PHARMACOKINETICS

OVERVIEW

Pharmacokinetics is the study of drug disposition in the body and focuses on the changes in **drug plasma concentration** . For any given drug and dose, the plasma concentration of the drug will rise and fall according to the rates of three processes: **absorption, distribution** , and **elimination.**

Absorption of a drug refers to the movement of drug into the bloodstream, with the rate dependent on the physical characteristics of the drug and its formulation. Distribution of a drug refers to the process of a drug leaving the bloodstream and going into the organs and tissues. Elimination of a drug from the blood relies on two processes: **biotransformation (metabolism)** of a drug to one or more metabolites, primarily in the liver; and the **excretion** of the parent drug or its metabolites, primarily by the kidneys. The relationship between these processes is shown in Figure 2 – 1 .

DRUG ABSORPTION

Drug absorption refers to the **passage of drug molecules** from the site of administration into the circulation. The process of drug absorption applies to all routes of administration, except for the topical route, where drugs are applied directly on the target tissue, and intravenous administration, where the drug is already in the circulation. Drug absorption requires that drugs cross one or more layers of cells and cell membranes. Drugs injected into the subcutaneous tissue and muscle bypass the epithelial barrier and are more easily absorbed through spaces between capillary endothelial cells. In the gut, lungs, and skin, drugs must first be absorbed through a layer of epithelial cells that have tight junctions. For this reason, drugs face a greater **barrier** to absorption after oral administration than after parenteral administration.

Processes of Absorption

Most drugs are absorbed by **passive diffusion** across a biologic barrier and into the circulation. The rate of absorption is proportional to the drug concentration gradient across the barrier and the surface area available for absorption at that site, known as **Fick's Law** . Drugs can be absorbed passively through cells either by lipid diffusion or by aqueousdiffusion. **Lipid diffusion** is a process in which the drug dissolves in the lipid components of the cell membranes. This process is facilitated by a high degree of lipid solubility of the drug. **Aqueous diffusion** occurs by passage through aqueous pores in cell membranes. Because aqueous diffusion is restricted to drugs with low molecular weights, many drugs are too large to be absorbed by this process.

A few drugs are absorbed by **active transport** or by **facilitated diffusion.** Active transport requires a **carrier molecule** and a form of **energy** , provided by hydrolysis of the terminal high-energy phosphate bond of ATP. Active transport can transfer drugs against a concentration gradient. For example, the antineoplastic drug, **5-fluorouracil** , undergoes active transport. Facilitated diffusion also requires a carrier molecule, but no energy is needed. Thus drugs or substances cannot be

transferred against a concentration gradient but diffuse faster than without a carrier molecule present. Some cephalosporin antibiotics, such as **cephalexin** , undergo facilitated diffusion by an oligopeptide transporter protein located in intestinal epithelial cells.

Effect of pH on Absorption of Weak Acids and Bases

Many drugs are weak acids or bases that exist in both ionized and non-ionized forms in the body. Only the **non-ionized form** of these drugs is sufficiently soluble in membrane lipids to cross cell membranes (Box 2-1). The ratio of the two forms at a particular site influences the **rate of absorption** and is also a factor in distribution and elimination. The protonated form of a weak acid is non-ionized, whereas the protonated form of a weak base is ionized. The ratio of the protonated form to the nonprotonated form of these drugs can be calculated using the **Henderson- Hasselbalch equation** (see Box 2-1). The pKa is the negative log of the ionization constant, particular for each acidic or basic drug. At a pH equal to the pK_a , **equal** amounts of the protonated and nonprotonated forms are present. If the pH is less than the pK_a , the protonated form predominates. If the pH is greater than the pK_a , the nonprotonated form predominates. In the stomach, with a pH of 1, weak acids and bases are highly protonated. At this site, the non-ionized form of weak acids ($pK_a = 3 – 5$) and the ionized form of weak bases

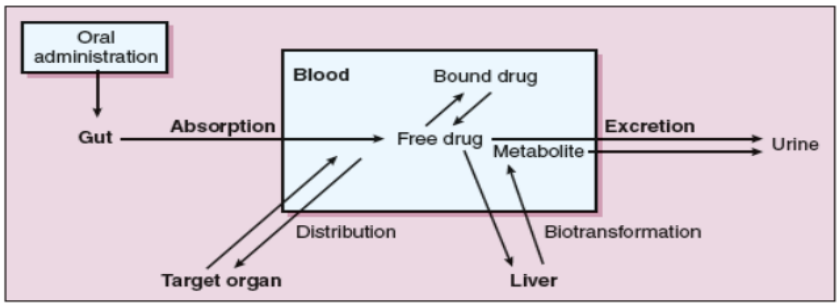


Figure 2–1. The absorption, distribution, biotransformation (metabolism), and excretion of a typical drug after its oral administration.

