

*Contributor: Sandra Earle*

The physiochemical properties of drugs determine how they will move and interact with the body. By understanding a few principles, predictions about how and where a drug will move in the body can be accurately made. These principles can then be applied to the processes that a drug undergoes as it moves through the body.

---

### Tips Worth Tweeting

- A drug must be sufficiently small and lipophilic, and must be uncharged (un-ionized), to undergo passive diffusion.
- Passive diffusion does not require energy—just a concentration gradient.
- Active transport requires a carrier, attraction to the carrier, and energy.
- Any fixed-capacity system can follow Michaelis-Menten kinetics and be nonlinear.
- Michaelis-Menten kinetics are determined by the system's capacity and affinity.
- If the drug concentration is much less than the concentration where half the carriers are occupied ( $K_m$ ), the system will be concentration-independent.
- Genetic polymorphisms can dictate how much enzyme capacity or transporter capacity an individual patient possesses.
- A drug must be dissolved to be absorbed.
- Consumption of food slows drug absorption, but may not change the amount of drug ultimately absorbed.
- Drugs can be metabolized by enzymes in the gut wall before reaching the systemic circulation.
- Drugs can be pumped out of the gut wall and back into the gut lumen after being absorbed.
- Efflux pumps can be up-regulated and down-regulated by drugs.
- Gut enzymes can be either induced or inhibited by drugs and food.
- Drugs can be metabolized in the liver before reaching the systemic circulation.
- The more highly protein bound a drug is, the more important binding displacement becomes.
- Only non-protein-bound drug (free drug) can move between membranes and interact with receptors or drug-metabolizing enzymes.
- Polar drugs can be excreted in the urine. Nonpolar drugs must be metabolized to make them more polar for excretion by the kidneys.
- The CYP450 family of enzymes is responsible for most drug metabolism.
- Drugs can be substrates, inducers, and inhibitors of specific isoenzymes in the CYP450 family.
- Enzyme induction will likely cause a decrease in drug concentration and therefore cause a possible decrease in or loss of therapeutic efficacy.
- Enzyme inhibition will likely cause an increase in drug concentration and,

therefore, an increase in pharmacologic effect or possible toxicity.

- Renal elimination includes three processes: filtration, secretion, and reabsorption.
- Secretion is a carrier-mediated system, and reabsorption is accomplished by passive diffusion.
- Movement of a drug through the membranes between a woman and her fetus and breastmilk occurs by passive diffusion.

**Key Terms**

**Carrier-mediated transport:** Transportation of a drug molecule via a carrier system requiring energy.

**Endocytosis:** Movement through a membrane by engulfment.

**Genotype:** Genetic sequencing for a protein.

**Hydrophilic:** “Water loving”; soluble in water, insoluble in nonpolar lipids. Similar to lipophobic (“lipid fearing”).

**Lipophilic:** “Lipid loving”; soluble in nonpolar lipids, insoluble in aqueous solutions. Similar to hydrophobic (“water fearing”). The higher the partition coefficient (PC), the more lipophilic the compound.

**Michaelis-Menten kinetics:** Description of a nonlinear rate of a reaction that can be applied to many processes.

**Paracellular transport:** Movement of a drug through a membrane by passing between cells.

**Partition coefficient (PC):** Ratio of drug concentrations at equilibrium between n-octanol (mimics lipophilic membranes) and water. The higher the PC, the more lipophilic the compound.

**P-glycoprotein (P-gp):** An important efflux pump found on the gut wall, blood–brain barrier, hepatocytes, and renal tubular cells.

**Phenotype:** How a genotype expresses itself.

**Polymorphism:** When at least two different phenotypes (1 wild + 1 or more mutations) occur in a population.

**Prodrug:** A drug that must be metabolized to acquire therapeutic efficacy.

**Transcellular transport:** Movement of a drug through a membrane by passing through the cell; can be passive diffusion or facilitated by a transporter or pump.

**PRINCIPLES**

**Membrane Transport**

Movement through membranes is essential to the transportation of a drug in the body. Membranes in the body are primarily lipoidal matrices dotted with proteins and, in some cases, aqueous channels. Drugs can move through the membrane cells (transcellular transport) or between the cells making up the membrane (paracellular transport). If the drug moves through the cell itself, it can move by simple passive diffusion; alternatively, movement can be facilitated by a transport system. Drugs can also cross membranes by endocytosis (i.e., a large molecule may be engulfed by the cell).

