Chapter 4
Drug Distribution

Debra Si Mui Sim

Abstract Once a drug enters the bloodstream, it will be carried by the blood to various parts of the body. In order for it to act on its target site(s) of action, the drug must leave the bloodstream to which it may later return. Such reversible transfer of substances between the blood and extravascular tissues is known as distribution. Distribution generally occurs rapidly for most drugs and is often much faster than elimination. How widespread a drug action is often depends on its distribution profile. Its ability to distribute to specific tissues depends on both physiological factors (e.g., tissue perfusion, membrane permeability) and drug properties (e.g., molecular size, degree of ionization, lipid solubility, relative binding to plasma protein and tissue protein). The volume of distribution ($V_d$) is the second most important pharmacokinetic parameter after plasma clearance ($CL$). It gives some idea as to the extent of distribution of a drug in the body. It also determines the loading dose ($D_L$) to be given during multiple dosing in order to achieve plasma steady-state concentration ($C_{ss}$) faster. Factors that alter the distribution of a drug (e.g., edema, sepsis, pregnancy) may contribute to failure in achieving the expected clinical outcome.

Keywords Volume of distribution • Plasma protein binding • Tissue protein binding • Perfusion-limited • Permeability-limited

Introduction

Once a drug enters the bloodstream, it will be carried by the blood to various parts of the body. In order for it to act on its target site(s) of action, the drug must leave the bloodstream to which it may later return. Such reversible transfer of substances between the blood and extravascular tissues is known as distribution. Distribution generally occurs rapidly for most drugs and is often much faster than elimination.
How widespread a drug action is often depends on its distribution profile. Its ability to distribute to specific tissues depends on both physiological factors and drug properties.

**How Drugs Are Distributed**

Drugs are transported to different parts of the body mainly by the circulatory system. The transfer of drugs between the blood and tissues takes place largely in the capillary bed. The capillary wall forms the blood-tissue barrier across which drugs must permeate to enter into the interstitial fluid. This is followed by the permeation of drugs from the interstitial fluid (ISF) to the intracellular fluid (ICF) through the membrane of the tissue cell (Fig. 4.1). As most drug receptors are located on the surface of cell membranes, it is not always necessary for drugs to enter the cells in order for it to be effective.

![Fig. 4.1](image-url) A schematic diagram showing the flow of solutes from blood to surrounding fluids and tissue-cells. Drug A, being more lipid soluble than Drug B, enters both interstitial (ISF) and intracellular fluids (ICF), whereas the polar Drug B, is only able to cross over into the interstitial fluid.
How Do Drugs Traverse Blood-Tissue Barriers

The ease with which drugs cross blood-tissue barrier depends on the structural and functional characteristics of the capillary endothelial cells at those tissue sites (Fig. 4.2). In most of the capillary beds, such as those of muscle, fat and nervous tissues, the capillary endothelium lacks pores and the cells are joined by tight non-permeable junctions. In other capillary beds, such as those of heart muscle, the endothelial cell allows the transport of fluid or macromolecules (e.g., insulin) in vesicles from the blood into the interstitium and vice versa. In some capillary beds, such as in the pancreas, gut, kidney glomeruli and endocrine glands, the endothelial lining behaves as though it were fenestrated by pores. In the liver, spleen and bone marrow, open spaces exist between endothelial cells, called intercellular clefts,

![Diagram of capillary types](image)

**Fig. 4.2** Different types of capillaries with varying degrees of permeability, their respective cross-sections and examples of typical locations where these capillary types are found
which allow free exchange of drugs (most of which have molecular weights of less than 900) between blood and the interstitium.

In summary, the capillary wall basically consists of an endothelial cell layer and a basement membrane enveloping it. The permeation of drugs across this capillary wall can occur by one of several processes such as passive diffusion, transcytosis (vesicular transport) and bulk flow as well as by carrier-mediated transport mechanisms such as facilitated diffusion or active transport.

Factors Affecting the Rate of Drug Distribution

After a drug enters the bloodstream, its rate of distribution to the various body tissues is governed predominantly by two factors, each of which is potentially rate-limiting: (1) the rate of blood flow (perfusion) to the tissue and (2) the ability of the drug to cross membranes (permeability) to enter the tissue.

For drugs which have high membrane permeability (e.g., thiopental, steroids and benzodiazepines), the rate of distribution to tissues depends mainly on the rate of blood flow to these tissues. Thus, tissue drug concentration would increase most rapidly in highly perfused tissues such as kidneys, liver, lung, heart and brain, more slowly in less well perfused tissues such as skeletal muscle, but very slowly in poorly perfused tissues, such as bone, fat and skin. The distribution of these lipophilic drugs is described as perfusion-limited.

On the other hand, drugs with poor membrane permeability (e.g., penicillins, aminoglycoside antibiotics, succinylcholine and vecuronium) would distribute more readily to tissues such as bone marrows, spleen, liver and muscle, where the capillary wall is more “leaky”, than to the brain, where the capillary wall seems to be impermeable. This selective distribution occurs despite a large amount of the drug being delivered to the highly perfused brain, and is an example of permeability-limited drug distribution.