($pK_a = 8 – 10$) will predominate. Hence, weak acids are more readily absorbed from the stomach than are weak bases. In the intestines, with a pH of 7, weak bases are also mostly ionized, but much less so than in the stomach, and weak bases are absorbed more readily from the intestines than from the stomach. However, weak acids can also be absorbed more readily from the intestines than from the stomach, despite their greater ionization in the intestines, because the intestines have a greater surface area than the stomach for absorption of the non-ionized form of a drug, and this outweighs the influence of greater ionization in the intestines.

DRUG DISTRIBUTION

Drugs are distributed to organs and tissues via the circulation, diffusing into interstitial fluid and cells from the circulation. Most drugs are not uniformly distributed throughout total body water, and some drugs are restricted to the extracellular fluid or plasma compartment. Drugs with sufficient lipid solubility can simply diffuse through membranes into cells. Other drugs are concentrated in cells by the phenomenon of **ion trapping** , which is described further below. Drugs can also be actively transported into cells. For example, some drugs are actively transported into hepatic cells, where they

may undergo enzymatic biotransformation. In the intestines, drug transport by **P-glycoprotein (Pgp)** in the blood-to-lumen direction leads to a secretion of various drugs into the intestinal tract, thereby serving as a detoxifying mechanism. The Pgp proteins also remove many drugs from tissues throughout the body, including anticancer agents. Inhibition of Pgp by amiodarone, erythromycin, propranolol, and other agents can increase tissue levels ofthese drugs and augment their pharmacologic effects.

Factors Affecting Distribution

Organ Blood Flow

The rate at which a drug is distributed to various organs after a drug dose is administered depends largely on the proportion of **cardiac output** received by the organs. Drugs are rapidly distributed to highly perfused tissues, namely the brain, heart, liver, and kidney, and this enables a rapid onset of action of drugs affecting these tissues. Drugs are distributed more slowly to less perfused tissues such as skeletal muscle and even more slowly to those with the lowest blood flow, such as skin, bone, and adipose tissue.

Plasma Protein Binding

Almost all drugs are reversibly bound to plasma proteins, primarily **albumin** , but also lipoproteins, glycoproteins, and β globulins. The extent of binding depends on the affinity of a particular drug for protein-binding sites and ranges from less than 10% to as high as 99% of the plasma concentration.

As the free (unbound) drug diffuses into interstitial fluid and cells, drug molecules dissociate from plasma proteins to maintain the equilibrium between free drug and bound drug. In general, acid drugs bind to albumin and basic drugs to glycoproteins and β globulins. Plasma protein binding is **saturable** , and a drug can be displaced from binding sites by other drugs that have a high affinity for such sites. However, most drugs are not used at high enough plasma concentrations to occupy the vast number of plasma protein binding sites. There are a few agents that may cause drug interactions by competing for plasma protein binding sites.

Molecular Size

Molecular size is a factor affecting the distribution of extremely large molecules, such as those of the anticoagulant **heparin** . Heparin is largely confined to the plasma compartment, although it does undergo some biotransformation in the liver.

Lipid Solubility

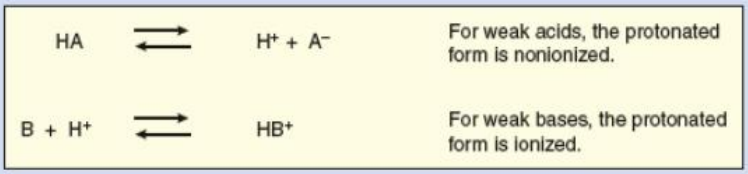
Lipid solubility is a major factor affecting the extent of drug distribution, particularly to the brain, where the **bloodbrain barrier** restricts the penetration of polar and ionized molecules. The barrier is formed by tight junctions between the capillary endothelial cells and also by the glial cells that surround the capillaries, which inhibit the penetration of polar molecules into brain neurons.

