

A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.



¹See p. 58 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of enzyme kinetics.

²See p. 5 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of acid-base chemistry.

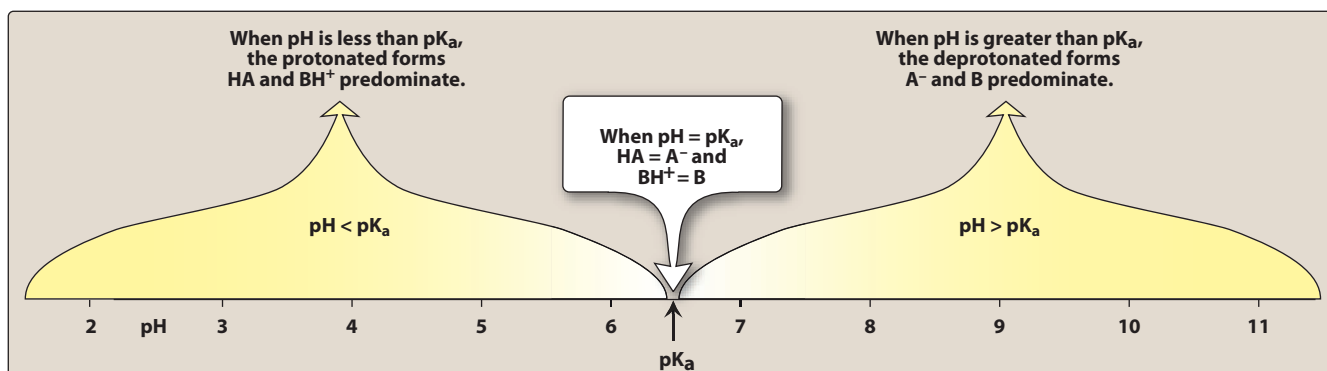


Figure 1.6

The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

strength of the weak acid or base, which is represented by the pK_a (Figure 1.6). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a , the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces. [Note: Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.]

- 2. Determination of how much drug will be found on either side of a membrane:** The relationship of pK_a and the ratio of acid-base concentrations to pH is expressed by the Henderson-Hasselbalch equation:³

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

$$\text{For acids: } pH = pK_a + \log \frac{[A^-]}{[HA]}$$

$$\text{For bases: } pH = pK_a + \log \frac{[B]}{[BH^+]}$$

This equation is useful in determining how much drug will be found on either side of a membrane that separates two compartments that differ in pH—for example, stomach (pH 1.0–1.5) and blood plasma (pH 7.4). [Note: The lipid solubility of the non-ionized drug directly determines its rate of equilibration.]

C. Physical factors influencing absorption

- 1. Blood flow to the absorption site:** Blood flow to the intestine is much greater than the flow to the stomach; thus, absorption from the intestine is favored over that from the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thus minimizing the absorption from SC administration.]



³See p. 6 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of the Henderson-Hasselbalch equation.

2. **Total surface area available for absorption:** Because the intestine has a surface rich in microvilli, it has a surface area about 1000-fold that of the stomach; thus, absorption of the drug across the intestine is more efficient.
3. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions), as well as anticholinergics (for example, *dicyclomine*), prolongs gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

IV. BIOAVAILABILITY

Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form. For example, if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7 or seventy percent.

A. Determination of bioavailability

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels achieved by IV injection—in which all of the agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100 percent for drugs delivered IV.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection (Figure 1.7).

B. Factors that influence bioavailability

1. **First-pass hepatic metabolism:** When a drug is absorbed across the GI tract, it enters the portal circulation before entering the systemic circulation (see Figure 1.3). If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is decreased. Many drugs, such as *propranolol* or *lidocaine*, undergo significant biotransformation during a single passage through the liver.
2. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are weak acids or weak bases. There are some drugs that are highly lipid-soluble, and they are transported in the aqueous solutions of the body on carrier proteins such as albumin.

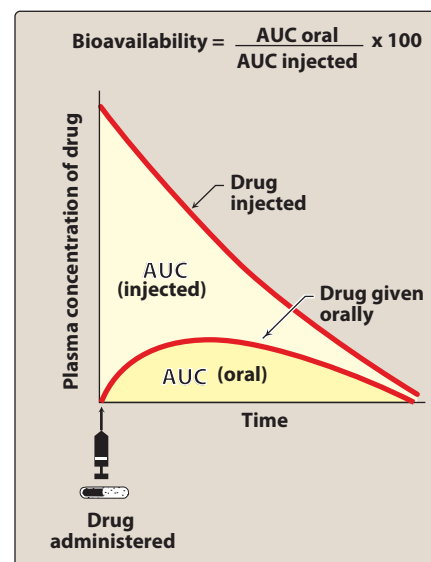


Figure 1.7

Determination of the bioavailability of a drug. (AUC = area under curve.)

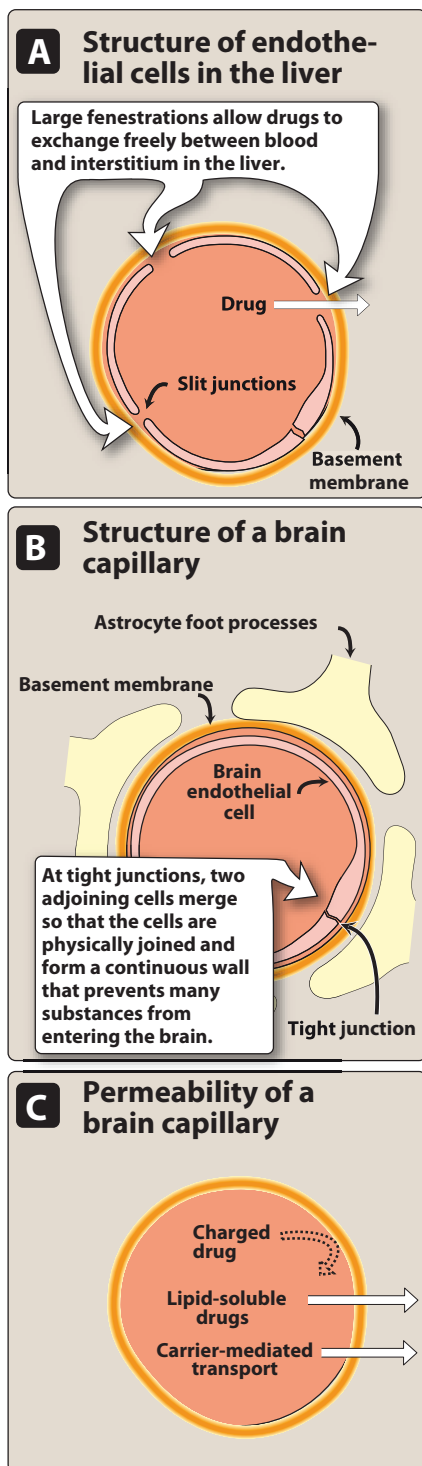


Figure 1.8
Cross-section of liver and brain capillaries.

3. Chemical instability: Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

4. Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

C. Bioequivalence

Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two related drugs with a significant difference in bioavailability are said to be bioinequivalent.

D. Therapeutic equivalence

Two similar drugs are therapeutically equivalent if they have comparable efficacy and safety. [Note: Clinical effectiveness often depends on both the maximum serum drug concentrations and on the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.]

V. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles; adipose tissue has a still lower rate of blood flow. This differential blood flow partly explains the short duration of hypnosis produced by a bolus IV injection of *thiopental* (see p. 135). The high blood flow, together with the superior lipid solubility of *thiopental*, permit it to rapidly move into the central nervous system (CNS) and produce anesthesia. Slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease, and consciousness is regained. Although this phenomenon occurs with all drugs to some extent, redistribution accounts for the extremely short duration of action of *thiopental* and compounds of similar chemical and pharmacologic properties.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

1. Capillary structure: Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.8). This contrasts

with the liver and spleen, where a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

a. Blood-brain barrier: To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. For example, a specific transporter for the large neutral amino acid transporter carries *levodopa* into the brain. By contrast, lipid-soluble drugs readily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells. Ionized or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions. These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier.

2. Drug structure: The chemical nature of a drug strongly influences its ability to cross cell membranes. Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, readily move across most biologic membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. By contrast, hydrophilic drugs, which have either a nonuniform distribution of electrons or a positive or negative charge, do not readily penetrate cell membranes, and therefore, must go through the slit junctions.

C. Binding of drugs to plasma proteins

Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Binding is relatively nonselective as to chemical structure and takes place at sites on the protein to which endogenous compounds, such as bilirubin, normally attach. Plasma albumin is the major drug-binding protein and may act as a drug reservoir; that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

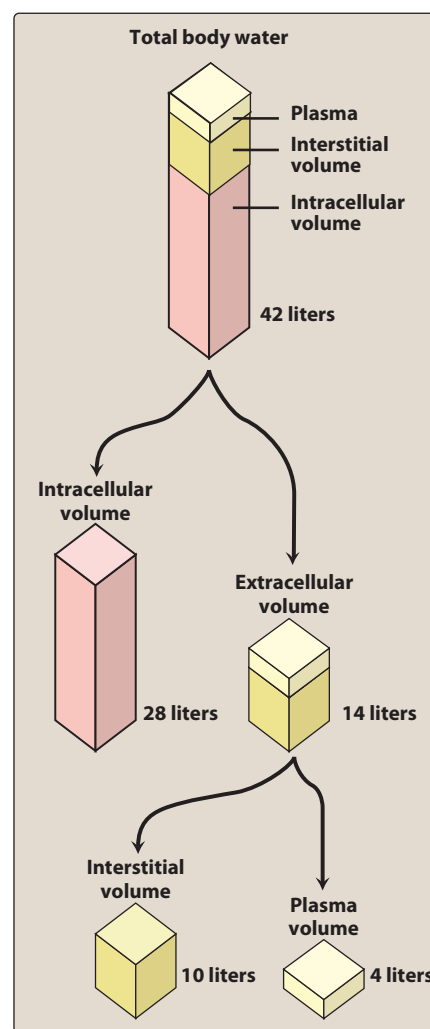


Figure 1.9
Relative size of various distribution volumes within a 70-kg individual.

VI. VOLUME OF DISTRIBUTION

The volume of distribution is a hypothetical volume of fluid into which a drug is dispersed. Although the volume of distribution has no physiologic or physical basis, it is sometimes useful to compare the distribution of a drug with the volumes of the water compartments in the body (Figure 1.9).

A. Water compartments in the body

Once a drug enters the body, from whatever route of administration, it has the potential to distribute into any one of three functionally distinct compartments of body water or to become sequestered in a cellular site.

1. Plasma compartment: If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a consequence, the drug distributes in a volume (the plasma) that is about six percent of the body weight or, in a 70-kg individual, about 4 L of body fluid. *Heparin* (see p. 236) shows this type of distribution.

2. **Extracellular fluid:** If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the water phase inside the cell. Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid. This is about twenty percent of the body weight, or about 14 L in a 70-kg individual. Aminoglycoside antibiotics (see p. 377) show this type of distribution.
3. **Total body water:** If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitium through the slit junctions, but it can also move through the cell membranes into the intracellular fluid. The drug, therefore, distributes into a volume of about sixty percent of body weight, or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent volume of distribution (see below).
4. **Other sites:** In pregnancy, the fetus may take up drugs and thus increase the volume of distribution. Drugs that are extremely lipid-soluble, such as *thiopental* (see p. 135), may also have unusually high volumes of distribution.

B. Apparent volume of distribution

A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular components—for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells). Therefore, the volume into which drugs distribute is called the apparent volume of distribution, or V_d . Another useful way to think of this constant is as the partition coefficient of a drug between the plasma and the rest of the body.

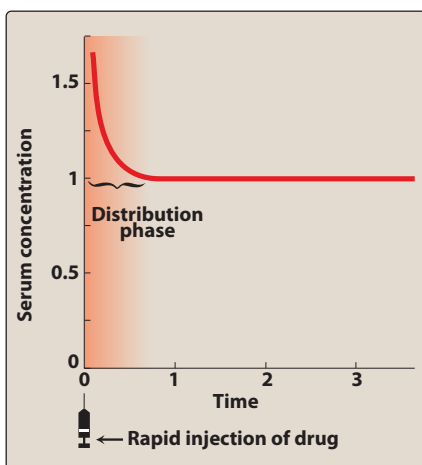


Figure 1.10

Drug concentrations in serum after a single injection of drug at time = 0. Assume that the drug distributes but is not eliminated.

1. Determination of V_d

- a. **Distribution of drug in the absence of elimination:** The apparent volume into which a drug distributes, V_d , is determined by injection of a standard dose of drug, which is initially contained entirely in the vascular system. The agent may then move from the plasma into the interstitium and into cells, causing the plasma concentration to decrease with time. Assume for simplicity that the drug is not eliminated from the body; the drug then achieves a uniform concentration that is sustained with time (Figure 1.10). The concentration within the vascular compartment is the total amount of drug administered, divided by the volume into which it distributes, V_d :

$$C = D/V_d \text{ or } V_d = D/C$$

where C = the plasma concentration of the drug and D = the total amount of drug in the body. For example, if 25 mg of a drug ($D = 25$ mg) are administered and the plasma concentration is 1 mg/L, then $V_d = 25 \text{ mg}/1 \text{ mg/L} = 25 \text{ L}$.

- b. **Distribution of drug when elimination is present:** In reality, drugs are eliminated from the body, and a plot of plasma

concentration versus time shows two phases. The initial decrease in plasma concentration is due to a rapid distribution phase in which the drug is transferred from the plasma into the interstitium and the intracellular water. This is followed by a slower elimination phase during which the drug leaves the plasma compartment and is lost from the body—for example, by renal or biliary excretion or by hepatic biotransformation (Figure 1.11). The rate at which the drug is eliminated is usually proportional to the concentration of drug, C ; that is, the rate for most drugs is first-order and shows a linear relationship with time—if $\ln C$ (where $\ln C$ is the natural log of C , rather than C) is plotted versus time (Figure 1.12). This is because the elimination processes are not saturated.