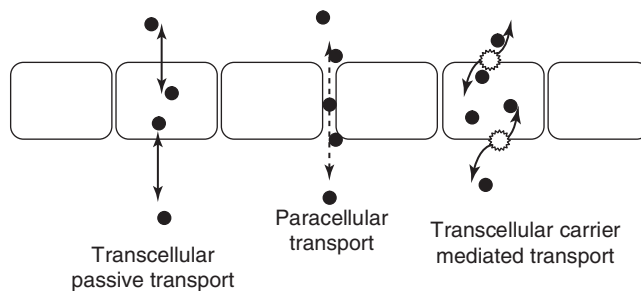
**Passive Diffusion**

Drugs move by passive diffusion by naturally following a concentration gradient. Because the movement is due to the energy of the molecules, no energy is required for the transport. The rate of transport is based on Fick’s first law of diffusion:

$$\text{Rate of transport} = \frac{\text{Permeability} \times \text{Surface area} \times \text{Concentration difference}}{\text{Membrane thickness}} \quad (2-1)$$

**Carrier-Mediated Transport**

Many drugs are transported via carrier systems rather than by passive diffusion. This method does not require the concentration gradient or permeability characteristics needed for passive diffusion, but a transporter and energy are required to move the drug. The number of transport sites will be limited, so competition for these sites may occur. Up- or down-regulation of



**Figure 2-1** Forms of Drug Molecule Transport

**Table 2-1 Factors That Enhance Drug Transport**

Membrane Properties That Enhance Transport by Passive Diffusion	
Membrane thickness	Very thin membranes, like those in blood capillaries, facilitate very rapid transport of even large, polar, charged molecules; the thicker the membrane, the more important the permeability characteristics of the drug.
Available surface area	Larger surface areas offer greater opportunity for transport; the small intestine is most important site of drug absorption because of its large surface area.
Drug Properties That Enhance Transport by Passive Diffusion	
Small size	Molecular weight of less than 300 g/mol increases the likelihood of passive diffusion. Protein-bound drugs not small enough.
Charge	Ionized drugs less likely to be transported. Use the Henderson-Hasselbalch equation to estimate the degree of ionization.
Lipophilic	Nonpolar/lipophilic drugs more likely to be transported; a higher oil:water partition coefficient (PC) predicts more rapid transport.
Large concentration gradient	A larger difference between concentrations on opposite sides of the membrane predicts faster transport to the less concentrated side.

the number of transporters may occur. The direction of the transport can be either into the cell (influx) or out of the cell (efflux). Some transporters are listed in Table 2-2.

**P-glycoprotein** (P-gp) is the best studied member of a family of efflux transporters called the multidrug resistance proteins (MRPs). It plays a major role in moving drugs from the intestinal wall back into the gut lumen. P-gp is also found in the liver (moves drugs from hepatocytes back into the blood), in the kidneys (moves drugs from tubular cells back into the urine), and as part of the blood–brain barrier (moves drugs from brain epithelial cells back into the blood). Its discovery on tumor cells that were resistant to anticancer drugs greatly increased awareness of this transporter.

**Table 2-2 Drug Transporters**

Influx Transporters	Efflux Transporters
OAT (organic anion transporter)	P-gp (P-glycoprotein)
OCT (organic cation transporter)	BCRP (breast cancer resistance protein) BSEP (bile salt export pump) MRP (multidrug resistance proteins)

Many drugs are substrates, inducers, and inhibitors of P-gp. These drugs are also commonly substrates of CYP3A4. P-gp may act as a “gatekeeper” to regulate exposure of drugs to CYP450 enzymes in the gut wall. P-gp can be up- and down-regulated by some drugs and foods—an important source of drug and disease interactions. Additionally, genetic variants of P-gp may be more or less effective than the wild type. As more is learned about this polymorphism, patient-specific information may become useful to determine individual dosing regimens based on P-gp phenotype.

### Michaelis-Menten Kinetics and Drug Transport

Any transport system that has a fixed capacity (i.e., carrier-mediated transport) is saturable at some point. When this occurs, the rate or extent of the process can no longer increase proportionally to the dose or concentration; that is, it is no longer a linear relationship. In this case, the process will follow Michaelis-Menten kinetics. The Michaelis-Menten relationship is shown in Equation 2-2. Hepatic metabolism, plasma protein binding, and facilitated (carrier-mediated) transport all follow this principle:

$$\text{Rate of Reaction} = \frac{V_{\max} \cdot C}{K_m + C} \quad (2-2)$$

where

- $V_{\max}$  = maximal rate of the reaction (capacity)
- $K_m$  = concentration at which  $\frac{1}{2}V_{\max}$  is reached (affinity)
- $C$  = concentration.

### Metabolism

In the case of drug metabolism by hepatic enzymes, hepatic intrinsic clearance ( $CL_{\text{int}}$ ) is governed by Michaelis-Menten kinetics:

$$CL_{\text{int}} = \frac{\text{Rate of Reaction}}{C} = \frac{V_{\max}}{K_m + C} \quad (2-3)$$

The maximal rate of metabolism ( $V_{\max}$ ) is determined by the number of enzymes available, or the capacity of the enzyme system. The number of enzymes (and, therefore,  $V_{\max}$ ) can be increased by the addition of an enzyme inducer. The drug concentration where 50% of  $V_{\max}$  is achieved is  $K_m$  and serves as a measure of the affinity of the system. The lower the value of  $K_m$ , the higher the affinity between drug and enzyme. Knowledge of relative  $K_m$  (which are often referred to as  $K_i$  in the literature) between two drugs could predict which drug would be preferentially metabolized and suggest which drug–drug interactions might occur.