DRUG BIOTRANSFORMATION

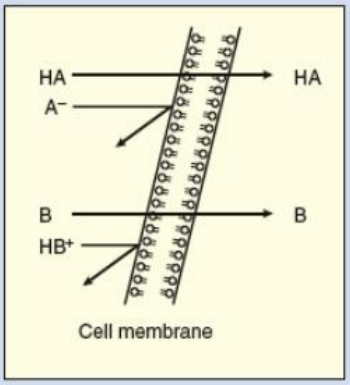
Drug **biotransformation** and **excretion** are the two processes responsible for the decline of the plasma drug concentration over time. Both of these processes contribute to the

BOX 2–1 EFFECT OF pH ON THE ABSORPTION OF A WEAK ACID AND A WEAK BASE

Weak **acids** (HA) donate a proton (H^+) to form anions (A^-), whereas **weak bases** (B) accept a proton to form cations (HB^+).



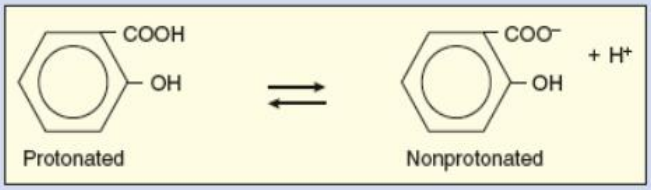
Only the **non-ionized form** of a drug can readily penetrate cell membranes.



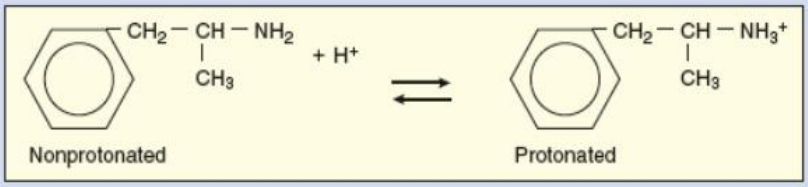
The pK_a of a weak acid or weak base is the **pH** at which there are equal amounts of the protonated form and the nonprotonated form. The **Henderson-Hasselbalch equation** can be used to determine the ratio of the two forms:

$$\log \frac{[\text{protonated form}]}{[\text{Nonrotonated form}]} = pK_a - pH$$

For **salicylic acid**, which is a weak acid with a pK_a of 3, log $[HA]/[A^-]$ is 3 minus the pH. At a pH of 2, then, log $[HA]/[A^-] = 3 - 2 = 1$. Therefore, $[HA]/[A^-] = 10/1$.



For **amphetamine**, which is a weak base with a pK_a of 10, log $[HB^+]/[B]$ is 10 minus the pH. At a pH of 8, then, log $[HB^+]/[B] = 10 - 8 = 2$. Therefore, $[HB^+]/[B] = 100/1$.



(Continued)

BOX 2–1 EFFECT OF pH ON THE ABSORPTION OF A WEAK ACID AND A WEAK BASE—cont'd

The following are the ratios of the protonated form to the nonprotonated form at different pH levels:

		Salicylic acid					Amphetamine			
Protonated		10	1	1	1	1	1000	100	10	1
	pH	2	3	4	5	6	7	8	9	10
Nonprotonated		1	1	10	100	1000	1	1	1	1

elimination of active drug from the body, and as discussed later in the chapter, **clearance** is a measure of the rate of elimination. Biotransformation, or **drug metabolism** , is the enzyme-catalyzed conversion of drugs to their metabolites. Most drug biotransformation takes place in the liver, but drug-metabolizing enzymes are found in many other tissues, including the gut, kidneys, brain, lungs, and skin.

Role of Drug Biotransformation

The fundamental role of drug-metabolizing enzymes is to **inactivate and detoxify** drugs and other foreign compounds (xenobiotics) that can harm the body. Drug metabolites are usually more water soluble than is the parent molecule and, therefore, they are more readily excreted by the kidneys.

No particular relationship exists between biotransformation and pharmacologic activity. Some drug metabolites are active, whereas others are inactive. Many drug molecules undergo attachment of polar groups, a process called **conjugation,** for more rapid excretion. As a general rule, most conjugated drug metabolites are inactive, but a few exceptions exist.