- c. Calculation of drug concentration if distribution is instantaneous:** Assume that the elimination process began at the time of injection and continued throughout the distribution phase. Then, the concentration of drug in the plasma, C , can be extrapolated back to time zero (the time of injection) to determine C_0 , which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. For example, if 10 mg of drug are injected into a patient and the plasma concentration is extrapolated to time zero, the concentration is $C_0 = 1 \text{ mg/L}$ (from the graph shown in Figure 1.12), and then $V_d = 10 \text{ mg}/1 \text{ mg/L} = 10 \text{ L}$.
- d. Uneven drug distribution between compartments:** The apparent volume of distribution assumes that the drug distributes uniformly, in a single compartment. However, most drugs distribute unevenly, in several compartments, and the volume of distribution does not describe a real, physical volume, but rather, reflects the ratio of drug in the extraplasmic spaces relative to the plasma space. Nonetheless, V_d is useful because it can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume the arrhythmia of a cardiac patient is not well controlled due to inadequate plasma levels of *digitalis*. Suppose the concentration of the drug in the plasma is C_1 and the desired level of *digitalis* (known from clinical studies) is a higher concentration, C_2 . The clinician needs to know how much additional drug should be administered to bring the circulating level of the drug from C_1 to C_2 :

$(V_d)(C_1)$ = amount of drug initially in the body

$(V_d)(C_2)$ = amount of drug in the body needed to achieve the desired plasma concentration

The difference between the two values is the additional dosage needed, which equals $V_d(C_2 - C_1)$.

2. Effect of a large V_d on the half-life of a drug

A large V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the plasma. If the V_d for a drug is large, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore,

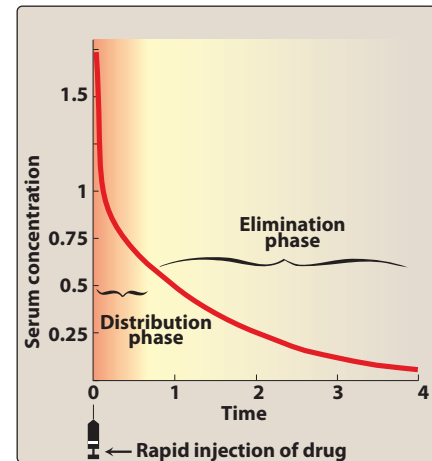


Figure 1.11

Drug concentrations in serum after a single injection of drug at time = 0. Assume that the drug distributes and is subsequently eliminated.

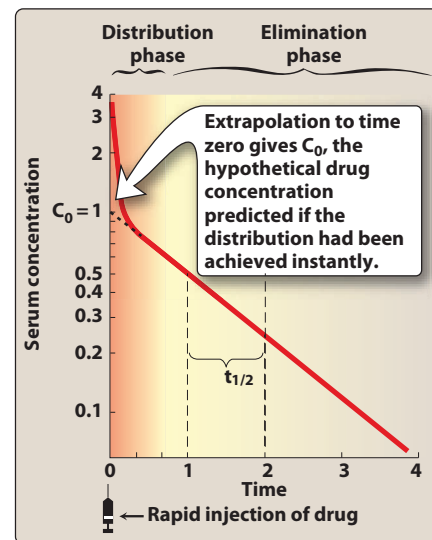


Figure 1.12

Drug concentrations in serum after a single injection of drug at time = 0. Data are plotted on a log scale.

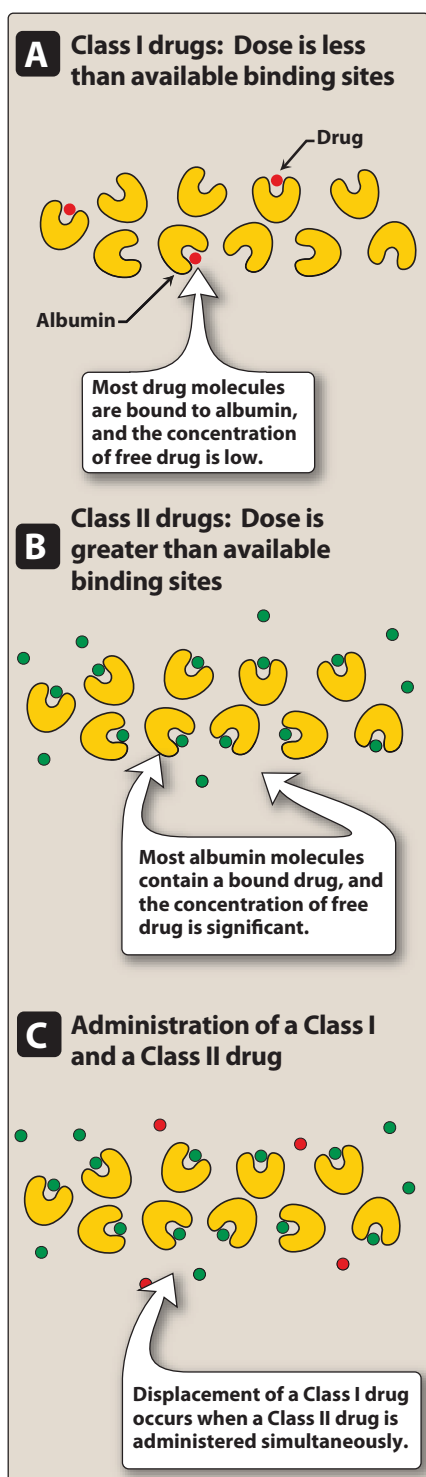


Figure 1.13

Binding of Class I and Class II drugs to albumin when drugs are administered alone (A and B) or together (C).

any factor that increases the volume of distribution can lead to an increase in the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some organ or compartment.]

VII. BINDING OF DRUGS TO PLASMA PROTEINS

Drug molecules may bind to plasma proteins (usually albumin). Bound drugs are pharmacologically inactive; only the free, unbound drug can act on target sites in the tissues, elicit a biologic response, and be available to the processes of elimination. [Note: Hypoalbuminemia may alter the level of free drug.]

A. Binding capacity of albumin

The binding of drugs to albumin is reversible and may show low capacity (one drug molecule per albumin molecule) or high capacity (a number of drug molecules binding to a single albumin molecule). Drugs can also bind with varying affinities. Albumin has the strongest affinities for anionic drugs (weak acids) and hydrophobic drugs. Most hydrophilic drugs and neutral drugs do not bind to albumin. [Note: Many drugs are hydrophobic by design, because this property permits absorption after oral administration.]

B. Competition for binding between drugs

When two drugs are given, each with high affinity for albumin, they compete for the available binding sites. The drugs with high affinity for albumin can be divided into two classes, depending on whether the dose of drug (the amount of drug found in the body under conditions used clinically) is greater than, or less than, the binding capacity of albumin (quantified as the number of millimoles of albumin multiplied by the number of binding sites; Figure 1.13).

- 1. Class I drugs:** If the dose of drug is less than the binding capacity of albumin, then the dose/capacity ratio is low. The binding sites are in excess of the available drug, and the bound-drug fraction is high. This is the case for Class I drugs, which include the majority of clinically useful agents.
- 2. Class II drugs:** These drugs are given in doses that greatly exceed the number of albumin binding sites. The dose/capacity ratio is high, and a relatively high proportion of the drug exists in the free state, not bound to albumin.
- 3. Clinical importance of drug displacement:** This assignment of drug classification assumes importance when a patient taking a Class I drug, such as *warfarin*, is given a Class II drug, such as a *sulfonamide antibiotic*. *Warfarin* is highly bound to albumin, and only a small fraction is free. This means that most of the drug is sequestered on albumin and is inert in terms of exerting pharmacologic actions. If a *sulfonamide* is administered, it displaces *warfarin* from albumin, leading to a rapid increase in the concentration of free *warfarin* in plasma, because almost 100 percent is now free, compared with the initial small percentage. [Note: The increase in *warfarin* concentration may lead to increased therapeutic effects, as well as increased toxic effects, such as bleeding.]

