Lecture 4

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 most drug present is eliminated in a given unit of time

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. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

t1/ 2= 0 693 *Vd / cl

where t1/2 is the elimination half-life, Vd is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, Vd is a constant.

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. Therefore, [C] is much greater than Km, and the velocity equation becomes

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

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.

Nomenclature: The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A .A second number indicates the specific isozyme, as in CYP3A4.

Specificity: Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes are responsible for the vast majority of P450-catalyzed reactions. They are CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2

Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam.*

Genetic variability: P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter drug efficacy and the risk of adverse events. CYP2D6, in particular, has been shown to exhibit genetic polymorphism. CYP2D6 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 CYP2D6 enzyme that activates the drug. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. For instance, c*lopidogrel* carries a warning that patients who are poor CYP2C19 metabolizers have a higher incidence of cardiovascular events (for example, stroke or myocardial infarction) when taking this drug. *Clopidogrel* is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite. Although CYP3A4 exhibits a greater than

10-fold variability between individuals, no polymorphisms have been identified so far for this P450 isozyme.

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 , 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.

. 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*).

. 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.