VI. 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.]

3. **Distal tubular reabsorption:** As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. This 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 (Figure 1.20).

VII. CLEARANCE BY OTHER ROUTES

Drug clearance may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are eliminated in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, *Isoflurane*). Elimination of drugs in breast milk may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

The total body (systemic) clearance, CL_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of elimination. The liver also contributes to drug clearance through metabolism and/or excretion into the bile. Total clearance is calculated using the following equation:

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

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

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

VIII. DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

To initiate drug therapy, the clinician must select the appropriate route of administration, dosage, and dosing interval. Selection of a regimen depends on various patient and drug factors, including how rapidly therapeutic levels of a drug must be achieved. The regimen is then further refined, or optimized, to maximize benefit and minimize adverse effects.

A. Continuous infusion regimens

Therapy may consist of a single dose of a drug, for example, a sleep-inducing agent, such as *zolpidem*. More commonly, drugs are continually administered, either as an IV infusion or in oral fixed-dose/fixed-time interval regimens (for example, "one tablet every 4 hours"). Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that the plasma and tissue levels remain relatively constant.

1. **Plasma concentration of a drug following IV infusion:** With continuous IV infusion, the rate of drug entry into the body is constant. Most drugs exhibit first-order elimination, that is, a constant fraction of the drug is cleared per unit of time. Therefore, the rate of drug elimination increases proportionately as the plasma concentration increases. Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.

   a. **Influence of the rate of infusion on steady-state concentration:** The steady-state plasma concentration (C_{ss}) is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the C_{ss} is doubled (Figure 1.21). Furthermore, the C_{ss} is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kid-