1.4: Distribution

The second stage of pharmacokinetics is the process known as drug **distribution**. Distribution is the process by which medication is dispersed throughout the body via the bloodstream. Once a drug enters into systemic circulation by absorption or direct administration, it must be distributed into interstitial and intracellular fluids to get to the target cells. The distribution of a drug throughout the body is dependent on common factors such as blood flow, plasma protein binding, lipid solubility, the blood-brain barrier, and the placental barrier. Other factors include capillary permeability, differences between blood/tissue, and volume of distribution.

Distribution of a medication can also cause unintended adverse or side effects. Drugs are designed to primarily cause one effect, meaning they bind more strongly to one specific receptor site and predictably cause or block an action. However, side effects can occur when the drug binds to other sites in addition to the target tissue, causing secondary side effects. These side effects can range from tolerable to unacceptable resulting in the discontinuation of the medication. For example, a person might take the pain reliever ibuprofen (Advil) to treat a sore leg muscle, and the pain may be subsequently relieved, but there may also be stomach irritation as a side effect that may cause the person to stop taking ibuprofen.

**Blood Flow**

The blood stream carries medications to their destinations in the body. Many factors can affect the blood flow and delivery of medication, such as decreased flow (due to dehydration), blocked vessels (due to atherosclerosis), constricted vessels (due to uncontrolled hypertension), or weakened pumping by the heart muscle (due to heart failure). As an example, when administering an antibiotic to a patient with diabetes with an infected toe, it may be difficult for the antibiotic to move through the blood vessels all the way to the cells of the toe that is infected.

Once the drug is in the bloodstream, a portion of it may exist as free drug, dissolved in plasma water. Some of the drug
will be reversibly taken up by red cells, and some will be reversibly bound to plasma proteins. For many drugs, the bound forms can account for 95-98% of the total. This is important because it is the free drug that traverses cell membranes and produces the desired effect. It is also important because a protein-bound drug can act as a reservoir that releases the drug slowly and thus prolongs its action. With drug distribution, it is important to consider both the amount of free drug that is readily available to tissues, as well as the potential drug reserve that may be released over time.

### Protein-Binding

A common factor impacting distribution of medication is plasma protein in the blood. Albumin is one of the most important proteins in the blood. Albumin levels can be decreased by several factors such as malnutrition and liver disease. A certain percentage of almost every drug gets bound to plasma proteins when it initially enters the bloodstream and starts to circulate. The portion of the drug that gets “protein-bound” is inactive while it is bound, but the portion of the drug that escapes initial protein binding becomes immediately “free” to bind to the target tissue and exert or block an action.

A patient taking several highly protein-bound medications often experiences greater side effects. Some drugs are able to competitively grab (or bind to) plasma proteins more easily than other drugs, thus taking up the available protein molecules first. This prevents secondary medications from binding strongly to protein and the intended target site. Instead, these medications float freely in the circulation without exerting action and increase the risk of side effects and toxicities.

![Figure 1.4 Protein binding is like available seats on a bus](https://med.libretexts.org/Bookshelves/Nursing/Nursing_Pharmacology_(OpenRN)/01%3A_Kinetics_and_Dynamics/1.04%3A...

Figure 1.4 Protein binding is like available seats on a bus

Think of protein binding like a bus stop (see Figure 1.4). Many passengers (or medication molecules) want to take a ride on the bus. Everyone is eager to get to their destination and interested in finding a seat. Some passengers are stronger and will get in the seats first (like drug molecules with greater protein-binding ability bind to the protein). Sometimes, there may not be enough seats on the bus, and some passengers are left at the bus stop. The passengers (medication molecules) who were left behind are “free” to move around and walk to their destination. They may strike out on their own and get “snatched” (connected to a target receptor site) while on foot. In a similar way, “free” drug particles that are not protein-bound are circulating in the bloodstream and connecting in a predictable fashion to receptor sites that have an affinity for that particular drug. These active drug molecules that did not bind to the protein (like those passengers that were unable to get a seat on the bus) will produce the first effect in the body. Over time, the medication molecules that are bound to the protein (like the passengers with seats on the bus) will get off the bus, start walking around, and get “snatched” to the receptor site that has affinity for them.
Blood-Brain Barrier

