DRUG CLEARANCE THROUGH METABOLISM

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug present is eliminated in a given unit of time.

Most drugs are eliminated according to first-order kinetics, although some, such as aspirin in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time.

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.

2. Zero-order kinetics: With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large.

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 (also called nonlinear kinetics). A constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration.

B. **Reactions of drug metabolism:** The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.

1. Phase I: Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH2. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on 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 oxidases). The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP, is a superfamily of heme-containing isozymes that are located in most cells, but primarily in the liver and GI tract.

DRUG CLEARANCE THROUGH METABOLISM (cont)

Inducers: The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Xenobiotics (chemicals not normally produced or expected to be present in the body, for example, drugs or environmental pollutants) may induce the activity of these enzymes. Certain drugs (for example, phenobarbital, rifampin, and carbamazepine) are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, with concurrent loss of pharmacologic effect. For example, rifampin, an antituberculosis drug (see Chapter 41), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors, thereby diminishing their ability to suppress HIV replication. St. John's wort is a widely used herbal product and is a potent CYP3A4 inducer. Many drug interactions have been reported with concomitant use of St. John's wort. Figure 1.18 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 the metabolite is inactive, 3) increased drug activity if the metabolite is active, and 4) decreased therapeutic drug effect.

Inhibitors: Inhibition of CYP isozyme activity is an important source of drug interactions that lead 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 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 anticoagulant effect and increased risk of bleeding. [Note: The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes.] Natural substances may also inhibit drug metabolism. For instance, grapefruit juice inhibits CYP3A4 and leads to higher levels and/or greater potential for toxic effects with drugs, such as nifedipine, clarithromycin, and simvastatin, that are metabolized by this system.

b. 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 aspirin in the liver), and hydrolysis (for example, of procaine).

DRUG CLEARANCE THROUGH METABOLISM (cont)

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 still too lipophilic to be excreted. 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 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. [Note: Drugs already possessing an –OH, –NH2, or –COOH group may enter phase II directly and become conjugated without prior phase I metabolism.] The highly polar drug conjugates are then excreted by the kidney or in bile.

DRUG CLEARANCE BY THE KIDNEY

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

A. Renal elimination of a drug Elimination of drugs via the kidneys into urine involves the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.

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 the Bowman space as part of the glomerular filtrate (Figure 1.19). The glomerular filtration rate (GFR) is normally about 125 mL/min but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

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 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. [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.]

DRUG CLEARANCE BY THE KIDNEY (cont)

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 urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization 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 alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

4. Role of drug metabolism: Most drugs are lipid soluble and, without chemical modification, would diffuse out of the 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 via phase I and phase II reactions (described above). The polar or ionized conjugates are unable to back diffuse out of the kidney lumen