Formation of Active Metabolites

Many pharmacologically active drugs, such as the sedativehypnotic agent **diazepam** (**VALIUM**), are biotransformed to active metabolites. Some agents, known as **prodrugs** , are administered as inactive compounds and then biotransformed to active metabolites. This type of agent is usually developed because the prodrug is better absorbed than its active metabolite. For example, the antiglaucoma agent **dipivefrin** (**PROPINE**) is a prodrug that is converted to its active metabolite, epinephrine, by corneal enzymes after topical ocular administration. Orally administered prodrugs, such as the antihypertensive agent **enalapril** (**VASOTEC**), are converted to their active metabolite by hepatic enzymes during their first pass through the liver.

First-Pass Biotransformation

Drugs that are absorbed from the gut reach the liver via the hepatic portal vein before entering the systemic circulation (Fig. 2 – 2). Many drugs, such as the antihypertensive agentmetabolites during their first pass through the gut wall and liver, and have low **bioavailability** (see below) after oral administration. This phenomenon is called the **first-pass effect** . Drugs administered by the sublingual or rectal route

undergo less first-pass metabolism and have a higher degree of bioavailability than do drugs administered by the oral route.

Phases of Drug Biotransformation

Drug biotransformation can be divided into two phases, each carried out by unique sets of metabolic enzymes. In many cases, phase I enzymatic reactions create or unmask a chemical group required for a phase II reaction. In some cases, however, drugs bypass phase I biotransformation and go directly to phase II. Although some phase I drug metabolites are pharmacologically active, most phase II drug metabolites are inactive.

Phase I Biotransformation

Phase I biotransformation includes oxidative, hydrolytic, and reductive reactions (Fig. 2 – 3).

OXIDATIVE REACTIONS . Oxidative reactions are the most common type of phase I biotransformation. They are catalyzed by enzymes isolated in the microsomal fraction of liver homogenates (the fraction derived from the endoplasmic reticulum) and by cytoplasmic enzymes.

The **microsomal cytochrome P450 (CYP) monooxygenase system** is a family of enzymes that catalyzes the biotransformation of drugs with a wide range of chemical structures. The microsomal **monooxygenase reaction** requires the following: CYP (a hemoprotein); a flavoprotein that is reduced by nicotinamide adenine dinucleotide phosphate (NADPH), called NADPH CYP reductase; and membrane lipids in which the system is embedded. In the drug- oxidizing reaction, one atom of oxygen is used to form a hydroxylated metabolite of a drug, as shown in Figure 2 – 4 , whereas the other atom of oxygen forms water when combined with electrons contributed by NADPH. The hydroxylated metabolite may be the end product of the reaction or serve as an intermediate that leads to the formation of another metabolite.

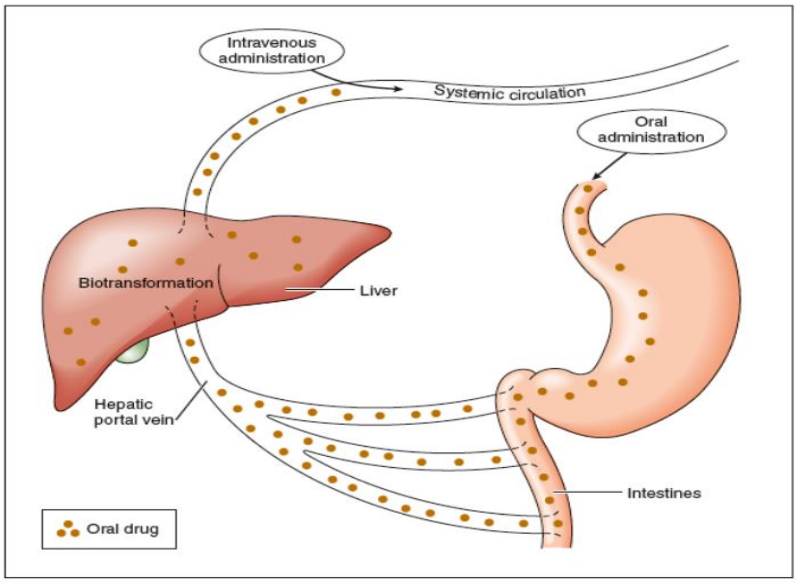


Figure 2–2. First-pass drug biotransformation. Drugs that are absorbed from the gut can be biotransformed by enzymes in the gut wall and liver before reaching the systemic circulation. This process lowers their degree of bioavailability.