C. Relationship of drug displacement to V_d

The impact of drug displacement from albumin depends on both the V_d and the therapeutic index (see p. 33) of the drug. If the V_d is large, the drug displaced from the albumin distributes to the periphery, and the change in free-drug concentration in the plasma is not significant. If the V_d is small, the newly displaced drug does not move into the tissues as much, and the increase in free drug in the plasma is more profound. If the therapeutic index of the drug is small, this increase in drug concentration may have significant clinical consequences. [Note: Clinically, drug displacement from albumin is one of the most significant sources of drug interactions.]

VIII. DRUG METABOLISM

Drugs are most often eliminated by biotransformation and/or excretion into the urine or bile. The process of metabolism transforms lipophilic drugs into more polar readily excretable products. The liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues, such as the kidney and the intestines. [Note: Some agents are initially administered as inactive compounds (pro-drugs) and must be metabolized to their active forms.]

A. Kinetics of metabolism

1. **First-order kinetics:** The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics:⁴

$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, $[C]$, is much less than the Michaelis constant, K_m , and the Michaelis-Menten equation reduces to,

$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

That is, the rate of drug metabolism is directly proportional to the concentration of free drug, and first-order kinetics are observed (Figure 1.14). This means that a constant fraction of drug is metabolized per unit of time.

2. **Zero-order kinetics:** With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore $[C]$ is much greater than K_m , and the velocity equation becomes

$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{[C]} = V_{\max}$$

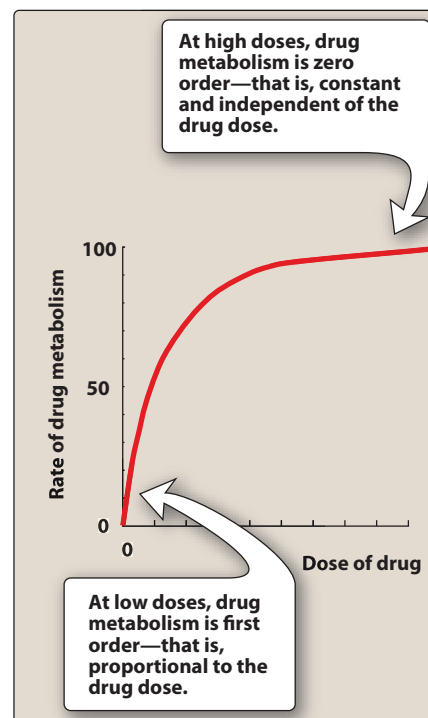


Figure 1.14

Effect of drug dose on the rate of metabolism.



⁴See p. 58 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of Michaelis-Menten kinetics.

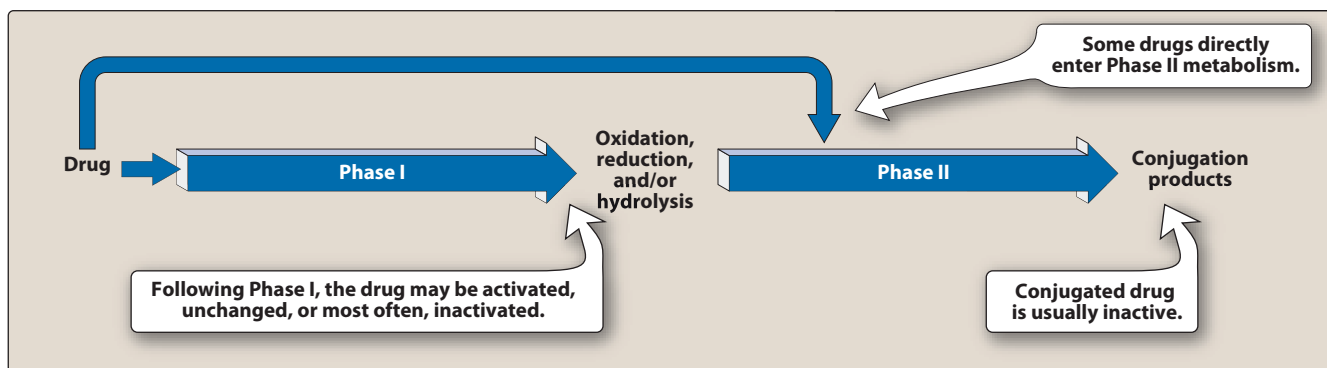


Figure 1.15

The biotransformation of drugs.

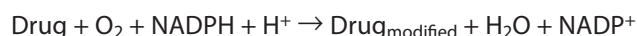
The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (sometimes referred to clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time.

B. Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules. Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II (Figure 1.15).

1. Phase I: Phase I reactions function to convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as $-OH$ or $-NH_2$. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

a. Phase I reactions utilizing the P450 system: The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed function oxidase):



The oxidation proceeds by the drug binding to the oxidized form of cytochrome P450, and then oxygen is introduced through a reductive step, coupled to NADPH:cytochrome P450 oxidoreductase.

b. Summary of the P450 system: The P450 system is important for the metabolism of many endogenous compounds (steroids, lipids, etc.) and for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP, is composed of many families of heme-containing isozymes that are located in most cells but are primarily found in the liver and GI tract. The family name is indicated by an arabic number followed by a capital letter for the subfamily (for example, CYP3A). Another number is added to indicate the specific isozyme (CYP3A4). There are many different genes, and many different enzymes; thus, the various P450s are known as isoforms. Six isozymes are responsible for the vast majority of P450-catalyzed reactions: CYP3A4, CYP2D6, CYP2C9/10, CYP2C19, CYP2E1, and CYP1A2. The percentages of currently available drugs that are substrates for these isozymes are

60, 25, 15, 15, 2, and 2 percent, respectively. [Note: An individual drug may be a substrate for more than one isozyme.] Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam*. As might be expected, these enzymes exhibit considerable genetic variability, which has implications for individual dosing regimens, and even more importantly, as determinants of therapeutic responsiveness and the risk of adverse events. CYP2D6, in particular, has been shown to exhibit genetic polymorphism.⁵ Mutations result in very low capacities to metabolize substrates. Some individuals, for example, obtain no benefit from the opioid analgesic *codeine* because they lack the enzyme that O-demethylates and activates the drug. This reaction is CYP2D6-dependent. The frequency of this polymorphism is in part racially determined, with a prevalence of five to ten percent in European Caucasians as compared to less than two percent of Southeast Asians. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. Although CYP3A4 exhibits a greater than ten-fold interindividual variability, no polymorphisms have been identified for this P450 isozyme.

- c. Inducers:** The cytochrome P450–dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Certain drugs, most notably *phenobarbital*, *rifampin*, and *carbamazepine*, are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformations of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, as measured by AUC, with concurrent loss of pharmacologic effect. For example, *rifampin*, an antituberculosis drug (see p. 402), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors,⁶ diminishing their ability to suppress HIV virion maturation. Figure 1.16 lists some of the more important inducers for representative CYP isozymes. Consequences of increased drug metabolism include: 1) decreased plasma drug concentrations, 2) decreased drug activity if metabolite is inactive, 3) increased drug activity if metabolite is active, and 4) decreased therapeutic drug effect. In addition to drugs, natural substances and pollutants can also induce CYP isozymes. For example, polycyclic aromatic hydrocarbons (found as air pollutants) can induce CYP1A. This has implications for certain drugs; for example, *amitriptyline* and *warfarin* are metabolized by P4501A2. Polycyclic hydrocarbons induce P4501A2, which decreases the therapeutic concentrations of these agents.