In most cases, metabolism is linear because drug concentrations achieved in the therapeutic range are much smaller than the  $K_m$  value of the system. In such a scenario, concentration is unimportant in the denominator of Equation 2-3 and, therefore, is unimportant in the determination of  $CL_{int}$ .  $CL_{int}$  would then be linear and determined only by the relative capacity (number of enzymes available or  $V_{max}$ ) and affinity (how attracted the drug is to the enzyme or  $K_m$ ) of the drug-enzyme system. This will result in concentration-independent, linear clearance of the drug (Figure 2-2):

$$CL_{int} = \frac{V_{max}}{K_m + C} \approx \frac{V_{max}}{K_m} \quad (2-4)$$

However, if  $K_m$  is not much smaller than the concentrations seen, then drug concentration becomes a determinant of the enzyme activity ( $CL_{int}$ ) and the clearance of the drug. This happens with phenytoin in the therapeutic range. In this case,  $CL_{int}$  and therefore the  $CL$  of phenytoin are partly determined by the concentration (as in Equation 2-3) and will be saturable. As concentration increases,  $CL_{int}$  will decrease, causing concentration-dependent or nonlinear metabolism and clearance (Figure 2-3).

Nonlinear metabolism makes dosing a challenge. Small changes in doses produce disproportionately large changes in concentrations. Also, because  $CL$  is constantly changing, there is no true  $t_{1/2}$ .

### Protein Binding and Carrier-Mediated Transport

Plasma protein binding and active, carrier-mediated transport are also saturable systems that exhibit nonlinearity. Again, each system will have a capacity ( $V_{max}$ ) and affinity ( $K_m$ ). In the case of plasma protein binding, the capacity will be determined by the number of binding sites available. The  $K_m$  or affinity measure is termed

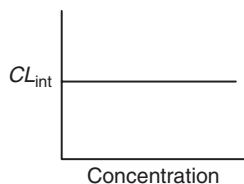


Figure 2-2 Concentration-independence

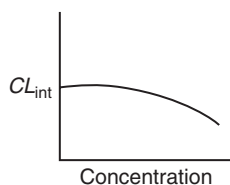


Figure 2-3 Concentration-dependence

$K_d$  in the case of binding and is the concentration producing half saturation of binding sites. If  $K_d$  is much greater than the concentrations achieved, binding will be concentration-independent and linear. Most drugs exhibit linear binding in the therapeutic range, although valproic acid and disopyramide demonstrate nonlinear binding in their therapeutic ranges. For these drugs, free fraction increases as concentration increases, making interpretation of total drug concentrations difficult.

Analogously, the capacity of carrier-mediated transport will be the number of carrier systems available;  $K_m$  is called  $K_T$  in this case. If  $K_T$  is much greater than the concentration, transport will be linear. If the concentration approaches  $K_T$ , transport will be concentration-dependent and will slow with increasing concentration.

### Pharmacogenomics

Genetic differences in individuals can affect drug movement and drug response. By understanding these

Table 2-3 Sources of Polymorphism

	Enzyme/Gene	Ethnic Frequency of Poor Metabolizers
Phase I enzymes	CYP 2D6	Approximately 10% of all Caucasians
	CYP 2C9	Approximately 3% of all Caucasians
	CYP 2C19	Approximately 20% of all Asians Approximately 3% of all African Americans and Caucasians
	Dihydropyrimidine dehydrogenase	Approximately 1% of the total population
Phase II enzymes	N-acetyltransferase	52% of all Caucasians 25% of all Asians
	Uridine diphosphate-glyucuronosyl-transferase	Approximately 10% of all Caucasians Approximately 3% of all Asians
	Thiopurine S-methyltransferase	1 in 300 Caucasians 1 in 2,500 Asians
	COMT	25% of all Caucasians
Pharmacologic receptors	Angiotensin-converting enzyme	
	$\beta_2$ receptors	
	Bradykinin receptors	
	Estrogen receptor- $\alpha$	
	Glycoprotein IIIa	
	Serotonin	

possible differences, predictions can be made about an individual's response to a given drug, and an optimal therapeutic plan can be developed.

Genetic differences in metabolizing enzymes and transport systems have been identified and can sometimes be used to optimize therapy. Genetic differences in pharmacologic receptors may be important in choice of therapy. "Polymorphism" is said to exist when there is a significant subpopulation with a specific variant gene expression. Some important sources of polymorphism are identified in Table 2-3.

## A DRUG'S TRIP THROUGH THE BODY

### Bioavailability

The bioavailability of a drug ( $F$ ) is determined by many factors, including the route of administration, dosage form, physiological status of the patient, and properties of the drug itself. If given orally, the drug must first be absorbed ( $f_a$ ). Then it must cross the gut wall without being metabolized or pumped back into the intestine by an efflux pump ( $f_g$ ). Finally the drug must circulate through the liver without undergoing metabolism ( $f_{lp}$ ) before reaching the systemic circulation, where it can act on receptors:

$$F = f_a \times f_g \times f_{lp} \quad (2-5)$$

### Absorption ( $f_a$ )

Most absorption in the gut occurs in the small intestine because of the great amount of surface area available there; this absorption usually results from passive diffusion. Before reaching the site of absorption, a drug must first be liberated from its dosage form. Then it must survive exposure to the acidic environment in the stomach without being destroyed and reach the absorption site without being adsorbed (bound) or complexed by food or another drug. Once it reaches the site of absorption, the drug will be absorbed either by passive diffusion or by active transport; this amount accounts for the fraction of drug absorbed ( $f_a$ ).