The most common chemical reactions catalyzed by CYP enzymes are aliphatic hydroxylation, aromatic hydroxylation, N-dealkylation, and O-dealkylation. Many **CYP isozymes** have been identified and cloned, and their role in metabolizing specific drugs elucidated. Each isozyme catalyzes a different but overlapping spectrum of oxidative reactions. Most drug biotransformation is catalyzed by three CYP families named CYP1, CYP2, and CYP3. The different CYP families are likely related by gene duplication and each family is divided into subfamilies, also clearly related by homologous protein sequences. The **CYP3A** subfamily catalyzes more than half of all microsomal drug oxidations. Many drugs alter drug metabolism by inhibiting or inducing CYP enzymes, and **drug interactions** can occur when these drugs are administered concurrently with other drugs that are metabolized by CYP (see Chapter 4). Two examples of **inducers of CYP** are the barbiturate, **Phenobarbital** , and the antitubercular drug, **rifampin** . The inducers stimulate the transcription of genes encoding CYP enzymes, resulting in increased messenger RNA (mRNA) and protein synthesis. Drugs that induce CYP enzymes activate the binding of **nuclear receptors** to enhancer domains of CYP genes, increasing the rate of gene transcription. A few drugs are oxidized by **cytoplasmic enzymes.** For example, **ethanol** is oxidized to aldehyde by alcohol dehydrogenase, and **caffeine** and the bronchodilator **theophylline** are metabolized by xanthine oxidase. Other cytoplasmicoxidases include **monoamine oxidase** , a site of action for some psychotropic medications.

HYDROLYTIC REACTIONS. Esters and amides are hydrolyzed by a variety of enzymes. These include cholinesterase and other plasma esterases that inactivate choline esters, local anesthetics, and drugs such as **esmolol** (**BREVIBLOC**), an agent for the treatment of tachycardia that blocks cardiac β_1-adrenergic receptors. There are few CYP enzymes that carry out hydrolytic reactions.

REDUCTIVE REACTIONS. Reductive reactions are less common than are oxidative and hydrolytic reactions. **Chloramphenicol** , an antimicrobial agent, and a few other drugs are partly metabolized by a hepatic nitro reductase, and this process involves CYP enzymes. **Nitroglycerin** , a vasodilator, undergoes reductive hydrolysis catalyzed by glutathione-organic nitrate reductase.

Phase II Biotransformation

In phase II biotransformation, drug molecules undergo **conjugation reactions** with an endogenous substance such as **acetate** , **glucuronate** , **sulfate** , or **glycine** (Fig. 2 – 5). Conjugation enzymes, which are present in the liver and other tissues, join various drug molecules with one of these endogenous substances to form water-soluble metabolites that are more easily excreted. Except for microsomal **glucuronosyltransferases** , these enzymes are located in the cytoplasm. Most conjugated drug metabolites are pharmacologically inactive.

GLUCURONIDE FORMATION. Glucuronide formation, the most common conjugation reaction, utilizes glucuronosyltransferases to conjugate a glucuronate molecule with the parent drug molecule.

ACETYLATION. Acetylation is accomplished by **N-acetyltransferase** enzymes that utilize acetyl coenzyme A (**acetyl CoA**) as a source of the acetate group.

SULFATION. Sulfotransferases catalyze the conjugation of several drugs, including the vasodilator **minoxidil** and the potassium-sparing diuretic **triamterene** , whose sulfate metabolites are pharmacologically active.

Pharmacogenomics

Since the completion of the human genome, it is now fully realized that there is a great degree of individual variation, called **polymorphism** , in the genes coding for drug-metabolizing enzymes. Modern genetic studies were triggered by rare fatalities in children being treating for leukemia using the thiopurine agent, 6-mercaptopurine (6-MP). It was discovered that the children died as a result of drug toxicity because they expressed a faulty variant of thiopurine methyltransferase, the enzyme that metabolizes 6-MP.