- d. Inhibitors:** Inhibition of CYP isozyme activity is an important source of drug interactions that leads to serious adverse events. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for

Isozyme: CYP2C9/10

| COMMON SUBSTRATES | INDUCERS |
|---|---|
| <i>Warfarin</i> <i>Phenytoin</i> <i>Ibuprofen</i> <i>Tolbutamide</i> | <i>Phenobarbital</i> <i>Rifampin</i> |

Isozyme: CYP2D6

| COMMON SUBSTRATES | INDUCERS |
|---|----------|
| <i>Desipramine</i> <i>Imipramine</i> <i>Haloperidol</i> <i>Propranolol</i> | |

Isozyme: CYP3A4/5

| COMMON SUBSTRATES | INDUCERS |
|---|---|
| <i>Carbamazepine</i> <i>Cyclosporine</i> <i>Erythromycin</i> <i>Nifedipine</i> <i>Verapamil</i> | <i>Carbamazepine</i> <i>Dexamethasone</i> <i>Phenobarbital</i> <i>Phenytoin</i> <i>Rifampin</i> |

Figure 1.16

Some representative P450 isozymes.



⁵See p. 473 in *Lippincott's Illustrated Reviews: Biochemistry* (4th ed.) for a discussion of genetic polymorphism.

⁶See p. 303 in *Lippincott's Illustrated Reviews: Microbiology* (2nd ed.) for a discussion of HIV protease inhibitors.

example, *ketoconazole*), leading to drug interactions. Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three of the CYP isozymes responsible for *warfarin* metabolism. If the two drugs are taken together, plasma concentrations of *warfarin* increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions. [Note: The more important CYP inhibitors are *erythromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.] *Cimetidine* blocks the metabolism of *theophylline*, *clozapine*, and *warfarin*. Natural substances such as grapefruit juice may inhibit drug metabolism. Grapefruit juice inhibits CYP3A4 and, thus, drugs such as *amlodipine*, *clarithromycin*, and *indinavir*, which are metabolized by this system, have greater amounts in the systemic circulation—leading to higher blood levels and the potential to increase therapeutic and/or toxic effects of the drugs. Inhibition of drug metabolism may lead to increased plasma levels over time with long-term medications, prolonged pharmacological drug effect, and increased drug-induced toxicities.

e. Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin* in liver), and hydrolysis (for example, of *procaine*).

2. Phase II: This phase consists of conjugation reactions. If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine*. Glucuronidation is the most common and the most important conjugation reaction. Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as *chloramphenicol*, which is inactivated by the addition of glucuronic acid (see p. 382). [Note: Drugs already possessing an $-OH$, $-HN_2$, or $-COOH$ group may enter Phase II directly and become conjugated without prior Phase I metabolism.] The highly polar drug conjugates may then be excreted by the kidney or bile.

3. Reversal of order of the phases: Not all drugs undergo Phase I and II reactions in that order. For example, *isoniazid* is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

IX. DRUG ELIMINATION

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. Other routes include the bile, intestine, lung, or milk in nursing mothers. A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drugs.

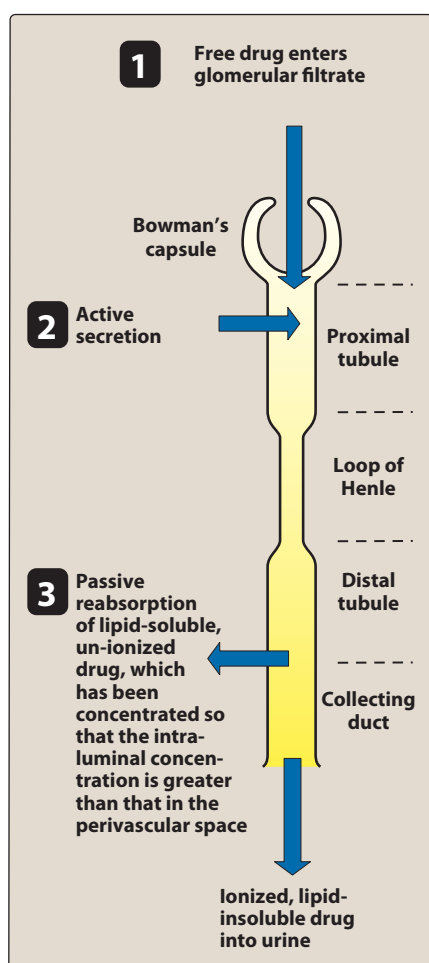


Figure 1.17
Drug elimination by the kidney.

A. Renal elimination of a drug

- 1. Glomerular filtration:** Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into Bowman's space as part of the glomerular filtrate (Figure 1.17). The glomerular filtration rate (125 mL/min) is normally about twenty percent of the renal plasma flow (600 mL/min). [Note: Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate]
- 2. Proximal tubular secretion:** Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport (carrier-requiring) systems, one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds; thus, competition between drugs for these carriers can occur within each transport system (for example, see *probenecid*, p. 513). [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.]
- 3. Distal tubular reabsorption:** As a drug moves toward the distal convoluted tubule, its concentration increases, and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be used to minimize the amount of back-diffusion, and hence, increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called "ion trapping." For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalizes the urine and keeps the drug ionized, thereby decreasing its reabsorption. If overdose is with a weak base, such as *cocaine*, acidification of the urine with NH_4Cl leads to protonation of the drug and an increase in its clearance.
- 4. Role of drug metabolism:** Most drugs are lipid soluble and without chemical modification would diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. To minimize this reabsorption, drugs are modified primarily in the liver into more polar substances using two types of reactions: Phase I reactions (see p. 14) that involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups, and Phase II reactions (see p. 16) that use conjugation with sulfate, glycine, or glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen (Figure 1.18).

B. Quantitative aspects of renal drug elimination

Plasma clearance is expressed as the volume of plasma from which all drug appears to be removed in a given time—for example, as mL/min. Clearance equals the amount of renal plasma flow multiplied by the

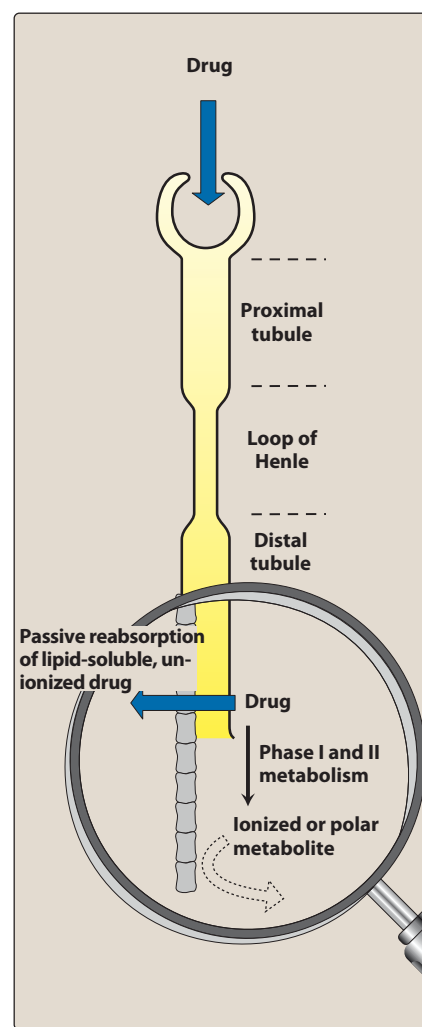


Figure 1.18
Effect of drug metabolism on reabsorption in the distal tubule.

extraction ratio, and because these are normally invariant over time, clearance is constant.