### Liberation

A drug must be dissolved to be absorbed. Most drugs are given as tablets, capsules, or solutions. A drug in a solution form is already dissolved and does not need to be liberated. In contrast, capsules must dissolve and release their contents containing the active drug, which must then dissolve to be available for absorption. Compressed tablets must also disintegrate into smaller particles before a drug can undergo dissolution. The smaller

the particle size in the formulation, the more quickly the drug will dissolve and be ready for absorption.

### Gastric Effects

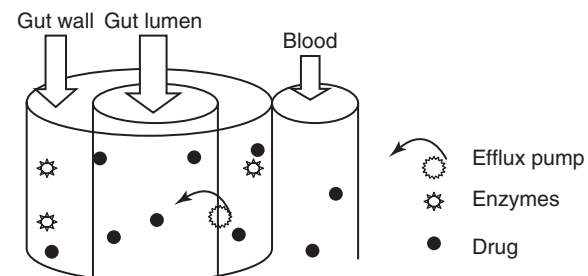
Gastric emptying time is often the rate-limiting step in absorption. Gastric emptying is slowed by consumption of food (especially fat). This relationship explains why it is recommended that many drugs be taken on an empty stomach. Drugs such as anticholinergics and diseases such as diabetes can also slow gastric emptying time, thereby slowing the absorption rate. The stomach is very acidic, and some drugs may be destroyed when exposed to the very low pH in this organ.

### Adsorption and Complexing

A drug may be adsorbed (bound) or complexed in the gastrointestinal lumen, in which case it will be found in the feces in the bound or complexed form. Adsorption occurs when a drug is attracted to and clings to another entity. Adsorption with charcoal, for example, is commonly used to prevent drugs from being absorbed in cases of overdose. Drugs can also complex with compounds to make them incapable of being absorbed. Calcium and iron supplements are common ions that will complex with drugs (e.g., tetracycline antibiotics or levothyroxine), making them too big for absorption.

### Gut Wall Metabolism and Efflux

Once the drug is absorbed into the gut wall ( $f_a$ ), efflux pumps (e.g., P-gp) in gut wall cells can propel the drug back into the gut lumen. Enzymes in the gut wall also may metabolize the drug. Cytochrome P450 (CYP450) 3A enzymes are found in high concentrations in the small intestinal wall. There is great potential for inducers and inhibitors of these systems to alter the fraction of drug escaping gut metabolism ( $f_g$ ). For example, grapefruit juice is an inhibitor of CYP450 3A and may significantly increase  $f_g$  for substrates of this enzyme (Figure 2-4).



**Figure 2-4** Drug Metabolization in the Gut

### First Pass Through the Liver

Once the drug has been absorbed ( $f_a$ ) and escapes metabolism or efflux from the gut wall ( $f_g$ ), it is then taken by the portal vein to the liver, which is the major organ responsible for clearance of drugs by metabolism. The liver is rich in enzymes for both Phase I and Phase II metabolism reactions. A fraction of the absorbed drug ( $f_{ip}$ ) may escape first-pass metabolism by the liver before reaching the systemic circulation. Drugs extensively metabolized by hepatic enzymes in the liver will often have a very low bioavailability if given by the oral route because much of the drug is metabolized in the first pass. For this reason, these drugs may need to be administered by a non-oral route to attain sufficient concentrations at receptor sites. Examples of routes that avoid first-pass metabolism are topical (e.g., patches) and parenteral.

### Biliary Clearance and Enterohepatic Cycling

Drugs may also undergo biliary elimination or enterohepatic cycling. In this case, after the drug is absorbed and delivered via the portal vein to the liver; a portion may be secreted—by active, carrier-mediated transport—into the bile and stored in the gallbladder. The drug in the bile will then be transported back into the intestine and possibly reabsorbed to complete what is called an enterohepatic cycle. Alternatively, the drug may not be reabsorbed and will be eliminated in the feces. Biliary transport of drugs can be competitively inhibited. Drugs that have high biliary clearance are often polar, ionized molecules with molecular weights greater than 250 g/mol.

Metabolites of drugs are often eliminated via biliary secretion (Figure 2-5).

### Distribution and Protein Binding

Once the drug reaches the systemic circulation, it is distributed throughout the body. The extent of this distribution is measured as volume of distribution and is an important determinant of how and where the drug may act and how long it stays in the body. When the drug reaches the circulation, it may become bound to a protein in the plasma. Only unbound drug can move to other tissues, where it may also be bound to tissue proteins. Because of the size of proteins, only free or unbound drug can pass through membranes from the plasma to and from the tissue and interact with pharmacologic receptors. The extent of protein binding is a major determinant of volume of distribution of a drug. Volume of distribution is important because it affects the elimination rate constant and half-life and must be considered in some dosing calculations.