Variations in Acetyltransferase Activity

Individuals exhibit slow or fast acetylation of some drugs because of genetically determined differences in Nacetyltransferase. Slow acetylators (SAs) were first identified by neuropathic effects of **isoniazid** , a drug to treat tuberculosis. These patients had higher plasma levels of isoniazid compared to other patients classified as rapid acetylators (RAs). The SA phenotype is autosomal recessive, although there are more than 20 allelic variants of the gene for N-acetyltransferase identified. In individuals with one wild-type enzyme and one faulty variant, an intermediate phenotype is observed. The **distribution** of these phenotypes varies from population to population. About 15% of Asians, 50% of Caucasians and Africans, and more than 80% of Mideast populations have the SA phenotype. Other drugs that may cause toxicity in the SA patient are **sulfonamide antibiotics** , the antiarrhythmic agent **procainamide** , and the antihypertensive agent **hydralazine.**

Variations in CYP2D6 and CYP2C19 Activity

Variations in oxidation of some drugs have been attributed to genetic differences in certain CYP enzymes. Genetic polymorphisms of CYP2D6 and CYP2C19 enzymes are well characterized, and human populations of “extensive metabolizers” and “poor metabolizers” have been identified.

These differences are caused by more than 70 identified variants in the CYP2D6 gene and more than 25 variants of the CYP2C19 genes, resulting from point mutations, deletions, or additions; gene rearrangements, or deletion or duplication of the entire gene. This gives rise to an increase, reduction, or complete loss of enzyme activity and to different levels of enzyme expression that result in **altered rates** of enzymatic reactions.

Most individuals are extensive metabolizers of CYP2D6 substrates, but 10% of Caucasians and a smaller fraction of Asians and Africans are poor metabolizers of substrates for CYP2D6. Psychiatric patients who are poor metabolizers of CYP2D6 drugs have been found to have a higher rate of adverse drug reactions than do those who are extensive metabolizers because of higher psychotropic drug plasma levels. In addition, poor metabolizers of CYP2D6 drugs have a reduced ability to metabolize **codeine** to morphine sufficiently to obtain adequate pain relief when codeine is administered for analgesia. Poor metabolizers of CYP2C19 substrates have higher plasma levels of proton pump inhibitors, such as **omeprazole** (**PRILOSEC**), whereas some extensive metabolizers of CYP2C19 drugs require larger doses of omeprazole to treat peptic ulcer.

Other Variations in Drug Metabolism Enzymes

About 1 of 3000 individuals exhibits a familial **atypical cholinesterase** that will not metabolize succinylcholine, a neuromuscular blocking agent, at a normal rate. Affected individuals are subject to prolonged apnea after receiving the usual dose of the drug. For this reason, patients should be screened for atypical cholinesterase before receiving succinylcholine. There are many more polymorphisms in both phase I and phase II metabolic enzymes. With more than 30 families of drug-metabolizing enzymes, all with genetic variants, a major development in pharmacotherapy will be the individual tailoring of drug and dose to each patient's genomic identity.

DRUG EXCRETION

Excretion is the removal of drug from body fluids and occurs primarily in the **urine** . Other routes of excretion from the body include in bile, sweat, saliva, tears, feces, breast milk, and exhaled air.

Renal Drug Excretion

Most drugs are excreted in the urine, either as the parent compound or as a drug metabolite. Drugs are handled by the kidneys in the same manner as are endogenous substances, undergoing processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. The amount of drug excreted is the sum of the amounts filtered and secreted minus the amount reabsorbed. The relationship between these processes, the rate of drug excretion, and renal clearance is shown in Box 2-2 .

Glomerular Filtration

Glomerular filtration is the first step in renal drug excretion. In this process, the free drug enters the renal tubule as a dissolved solute in the plasma filtrate (see Box 2-2). If a drug has a large fraction bound to plasma proteins, as is the case with the anticoagulant **warfarin** , it will have a low rate of glomerular filtration.

Active Tubular Secretion

Some drugs, particularly weak acids and bases, undergo active tubular secretion by transport systems located primarily in proximal tubular cells. This process is competitively inhibited by other drugs of the same chemical class. For example, the secretion of penicillins and other weak acids is inhibited by **probenecid** , an agent used to treat gout. Active tubular secretion is not affected by plasma protein binding. This is due to the equilibrium of free drug and bound drug such that when free drug is actively transported across the renal tubule, this fraction of free drug is replaced by a fraction that dissociates from plasma proteins.