1. Extraction ratio: This ratio is the decline of drug concentration in the plasma from the arterial to the venous side of the kidney. The drugs enter the kidneys at concentration C_1 and exit the kidneys at concentration C_2 . The extraction ratio = C_2/C_1 .

2. Excretion rate: The excretion ratio is determined the equation:

$$\text{Excretion rate} = (\text{clearance})(\text{plasma concentration})$$

$$\text{mg/min} \qquad \text{mL/min} \qquad \text{mg/mL}$$

The elimination of a drug usually follows first-order kinetics, and the concentration of drug in plasma drops exponentially with time. This can be used to determine the half-life, $t_{1/2}$, of the drug (the time during which the concentration of a drug at equilibrium decreases from C to $1/2C$):

$$t_{1/2} = \ln 0.5/k_e = 0.693 V_d/CL$$

where k_e = the first-order rate constant for drug elimination from the total body and CL = clearance.

C. Total body clearance

The total body (systemic) clearance, CL_{total} or CL_t , is the sum of the clearances from the various drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion; however, the liver also contributes to drug loss through metabolism and/or excretion into the bile. A patient in renal failure may sometimes benefit from a drug that is excreted by this pathway, into the intestine and feces, rather than through the kidney. Some drugs may also be reabsorbed through the enterohepatic circulation, thus prolonging their half-life. Total clearance can be calculated by using the following equation:

$$CL_{\text{total}} = CL_{\text{hepatic}} + CL_{\text{renal}} + CL_{\text{pulmonary}} + CL_{\text{other}}$$

It is not possible to measure and sum these individual clearances. However, total clearance can be derived from the steady-state equation:

$$CL_{\text{total}} = k_e V_d$$

D. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. It is important to be able to predict in which patients a drug is likely to have a change in half-life. The half-life of a drug is increased by 1) diminished renal plasma flow or hepatic blood flow—for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased extraction ratio—for example, as seen in renal disease; and 3) decreased metabolism—for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis. On the other hand, the half-life of a drug may decrease by 1) increased hepatic blood flow, 2) decreased protein binding, and 3) increased metabolism.

X. KINETICS OF CONTINUOUS ADMINISTRATION

The preceding discussion describes the pharmacokinetic processes that determine the rates of absorption, distribution, and elimination of a drug.

Pharmacokinetics also describes the quantitative, time-dependent changes of both the plasma drug concentration and the total amount of drug in the body, following the drug's administration by various routes, with the two most common being IV infusion and oral fixed-dose/fixed-time interval regimens (for example, "one tablet every 4 hours"). The interactions of the processes previously described determine the pharmacokinetics profile of a drug. The significance of identifying the pharmacokinetics of a drug lies not only in defining the factors that influence its levels and persistence in the body, but also in tailoring the therapeutic use of drugs that have a high toxic potential. [Note: The following discussion assumes that the administered drug distributes into a single body compartment. In actuality, most drugs equilibrate between two or three compartments and, thus, display complex kinetic behavior. However, the simpler model suffices to demonstrate the concepts.]

A. Kinetics of IV infusion

With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first order; that is, a constant fraction of the agent is cleared per unit of time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases, and at every point in time, it is proportional to the plasma concentration of the drug.

1. Steady-state drug levels in blood: Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate. Thus, a steady-state is achieved in which the plasma concentration of drug remains constant. [Note: The rate of drug elimination from the body = $(CL_t)(C)$, where CL_t = total body clearance (see p. 18) and C = the plasma concentration of drug.] Two questions can be asked about achieving the steady-state. First, what is the relationship between the rate of drug infusion and the plasma concentration of drug achieved at the plateau, or steady state? Second, what length of time is required to reach the steady state drug concentration?

2. Influence of the rate of drug infusion on the steady state: A steady-state plasma concentration of a drug occurs when the rate of drug elimination is equal to the rate of administration (Figure 1.19), as described by the following equation:

$$C_{ss} = R_0/k_e V_d = R_0/CL_t$$

where C_{ss} = the steady-state concentration of the drug, R_0 = the infusion rate (for example, mg/min), k_e is the first-order elimination rate constant, and V_d = the volume of distribution. Because k_e , CL_t , and V_d are constant for most drugs showing first-order kinetics, C_{ss} is directly proportional to R_0 ; that is, the steady-state plasma concentration is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the plasma concentration ultimately achieved at the steady state is doubled (Figure 1.20). Furthermore, the steady-state concentration is inversely proportional to the clearance of the drug, CL_t . Thus, any factor that decreases clearance, such as liver or kidney disease, increases the steady-state concentration of an infused drug (assuming V_d remains constant). Factors that increase clearance of a drug, such as increased metabolism, decrease the steady-state concentrations of an infused drug.

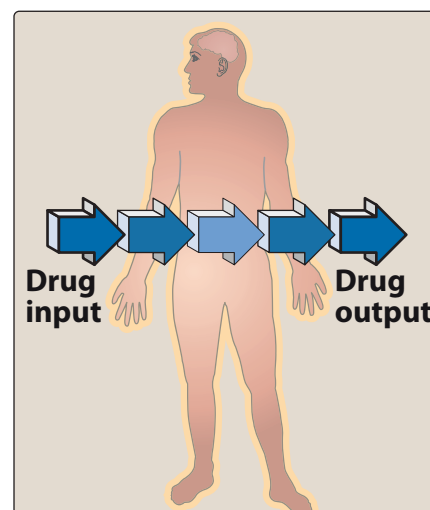


Figure 1.19

At steady state, input (rate of infusion) equals output (rate of elimination).

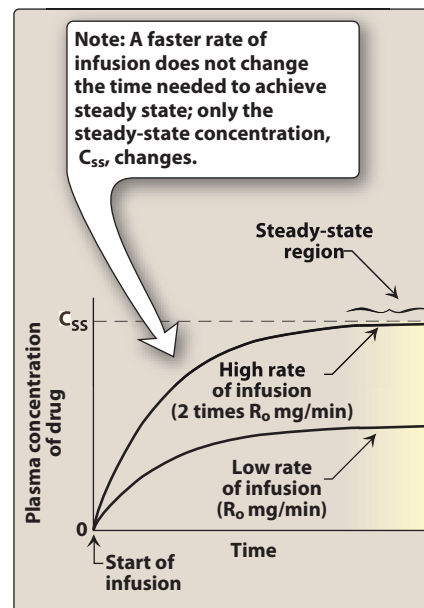


Figure 1.20

Effect of infusion rate on the steady-state concentration of drug in the plasma. (R_0 = rate of infusion of a drug.)