#### Distribution

Three different volumes of distribution may be utilized in pharmacokinetics: central volume of distribution ( $V_c$ ), volume of distribution at steady state ( $V_{ss}$ ), and apparent volume of distribution ( $V_{dapparent}$ ). The first two are physiologic volumes, and the third is a calculated value.

#### Central Volume of Distribution

Initially, the drug will become distributed in the plasma and highly perfused organs. This is generally called the

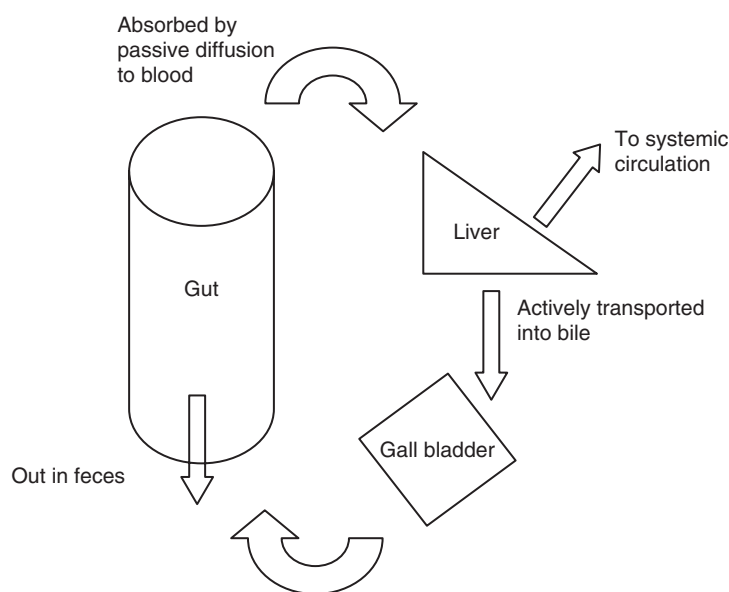


Figure 2-5 Enterohepatic Cycling

central volume of distribution and is used to calculate loading doses.

### Steady-State Volume of Distribution

As a drug reaches its steady state, it moves into other tissues in the body. In an average 70-kg patient, the plasma volume ( $V_p$ ) is approximately 3 L (0.04 L/kg) and the tissue volume ( $V_T$ ) is approximately 39 L (0.56 L/kg). Distribution of a drug depends on how highly it is bound in the plasma compartment in relation to the tissue compartment. Because only free or unbound drug can move between plasma and tissue compartments, drug molecules that are bound to plasma proteins are “stuck” in the smaller plasma compartment and cannot move to the tissue compartment; therefore, such a drug will have a smaller volume of distribution. The opposite case can also be true: if a drug is more highly bound in the larger tissue compartment, it will have a relatively large volume of distribution. This relationship is described in Equation 2-6 and Figure 2-6:

$$V_{ss} = V_p + \left( V_T \cdot \frac{f_{up}}{f_{ut}} \right), \quad (2-6)$$

where

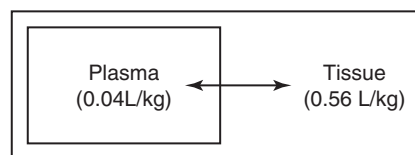
$$\begin{aligned} f_{up} &= \text{fraction unbound in plasma} \\ f_{ut} &= \text{fraction unbound in tissues.} \end{aligned}$$

### Apparent Volume of Distribution

The apparent volume of distribution is the calculated volume necessary to account for the resulting concentration when a known amount of drug is given. This is not a physiologic volume but is often considered to be similar to  $V_{ss}$ :

$$C = \frac{\text{Dose}}{V}. \quad (2-7)$$

The size and lipophilicity of drugs also determine where they are distributed. Large molecules will not be able to leave the plasma compartment and will have a volume of distribution roughly equal to the  $V_p$ . ( $V_p$  is the smallest possible volume for a drug.) Relatively small, but polar drugs will not be able to traverse lipophilic cell membranes and, therefore, will be able to reach only the plasma and interstitial volumes (approximately 0.17 L/kg). Small, lipophilic drug molecules will be able to move throughout all the available spaces.



**Figure 2-6** Size and Lipophilicity of Drugs Determines Distribution

### Protein Binding

Protein binding is important for many reasons. Only free drug is active and able to move through membranes and interact with receptors, so protein binding is important in determining active concentrations and volumes. Also, in many cases, only free drug can be cleared; therefore, clearance may be dependent upon the unbound fraction in plasma ( $f_{up}$ ). Drugs are bound to proteins in a reversible fashion. The fraction bound is determined by the capacity (amount of protein available) and the affinity of the drug for the binding site (see the earlier discussion of Michaelis-Menten pharmacokinetics).



### Significance of Protein Binding

In clinical practice, total concentrations (both free and bound) of drugs are measured. To determine the free concentration of a drug, the total concentration should be multiplied by the fraction unbound (free fraction) in the plasma ( $f_{up}$ ):

$$C_{free} = C_{tot} \cdot f_{up}. \quad (2-8)$$

Equation 2-8 illustrates the importance of knowing whether plasma protein binding has changed. Protein binding changes are significant only if the drug is highly bound to begin with. The more highly bound, the more significant binding changes will be.