Passive Tubular Reabsorption

The extent to which a drug undergoes passive reabsorption across renal tubular cells and into the circulation depends on the **lipid solubility** of the drug. Drug biotransformation facilitates drug elimination by forming polar drug metabolites that are not as readily reabsorbed as the less-polar parent molecules. Most nonelectrolytes, including **ethanol** , are passively reabsorbed across tubular cells. Ionized weak acids and bases are not reabsorbed across renal tubular cells, and they are more rapidly excreted in the urine than are non-ionized drugs that undergo passive reabsorption. The proportion of ionized and non-ionized drugs is affected by **renal tubular pH** , which can be manipulated to increase the excretion of a drug after a drug overdose (Box 2-3) .

Biliary Excretion and Enterohepatic Cycling

Many drugs are excreted in the bile as the parent compound or a drug metabolite. Biliary excretion favors compounds with molecular weights that are higher than 300 and with both polar and lipophilic groups; smaller molecules are excreted only in negligible amounts. Conjugation, particularly with **glucuronate** , increases biliary excretion.

Numerous conjugated drug metabolites, including both the glucuronate and sulfate metabolites of steroids, are excreted in the bile. After the bile empties into the intestines, a fraction of the drug may be reabsorbed into the circulation and eventually return to the liver. This phenomenon is called **enterohepatic cycling** (Fig. 2 – 6). Excreted conjugated drugs can be hydrolyzed back to the parent drug by intestinal bacteria, and this facilitates the drug's reabsorption. Thus, biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete, that is, when some of the excreted drug is not reabsorbed from the intestine

Other Routes of Excretion

Sweat and saliva represent minor routes of excretion for some drugs. In pharmacokinetic studies, saliva measurements are sometimes used because the saliva concentration of a drug often reflects the intracellular concentration of the drug in target tissues.

QUANTITATIVE PHARMACOKINETICS

To derive and use expressions for pharmacokinetic parameters, the first step is to establish a mathematical model that accurately relates the plasma drug concentration to the rates of drug absorption, distribution, and elimination. The **one-compartment model** is the simplest model of drug disposition, but the **two-compartment model** provides a more accurate representation of the pharmacokinetic behavior of many drugs (Fig. 2 – 7). With the one-compartment model, drug undergoes absorption into the blood according to the rate constant, k_a , and elimination from the blood with a rate constant, k_e . In the two-compartment model, drugs are absorbed into the central compartment (blood), distributed from the central compartment to the peripheral compartment (the tissues), and eliminated from the central compartment. Regardless of the model used, rate constants can be determined for each process and used to derive expressions for other pharmacokinetic parameters, such as the **elimination half-life ($t_{1/2}$)** of a drug. In this section, the most important parameters of pharmacokinetics are explained in greater detail.

Drug Plasma Concentration Curves

Figure 2 – 8A shows a standardized **drug plasma concentration curve** over time after oral administration of a typical drug. The Y-axis is a linear scale of drug plasmaconcentration, often in μg/mL or mg/L, and the X-axis is a time scale, usually in hours. Parameters of the plasma drug concentration curve are the **maximum concentration** (**C_{max}**) , the time needed to reach the maximum (**T_{max}**) , the **minimum effective concentration** (**MEC)** , and the **duration of action** . A measure of the total amount of drug during the time course is given by the **area under the curve (AUC)** . These measures are useful for comparing the **bioavailability** of different pharmaceutical formulations or of drugs given by different routes of administration.

Bioavailability (F)

Bioavailability is defined as the **fraction (F)** of the administered dose of a drug that reaches the systemic circulation in an active form. As shown in Figure 2 – 8B , the oral bioavailability of a particular drug is determined by dividing the AUC of an orally administered dose of the drug (AUC_{oral}) by the AUC of an intravenously administered dose of the same drug (AUC_{IV}). By definition, an intravenously administered drug has 100% bioavailability. The bioavailability of drugs administered intramuscularly or via other routes can be determined in the same manner as the bioavailability of drugs administered orally. The bioavailability of orally administered drugs is of particular concern because it can be reduced by many pharmaceutical and biologic factors. Pharmaceutical factors include the rate and extent of tablet disintegration and drug dissolution.