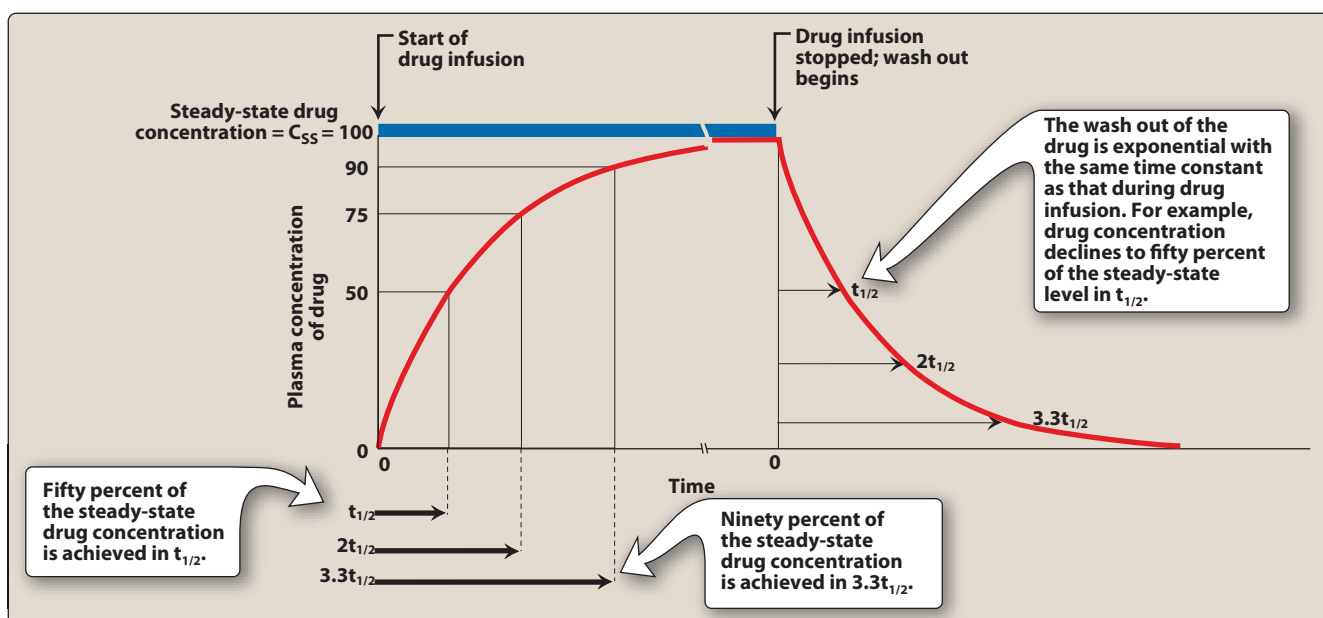


Figure 1.21

Rate of attainment of steady-state concentration of a drug in the plasma.

3. Time required to reach the steady-state drug concentration: The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level, C_{ss} (Figure 1.21). The fractional rate of approach to a steady state is achieved by a first-order process.

a. Exponential approach to steady state: The rate constant for attainment of steady state is the rate constant for total body elimination of the drug, k_e . Thus, fifty percent of the final steady-state concentration of drug is observed after the time elapsed since the infusion, t , is equal to $t_{1/2}$, where $t_{1/2}$ (or half-life) is the time required for the drug concentration to change by fifty percent. Waiting another half-life allows the drug concentration to approach 75 percent of C_{ss} (see Figure 1.21). The drug concentration is ninety percent of the final steady-state concentration in 3.3 times $t_{1/2}$. For convenience, therefore, one can assume that a drug will reach steady-state in about four half-lives. The time required to reach a specific fraction of the steady-state is described by

$$f = 1 - e^{-k_e t}$$

where f = the fractional shift (for example, 0.9 if the time to reach ninety percent of the steady-state concentration was being calculated) and t = the time elapsed since the start of the infusion.

b. Effect of the rate of drug infusion: The sole determinant of the rate that a drug approaches steady state is the $t_{1/2}$ or k_e , and this rate is influenced only by the factors that affect the half-life. The rate of approach to steady state is not affected by the rate of drug infusion. Although increasing the rate of infusion of a drug increases the rate at which any given concentration of drug in the plasma is achieved, it does not influence the time required

to reach the ultimate steady-state concentration. This is because the steady-state concentration of drug rises directly with the infusion rate (see Figure 1.20).

- c. Rate of drug decline when the infusion is stopped:** When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching the steady state (see Figure 1.21). This relationship is expressed as

$$C_t = C_0 - e^{-k_e t}$$

where C_t = the plasma concentration at any time, C_0 = the starting plasma concentration, k_e = the first-order elimination rate constant, and t = the time elapsed.

- d. Loading dose:** A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a “loading dose” of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose). In general, the loading dose can be calculated as

$$\text{Loading dose} = (V_d)(\text{desired steady-state plasma concentration})$$

B. Kinetics of fixed-dose/fixed-time-interval regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses, given at fixed-time intervals, result in time-dependent fluctuations in the circulating level of drug.

- 1. Single IV injection:** For simplicity, assume the injected drug rapidly distributes into a single compartment. Because the rate of elimination is usually first order in regard to drug concentration, the circulating level of drug decreases exponentially with time (Figure 1.22). [Note: The $t_{1/2}$ does not depend on the dose of drug administered.]
- 2. Multiple IV injections:** When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.23). Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body at the time that the second dose is administered, and some from the second dose remains at the time that the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug loss (driven by an elevated plasma concentration) exactly balances the rate of drug administration—that is, until a steady state is achieved.
 - a. Effect of dosing frequency:** The plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of the swings in drug concentration. However, the steady-state concentration of the drug, and the rate at which the steady-state is approached, are not affected by the frequency of dosing.

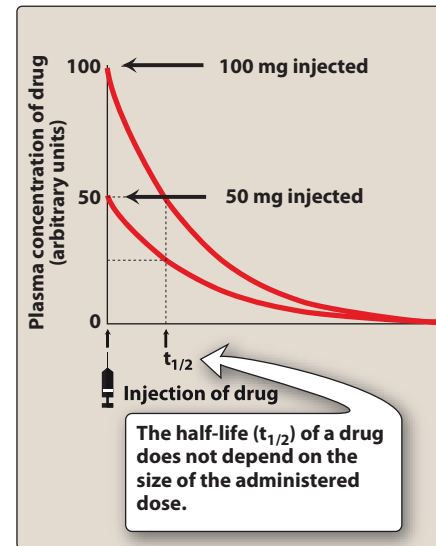


Figure 1.22

Effect of the dose of a single intravenous injection of drug on plasma levels.

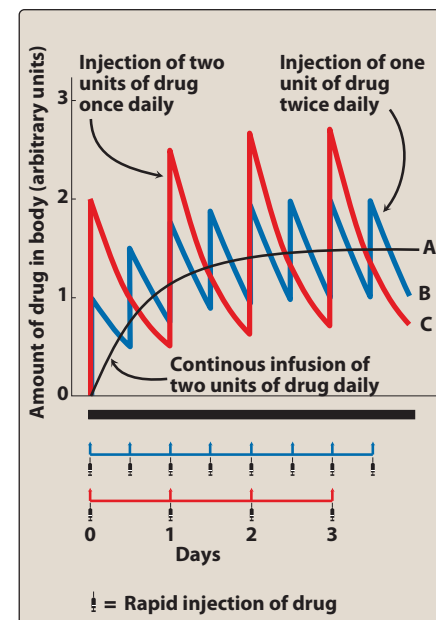


Figure 1.23

Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of twelve hours.