Plasma protein binding also is a determinant of the hepatic clearance of low extraction (i.e., non-first-pass drugs) (Equation 2-9) and glomerular filtration clearance in the kidney (Equation 2-10). In both of these cases, only free drug is available for clearance:

$$CL_{H,Low E} \approx CL_{int} \times f_{up} \quad (2-9)$$

$$CL_{gf} = GFR \times f_{up}. \quad (2-10)$$

Changes in protein binding can occur as a result of changes in the amount of plasma proteins available (capacity) or competitive inhibition of binding (relative affinity) through binding displacement.

### Binding Proteins

Drugs are bound in the plasma primarily to albumin,  $\alpha_1$ -acid glycoprotein (AAG), and lipoproteins. The quantity of each of these proteins can be altered by disease states (Table 2-4).

Competition between drugs for AAG and/or albumin binding sites may result in displacement of the drug with lower affinity for the site ( $\uparrow K_d$ ). This will cause the  $f_{up}$  to increase for that drug. Competitive displacement does not occur with lipoproteins.

**Table 2-4 Protein Binding**

Binding Protein	Drugs to Which the Protein Preferentially Binds	Disease States That Alter Proteins
Albumin	Weak acids	Renal failure Cirrhosis Burns Pregnancy Surgery } ↓ <sub>alb</sub>
AAG	Weak bases and neutral	Crohn's disease Cancer Rheumatoid arthritis AMI Trauma } ↑ <sub>AAG</sub>
Lipoproteins	Weak bases and neutral	Changes in cholesterol levels

**Consequences**

If the  $f_{up}$  of a drug increases due to a decrease in the number of binding protein sites available or competitive displacement, an increase in the free concentration of the drug will occur (Equation 2-8). This increase will likely be temporary, because the clearance rate is often also dependent upon the  $f_{up}$  of the drug (Equations 2-9 and 2-10). This is the case for low-extraction drugs. An increase in the  $f_{up}$  of such a drug results in an increase in clearance. After SS is reestablished, there will be no change in the free concentration (and, therefore, no change in pharmacologic effect), but the total concentration will be decreased. In practice, lower plasma concentrations of drugs that are observed under these circumstances may be misinterpreted as an indication of a need for dosage increase.

**Metabolism**

After a drug has been absorbed and distributed, it will be eliminated by being metabolized or by being excreted, or by a combination of the two. Polar drugs are more easily excreted in the urine. More lipophilic drugs may need to be metabolized into a new, more polar form to make them suitable for renal elimination.

Metabolism primarily occurs in the liver, but any tissue with metabolizing enzymes (e.g., the gut wall) can be a site of biotransformation. Two major classes of reactions result in metabolism: Phase I reactions and Phase II reactions. Drugs may undergo metabolism by any combination of these reactions.

**Phase I**

Phase I reactions make compounds more polar with simple, nonsynthetic oxidation, reduction, and

hydrolysis reactions. The CYP450 family of enzymes is most responsible for drug metabolism. This large group of enzymes can be broken down into several isoenzyme subfamilies. A drug may be a substrate, an inducer, or an inhibitor of any of these subfamilies. Some drugs induce or inhibit their own metabolism. Genetic polymorphisms seen in 2D6, 2C9, and 2C19 (Table 2-5) may be sources of many drug interactions and toxicities.

**Phase II**

Phase II reactions are conjugation reactions that generally attach a group to the drug molecule that makes the molecule more polar. Glucuronidation, sulfation, acetylation, and methylation are all examples of Phase

**Table 2-5 Selected Examples of CYP Isoenzyme Substrates, Inducers, and Inhibitors**

CYP Isoenzyme	Substrates	Inducers	Inhibitors
1A2	Theophylline Caffeine	Charbroiled food Smoking Phenytoin St. John's wort	Erythromycin Ketoconazole Omeprazole Oral contraceptives
2C9	S-warfarin Phenytoin Fluvastatin Glipizide Glyburide	Phenobarbital Phenytoin Rifampin Carbamazepine	Cimetidine Fluconazole Fluoxetine Fluvastatin Sertraline
2C19	Omeprazole Lansoprazole Diazepam	Phenobarbital Phenytoin Rifampin Carbamazepine	Fluconazole Fluoxetine Fluvastatin Sertraline
2D6	β-blockers Codeine Dextromethorphan Fluoxetine TCA	St. John's wort Ritonavir Phenobarbital Phenytoin Rifampin Carbamazepine	Cocaine Ritonavir Paroxetine Fluoxetine Bupropion
3A4	Cyclosporine Saquinavir Ritonavir Lovastatin Tacrolimus Tamoxifen Nifedipine Verapamil Zolpidem	St. John's wort Ritonavir Phenobarbital Phenytoin Rifampin Carbamazepine	Erythromycin Fluconazole Fluoxetine Grapefruit juice Saquinavir Zileuton Clarithromycin St. John's wort

II reactions. Genetic polymorphisms also play a role in Phase II enzymes. (Table 2-3) The enzymes responsible for Phase II reactions can be induced or inhibited by drugs in the same fashion as the CYP450 enzymes.