Biologic factors include the effects of food, which can sequester or inactivate a drug; the effects of gastric acid, which can inactivate a drug; and the effects of gut and liver enzymes, which can metabolize a drug during its absorption and first pass through the liver. The CYP3A4 isozyme found in intestinal enterocytes and hepatic cells is a particularly important catalyst of first-pass drug metabolism. CYP3A4 works in conjunction with Pgp (described in the section titled "Drug Distribution") as the 3A4 isozyme located in enterocytes inactivates drugs transported into the intestinal lumen by Pgp.

Volume of Distribution

The volume of distribution (**V_d**) is defined as the volume of fluid in which a drug would need to be dissolved to have the **same concentration** as it does in plasma. The V_d does not represent the volume in a particular body fluid compartment (Fig. 2 – 9A); instead, as shown in Figure 2 – 9B , it is an apparent volume that represents the relationship between the dose of a drug and the resulting plasma concentration of the drug.

Calculation of V_d

After intravenous drug administration, the plasma drug concentration falls rapidly at first, as the drug is distributed from the central compartment to the peripheral compartment. The V_d is calculated by dividing the dose of a drug given intravenously by the plasma drug concentration immediately after the distribution phase (α). As shown in Figure 2 – 9C , this drug concentration can be determined by extrapolating the plasma drug concentration back to timezero from the linear part of the elimination phase (β). Note that the Y-axis in this case is plotted on a **log scale** so that the exponential elimination phase is converted to a straight line. The plasma drug concentration at time zero (**C_0**) represents the plasma concentration of a drug that would be obtained if it were instantaneously dissolved in its V_d. The equation for calculating V_d is rearranged to determine the dose of a drug that is required to establish a specified plasma drug concentration (see below).

Interpretation of V_d

Although the V_d does not correspond to an actual body fluid compartment, it does provide a measure of the extent of distribution of a drug. A low V_d that approximates plasmavolume or extracellular fluid volume usually indicates that the drug's distribution is restricted to a particular compartment (the plasma or extracellular fluid). The anticoagulant **warfarin** has a V_d of about 8 L, which reflects a high degree of plasma protein binding. When the V_d of a drug is equivalent to total body water (about 40 L, as occurs with ethanol), this usually indicates that the drug has reached the intracellular fluid as well. Some drugs have a V_d that is much larger than total body water. A large V_d may indicate that the drug is concentrated intracellularly, with a resulting low concentration in the plasma. Many weak bases, such as the antidepressant **fluoxetine** (**PROZAC**), have a large V_d (40 – 55 L) because of the phenomenon of intracellular **ion trapping.** Weak bases are less ionized within plasma than they are within cells because intracellular fluid usually has a lower pH than extracellular

fluid. After a weak base diffuses into a cell, a larger fraction is ionized in the more acidic intracellular fluid. This restricts its diffusion out of a cell and results in a large V_d. A large V_d may also result from sequestration into fat tissue, such as occurs with the antimalarial agent **chloroquine** .

Drug Clearance

Clearance (**Cl**) is the most fundamental expression of drug elimination. It is defined as the volume of body fluid (blood) from which a drug is removed per unit of time. Whereas the clearance of a particular drug is **constant** , it is important to note that the amount of drug contained in the clearance volume will **vary** with the plasma drug concentration.

RENAL CLEARANCE. Renal clearance can be calculated as the renal excretion rate divided by the plasma drug concentration (see Box 2-2). Drugs that are eliminated primarily by glomerular filtration, with little tubular secretion or reabsorption, will have a renal clearance that is approximately equal to the creatinine clearance, which is normally about 100 mL/min in an adult. A renal drug clearance that is higher than the creatinine clearance indicates that the drug is a substance that undergoes tubular secretion. A renal drug clearance that is lower than the creatinine clearance suggests that the drug is highly bound to plasma proteins or that it undergoes passive reabsorption from the renal tubules.

HEPATIC CLEARANCE. Hepatic clearance is more difficult to determine than renal clearance. This is because hepatic drug elimination includes the biotransformation and biliary excretion of parent compounds. For this reason, hepatic clearance is usually determined by multiplying hepatic blood flow by the arteriovenous drug concentration difference.