Medications destined for the central nervous system (the brain and spinal cord) face an even larger hurdle than protein-binding; they must also pass through a nearly impenetrable barricade called the **blood-brain barrier**. This blockade is built from a tightly woven mesh of capillaries that protect the brain from potentially dangerous substances, such as poisons or viruses. Only certain medications made of lipids (fats) or have a “carrier” can get through the blood-brain barrier.

Research scientists have devised ways for certain medications to penetrate the blood-brain barrier. An example of this is the brand-named medication Sinemet®, which is a combination of two drugs: carbidopa and levadopa. Carbidopa is designed to carry the levadopa medication across the blood-brain barrier, where it enters the brain and is converted into dopamine to exert its effect on Parkinson’s disease symptoms.

Some medications inadvertently bypass the blood-brain barrier and impact an individual’s central nervous system function. For example, diphenhydramine (Benadryl®) is an antihistamine used to decrease allergy symptoms. However, it can also cross the blood-brain barrier, depress the central nervous system, and cause the side effect of drowsiness. In the case of a person who has difficulty falling asleep, this drowsy side effect may be useful, but for another person it may be problematic, as they try to safely carry out daily activities.

Placental Barrier

It is always important to consider the effects of medication during pregnancy or for patients who may become pregnant. The placenta is permeable to some medications, while others have not been specifically studied in pregnant patients. Some drugs can cause harm to the unborn fetus during any trimester. Therefore, it is imperative to always consult a healthcare provider regarding the safety of medications for use during pregnancy. This imperative is assumed in the remaining chapters discussing medication classes, and nurses should always check the most recent, evidence-based drug references before administering medications during pregnancy.

Lifespan Considerations

**Neonate & Pediatric:** Fat content in young patients is decreased because of greater total body water. Additionally, for the growing pediatric patient, the liver is still forming, and protein binding capacity is decreased and the developing blood-brain barrier allows more drugs to enter the brain.

**Older Adult:** The aging adult patient will experience a decrease in total body water and muscle mass. Body fat may increase and subsequently result in a longer duration of action for many medications. Serum albumin often also decreases, resulting in more active free drug within the body. This is one reason why many older adult patients require lower levels of medication.

Table 1.2 describes other factors that impact drug distribution.

**Table 1.2. Other Factors that Impact Drug Distribution**
1) Tissue differences in rates of uptake of drugs.

- Blood flow: distribution occurs most rapidly into tissues with a greater number of blood vessels that allow high blood flow (lungs, kidneys, liver, brain) and least rapidly in tissues with fewer numbers of blood vessels resulting in low blood flow (fat).

- Capillary permeability: permeability of capillaries is tissue-dependent. Distribution rates are relatively slower or non-existent into the CNS because of the tight junction between capillary endothelial cells and the blood-brain barrier. Capillaries of the liver and kidney are more porous, allowing for greater permeability.

2) Differences in tissue/blood ratios at equilibrium

- Dissolution of lipid-soluble drugs in adipose tissue
- Binding of drugs to intracellular sites
- Plasma protein-binding

3) Apparent Volume of Distribution

- Fluid compartments: plasma, extracellular water, total body water.
- The plasma half-life of a drug
  - **Half-life** is the amount of time it takes for half of the medication to be eliminated in the body. Half-life directly correlates to the duration of the therapeutic effect of a medication. Many factors can influence half-life, for example, liver disease or kidney dysfunction.
  - Information about half-life of a medication can be found in evidence-based medication references. For example, in the "Clinical Pharmacology" section of the Daily Med reference for furosemide, the half-life is approximately 2 hours.