### Alteration in Enzymes

Hepatic clearance of a drug is highly dependent upon the activity of the enzyme(s) responsible for its metabolism (hepatic intrinsic clearance or  $CL_{int}$ ). It is also dependent upon the rate of introduction of the drug to the liver (liver blood flow,  $Q$ ) and the fraction of drug unbound to plasma proteins ( $f_{up}$ ). If, however, the drug has a high affinity for the enzymes and the  $CL_{int}$  is very large in comparison to  $Q$ , liver blood flow will be the rate-limiting step and will determine hepatic clearance. Such an agent is called a high-extraction or high-first-pass drug:

$$CL_{high E} \approx Q. \quad (2-11)$$

If the drug does not have a high affinity for the enzyme and  $Q$  is much greater than  $CL_{int}$ ,  $CL_{int}$  and the unbound drug fraction become the rate-limiting step and, therefore, the determinant of the clearance of these drugs. Agents that exhibit this property are called low-extraction drugs:

$$CL_{low E} \approx CL_{int} \cdot f_{up}. \quad (2-12)$$

Changes in enzyme activity will alter the clearance of only low-extraction drugs. However,  $CL_{int}$  is a determinant of the fraction that escapes the first-pass effect ( $f_{fp}$ ) for high-extraction drugs:

$$f_{fp} \approx \frac{Q}{CL_{int} \cdot f_{up}}. \quad (2-13)$$

### Enzyme Induction

Hepatic enzymes may be induced by drugs, or a patient may have more enzyme available because of genetic predisposition. Occasionally, drugs may induce the enzymes responsible for their own clearance (i.e., carbamazepine). When enzymes are induced,  $V_{max}$  (the capacity of the system) is increased. This change generally happens slowly because new enzymes must be synthesized to increase the number available.

Enzyme induction results in an increase in clearance of low-extraction drugs and a decrease in  $f_{fp}$  of orally administered, high-extraction drugs. In both cases, drug concentrations will be decreased. This could result in a lack of efficacy of the drug. In both cases, an increase in dose rate may be necessary:

$$\downarrow C_{ss,low E} = \frac{F \cdot DR}{CL} \approx \frac{F \cdot DR}{\uparrow CL_{int} \cdot f_{up}}.$$

$$\downarrow C_{ss,high E} = \frac{F \cdot DR}{CL} \approx \frac{f_a \cdot f_g \cdot \frac{Q}{\uparrow CL_{int} \cdot f_{up}} DR}{Q}.$$

Induction of metabolism may increase transformation of a prodrug (the inactive parent compound) to the active metabolite. Enzyme induction may also result in problems if the metabolite formed is toxic.

When an inducer is discontinued, enzyme activity ( $CL_{int}$ ) will return to normal over time. This will result in the opposite effect seen from the induction. The net effect will be similar to that following addition of an enzyme inhibitor (discussed in this next section), and may result in unexpected drug interactions.

### Enzyme Inhibition

Hepatic enzymes can be competitively or noncompetitively inhibited, or a reduced number of enzymes may be genetically predetermined (Table 2-5). Two drugs metabolized by the same enzyme may compete for that enzyme's active site. The drug with the higher affinity for the enzyme (lower  $K_m$ ) would be preferentially metabolized; such drugs are called competitive inhibitors. Compounds with imidazole, pyridine, or quinolone groups have a high propensity for causing enzyme inhibition. Some drugs can inhibit the enzymes needed for their own metabolism; they are called auto-inhibitors (e.g., clarithromycin). Enzyme inhibition happens relatively quickly. The onset of potential increased effects or toxicity is only dependent upon the half-lives of the inhibitor and the substrate.

Enzyme inhibition may decrease the clearance of low-extraction drugs and increase the  $f_{fp}$  of orally administered, high-extraction drugs. In both cases, concentrations will be increased and toxicity or concentration-related side effects may occur. A decrease in dosage may be necessary:

$$\uparrow C_{ss,low E} = \frac{F \cdot DR}{CL} \approx \frac{F \cdot DR}{\downarrow CL_{int} \cdot f_{up}}.$$

$$\uparrow C_{ss,high E} = \frac{F \times DR}{CL} \approx \frac{f_a \cdot f_g \cdot \frac{Q}{\downarrow CL_{int} \cdot f_{up}} DR}{Q}.$$

Inhibition of enzymes that metabolize a prodrug may result in lack of efficacy due to decreased conversion to the active metabolite form. Decreased enzyme activity may have a positive effect if the metabolite formed is toxic.

When an inhibitor is discontinued, enzyme activity ( $CL_{int}$ ) will increase to normal levels fairly quickly in cases of competitive inhibition. This will result in the opposite effect seen with enzyme inhibition.

## Excretion

Excretion results in elimination of a drug from the body without changes being made in the drug molecule. If a drug is more polar, it is more likely to be excreted unchanged by the kidneys. A drug that is more lipophilic will need to be metabolized before it is suitable for excretion. The kidney is the primary site of excretion, but drugs may also be excreted through bile, saliva, breastmilk, placenta, and lungs.