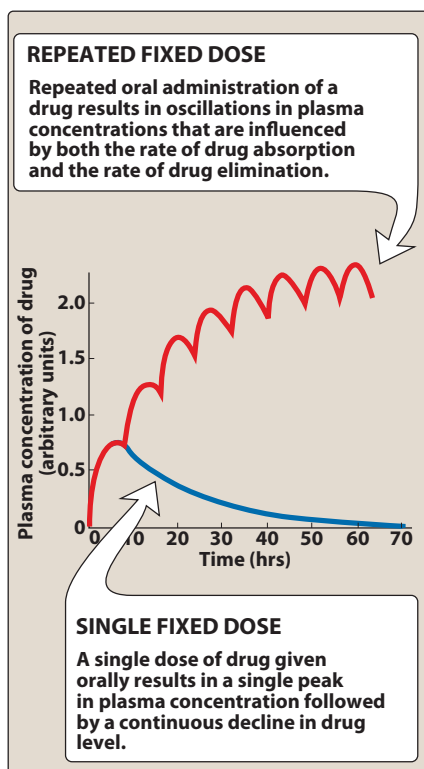


Figure 1.24

Predicted plasma concentrations of a drug given by repeated oral administrations.

b. Example of achievement of steady state using different dosage regimens:

Curve B of Figure 1.23 shows the amount of drug in the body when 1 g of drug is administered IV to a patient and the dose is repeated at a time interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is taken. The minimal amount of drug during the dosing interval progressively increases and approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate at which the drug is administered—that is, the “rate in” equals the “rate out.” As in the case for IV infusion, ninety percent of the steady-state value is achieved in 3.3 times $t_{1/2}$.

- 3. Orally administered drugs:** Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose/fixed-time-interval regimen—for example, a specific dose taken one, two, or three times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of drug elimination (Figure 1.24). This relationship can be expressed as:

$$C_{ss} = \frac{1}{(k_e)(V_d)} \frac{(D)(F)}{T}$$

where D = the dose, F = the fraction absorbed (bioavailability), T = dosage interval, C_{ss} = the steady-state concentration of the drug, k_e = the first-order rate constant for drug elimination from the total body, and V_d = the volume of distribution.

Study Questions

Choose the ONE best answer.

1.1 Which one of the following statements is correct?

- A. Weak bases are absorbed efficiently across the epithelial cells of the stomach.
- B. Coadministration of atropine speeds the absorption of a second drug.
- C. Drugs showing a large V_d can be efficiently removed by dialysis of the plasma.
- D. Stressful emotions can lead to a slowing of drug absorption.
- E. If the V_d for a drug is small, most of the drug is in the extraplasmaic space.

Correct answer = D. Both exercise and strong emotions prompt sympathetic output, which slows gastric emptying. In the stomach, a weak base is primarily in the protonated, charged form, which does not readily cross the epithelial cells of the stomach. *Atropine* is a parasympathetic blocker and slows gastric emptying. This delays the rate of drug absorption. A large V_d indicates that most of the drug is outside the plasma space, and dialysis would not be effective. A small V_d indicates extensive binding to plasma proteins.

1.2 Which one of the following is true for a drug whose elimination from plasma shows first-order kinetics?

- A. The half-life of the drug is proportional to the drug concentration in plasma.
- B. The amount eliminated per unit of time is constant.
- C. The rate of elimination is proportional to the plasma concentration.
- D. Elimination involves a rate-limiting enzymic reaction operating at its maximal velocity (V_m).
- E. A plot of drug concentration versus time is a straight line.

Correct answer = C. The direct proportionality between concentration and rate is the definition of first order. The half-life of a drug is a constant. For first-order reactions, the fraction of the drug eliminated, not the amount of drug, is constant. A rate limiting reaction operating at V_m would show zero-order kinetics. First-order kinetics shows a linear plot of \log [drug concentration] versus time.

1.3 A patient is treated with drug A, which has a high affinity for albumin and is administered in amounts that do not exceed the binding capacity of albumin. A second drug, B, is added to the treatment regimen. Drug B also has a high affinity for albumin but is administered in amounts that are 100 times the binding capacity of albumin. Which of the following occurs after administration of drug B?

- A. An increase in the tissue concentrations of drug A.
- B. A decrease in the tissue concentrations of drug A.
- C. A decrease in the volume of distribution of drug A.
- D. A decrease in the half-life of drug A.
- E. Addition of more drug A significantly alters the serum concentration of unbound drug B.

Correct answer = A. Drug A is largely bound to albumin, and only a small fraction is free. Most of drug A is sequestered on albumin and is inert in terms of exerting pharmacologic actions. If drug B is administered, it displaces drug A from albumin, leading to a rapid increase in the concentration of free drug A in plasma, because almost 100 percent is now free. Drug A moves out of the plasma into the interstitial water and the tissues. The V_d of drug A increases, providing less drug to the organ of excretion and prolonging the overall lifetime of the drug. Because drug B is already 100-fold in excess of its albumin-binding capacity, dislodging some of drug B from albumin does not significantly affect its serum concentration.

1.4 The addition of glucuronic acid to a drug:

- A. Decreases its water solubility.
- B. Usually leads to inactivation of the drug.
- C. Is an example of a Phase I reaction.
- D. Occurs at the same rate in adults and newborns.
- E. Involves cytochrome P450.

Correct answer = B. The addition of glucuronic acid prevents recognition of the drug by its receptor. Glucuronic acid is charged, and the drug conjugate has increased water solubility. Conjugation is a Phase II reaction. Neonates are deficient in the conjugating enzymes. Cytochrome P450 is involved in Phase I reactions.

1.5 Drugs showing zero-order kinetics of elimination:

- A. Are more common than those showing first-order kinetics.
- B. Decrease in concentration exponentially with time.
- C. Have a half-life independent of dose.
- D. Show a plot of drug concentration versus time that is linear.
- E. Show a constant fraction of the drug eliminated per unit of time.

Correct answer = D. Drugs with zero-order kinetics of elimination show a linear relationship between drug concentration and time. In most clinical situations, the concentration of a drug is much less than the Michaelis constant (K_m). A decrease in drug concentration is linear with time. The half-life of the drug increases with dose. A constant amount of drug is eliminated per unit of time.

1.6 A drug, given as a 100-mg single dose, results in a peak plasma concentration of 20 $\mu\text{g/mL}$. The apparent volume of distribution is (assume a rapid distribution and negligible elimination prior to measuring the peak plasma level):

- A. 0.5 L.
- B. 1 L.
- C. 2 L.
- D. 5 L.
- E. 10 L.

Correct answer = D. $V_d = D/C$, where D = the total amount of drug in the body, and C = the plasma concentration of drug. Thus, $V_d = 100 \text{ mg}/20 \text{ mg/mL} = 5 \text{ L}$.

1.7 A drug with a half-life of 12 hours is administered by continuous IV infusion. How long will it take for the drug to reach ninety percent of its final steady-state level?

- A. 18 hours.
- B. 24 hours.
- C. 30 hours.
- D. 40 hours.
- E. 90 hours.

Correct answer = D. One approaches ninety percent of the final steady state in $(3.3)(t_{1/2}) = (3.3)(12) = \sim 40$ hours.

1.8 Which of the following results in a doubling of the steady-state concentration of a drug?

- A. Doubling the rate of infusion.
- B. Maintaining the rate of infusion but doubling the loading dose.
- C. Doubling the rate of infusion and doubling the concentration of the infused drug.
- D. Tripling the rate of infusion.
- E. Quadrupling the rate of infusion.

Correct answer = A. The steady-state concentration of a drug is directly proportional to the infusion rate. Increasing the loading dose provides a transient increase in drug level, but the steady-state level remains unchanged. Doubling both the rate of infusion and the concentration of infused drug leads to a four-fold increase in the steady-state drug concentration. Tripling or quadrupling the rate of infusion leads to either a three- or four-fold increase in the steady-state drug concentration.