# Pharmacology I

Lecture 2

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## Drug distribution:

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

For drugs administered IV, absorption is not a factor, and the initial phase (from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug.

**A. Blood flow**

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow.

**B. Capillary permeability**

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass. In the brain, the capillary structure is continuous, and there are no slit junctions. To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or be actively transported.

By contrast, lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. Ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

**C. Binding of drugs to plasma proteins and tissues**

**1. Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows their transfer out of the vascular compartment. Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). This maintains the free drug concentration as a constant fraction of the total drug in the plasma.

**2. Binding to tissue proteins:** Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood. Drugs may accumulate as a result of binding to lipids, proteins, or nucleic acids. Drugs may also be actively transported into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity.

**D. Lipophilicity**

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. In contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

## E. Volume of distribution:

The apparent volume of distribution, $V_d$, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero ($C_0$).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although $V_d$ has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

The fact that drug clearance is usually a first-order process allows calculation of $V_d$. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration ($C_p$) versus time. The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine $C_0$, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of $V_d$ as

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and $C_0$ = 1 mg/L, then $V_d$ = 10 mg/1 mg/L = 10 L.

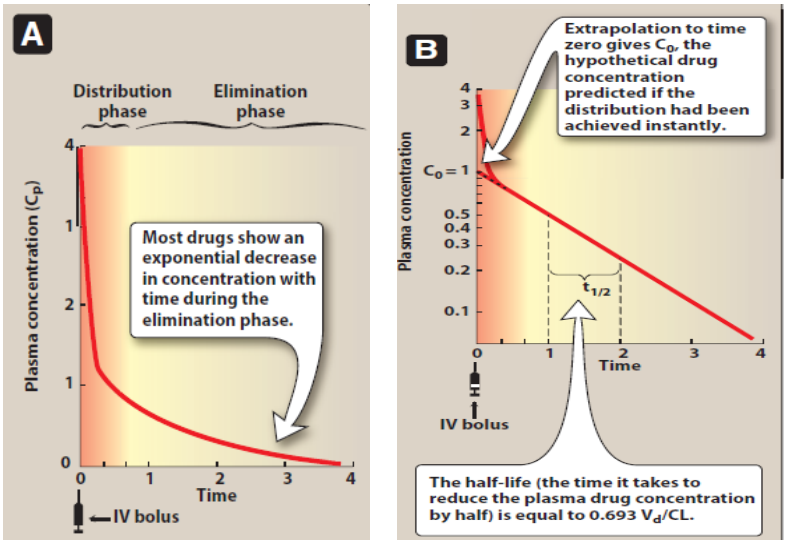

**Figure 1: Drug concentrations in plasma after a single injection of drug at time = 0. A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale.**

## 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.

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.

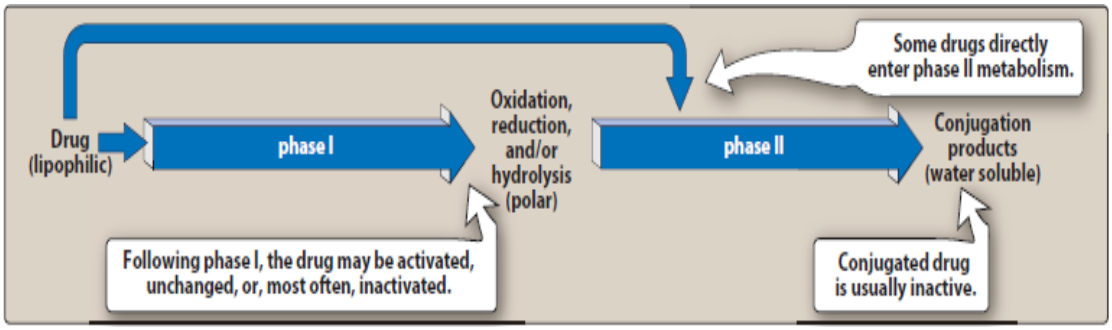


**Figure 2: The biotransformation of drugs**

## Drug clearance through 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.

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. 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.

**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.

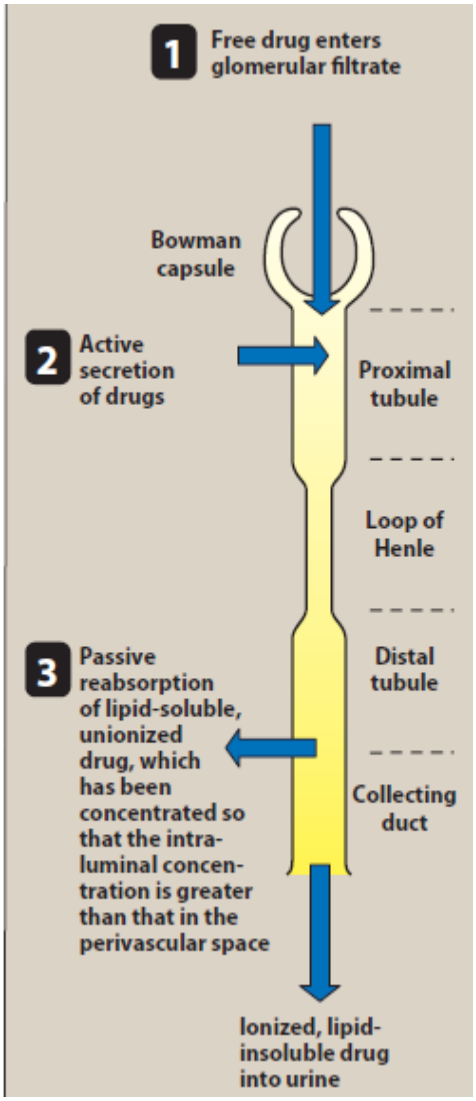


**Figure 3:** Drug elimination by the kidney