### Renal Excretion

Three processes are involved in renal clearance: filtration, secretion, and reabsorption. Filtration and secretion add drug to the glomerular filtrate for elimination, while reabsorption removes drug from the glomerular filtrate and returns it to the blood (Figure 2-7).

- **Filtration.** Only free drug can be filtered because bound drug is too large. Therefore filtration clearance (glomerular filtration rate, GFR) is determined by blood flow to the glomerulus and the fraction of unbound drug ( $f_{up}$ ); see Equation 2-10.
- **Secretion.** Tubular secretion occurs in the proximal tubule. It is a carrier-mediated transport process requiring energy. The carriers moving a drug are specific for either acids or bases. Drugs that compete for these carriers may cause drug interactions; that is, acids will compete with acids and bases with bases. The drug with the higher affinity (lower  $K_T$ ) will be preferentially transported from the blood into the renal tubules for excretion.
- **Reabsorption.** Drugs can be reabsorbed back into the blood in the distal tubule. While some drugs (e.g., lithium) and nutrients undergo active reabsorption, most drugs are subject to simple passive diffusion (driven by a concentration gradient) for this process. Drugs must be lipophilic and non-ionized to be reabsorbed. Therefore alterations in urine pH or concentration gradient can alter reabsorption. For example, if the urine is alkalinized by sodium bicarbonate, weak acids would be more ionized, decreasing reabsorption; weak bases would be less ionized, favoring reabsorption. Conversely, if the urine were acidified by taking large doses of vitamin C, weak acids would be less ionized, favoring reabsorption, and weak bases would be more ionized, decreasing reabsorption.

Analyzing the net effect of these three processes allows prediction of drug interactions. If renal clearance is less than filtration clearance, the predominant process must be reabsorption. If renal clearance is greater than filtration clearance, secretion must be the predominant process.

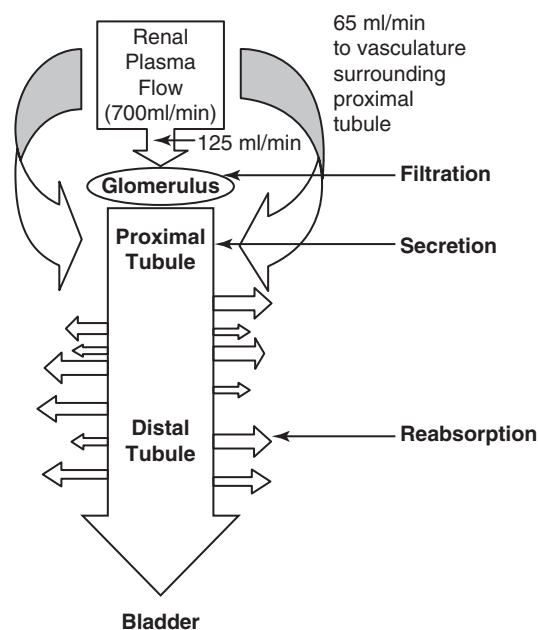


Figure 2-7 Representation of Renal Clearance in Kidney

### Breastmilk

Excretion of drugs into breastmilk is of great concern to nursing mothers. Most drug excretion in human milk occurs through passive diffusion. As a consequence, the drug must be small enough (low molecular weight and/or unbound), lipophilic enough, and un-ionized to pass into breastmilk. There must also be a concentration gradient. The choice of a drug that is unlikely to diffuse through a membrane would be prudent in nursing mothers.

- **Concentration gradient.** A concentration gradient arises if any drug is present in the blood; therefore, nursing when blood concentrations are at their lowest would decrease this gradient. It is good practice to suggest breastfeeding a child just before taking the medication.
- **Size.** Drugs with a molecular weight less than 300 daltons will be small enough to diffuse into breastmilk, but those with a molecular weight greater than 6,000 daltons will be too large.
- **Ionic character.** Breastmilk has a pH of approximately 7.1, making it slightly more acidic than blood (pH 7.4). Drugs that are weak bases will become more highly ionized when moving to the more acidic milk side of the membrane. Ionization will inhibit such a drug from being able to move back into the blood, so weak bases will become trapped in breastmilk—a phenomenon called “ion trapping.” Therefore weak bases are often less desirable for use by nursing mothers.
- **Lipophilicity.** A very low partition coefficient (low lipophilicity) helps minimize transport of drug from blood to milk.

**Placenta**

Predicting the movement of a drug from the mother's blood to the placenta and on to the fetus is important to pregnant women. Most placental transport occurs via passive diffusion, so the principles involved in breast-milk transfer of drugs also apply to placental transfer. Drugs with a  $pK_a$  in the range of 4.3–8.5 are likely to be transferred across the placenta. Fetal plasma and amniotic fluid are more acidic than maternal blood; therefore, ion trapping of weak bases on the baby's side of

the placenta can occur. Drugs with a molecular weight less than 600 daltons are more likely to be transferred.

**CONCLUSION**

By applying the principles of biopharmaceutics, patient care can be improved by the pharmacist. Knowing the physiochemical properties of a drug can help the healthcare team as a whole make better drug therapy choices and anticipate drug interactions.