Clinical Correlation – Distribution of Perfusion-Limited Versus Permeability-Limited Drugs

This means therefore lipophilic drugs such as thiopental gets into the brain more quickly than into skeletal muscle, whereas polar drugs such as vecuronium gets into skeletal muscle faster than into the brain. It also means that when there is a marked change in tissue perfusion, such as during circulatory shock, the distribution of drugs which are perfusion-limited would be affected more than those which are permeability-limited. Conversely, when there is a marked change to the tissue pH or amount of proteins in plasma, as may occur in sepsis, severe burns or traumatic injuries, the distribution of permeability-limited drugs to those areas would be affected more than that of perfusion-limited drugs.
Factors Affecting the Extent of Drug Distribution

Distribution is a reversible process. Hence, the exchange of drug molecules across a barrier would continue until the concentrations of the free drugs on both sides of the barrier are the same. While tissue perfusion has a major effect on the rate of distribution of drugs to various tissues, drug properties and membrane permeability play a greater role on the extent of drug distribution at equilibrium.

Important physicochemical properties of drugs which affect their extent of distribution include molecular size, degree of ionization, octanol:water partition coefficient and their relative affinities for tissue and plasma proteins.

Drugs with large molecular weight (e.g., heparin) and those which are extensively bound to plasma protein (e.g., warfarin) have difficulty crossing the capillary wall into the interstitium. Their distribution would be restricted to mainly the plasma compartment (3 L/70 kg). Polar drugs such as gentamicin and vecuronium cross the capillary endothelium readily (by bulk flow) into the extravascular fluid compartment (14 L/70 kg) but cannot diffuse into the tissue cell. In contrast, lipophilic drugs such as diazepam and theophylline diffuse easily into intracellular fluid compartment and distribute into total body water (42 L/70 kg). Some drugs (e.g., digoxin and chloroquine) bind extensively to extravascular tissue proteins resulting in volume of distribution ($V_d$) values that far exceed the total body water volume. This phenomenon can be observed even with drugs (e.g., fluoxetine and imipramine) which have extensive plasma protein binding (Table 4.1).

The volume of distribution ($V_d$) is the second most important pharmacokinetic parameter after plasma clearance (CL). It determines the loading dose ($D_L$) to be given during multiple dosing in order to achieve plasma steady-state concentration ($C_{ss}$) faster, according to the equation $D_L = V_dC_{ss}$. An obvious consequence of having a large $V_d$ is that a large loading dose is needed for this purpose.

Ageing is accompanied by changes in body fat, lean body mass and total body water. These changes result in reduced $V_d$ of water soluble drugs, e.g., digoxin, (which may lead to increased initial drug concentration) and increased $V_d$ of lipophilic drugs, e.g., benzodiazepines (which may lead to increased elimination half-life and prolonged effect). Both types of drug may therefore require a reduction in dose and/or dose interval.

Table 4.1 Volumes of distribution ($V_d$) and degree of plasma protein binding for selected drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bound in plasma (%)</th>
<th>$V_d$ (L/70 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Extensive</td>
<td>4</td>
</tr>
<tr>
<td>Warfarin</td>
<td>99</td>
<td>10</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;10</td>
<td>22</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>Theophylline</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td>Diazepam</td>
<td>99</td>
<td>77</td>
</tr>
<tr>
<td>Digoxin</td>
<td>25</td>
<td>500</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>61</td>
<td>13,000</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>94</td>
<td>2,450</td>
</tr>
<tr>
<td>Imipramine</td>
<td>90</td>
<td>1,300</td>
</tr>
</tbody>
</table>
Binding of Drugs to Plasma Proteins

In the plasma, drugs may bind to various proteins, primarily albumin but also to \( \alpha_1 \)-acid glycoprotein, globulins (low capacity but high affinity) and lipoproteins. This binding is reversible and occurs to varying extents for different drugs (e.g. <10% for gentamicin to >99% for warfarin and diazepam). Many acidic drugs, such as salicylates and penicillins, and some neutral or basic drugs bind to albumin (low affinity but high capacity), while \( \alpha_1 \)-acid glycoprotein binds mainly basic drugs such as lignocaine and propranolol. Plasma globulins (\( \alpha, \beta, \gamma \)-globulins) have low capacity but high affinity for the binding of endogenous substances such as corticosteroids.

Drugs exist in the plasma in the unbound (i.e. free) and bound (to plasma proteins) forms, which are in equilibrium with each other.

\[
\text{Drug} + \text{Protein} \leftrightarrow \text{Drug-Protein}
\]

The protein-bound drug is a large complex which cannot readily permeate cell membranes to enter the target site; hence restricting its distribution and also its pharmacological activity. Furthermore, protein-bound drugs are also not excreted readily.

Plasma protein binding of drugs is subject to saturation and competitive displacement. This is because there are limited binding sites on the protein for binding drugs at any one time. Therefore, drugs with a higher affinity for the same binding site on the protein would displace the bound drugs, resulting in a transient increase in the unbound concentration of the displaced drug. This could potentially lead to enhanced drug actions. However, drug-drug interactions involving protein-binding displacement are generally not clinically important as the displaced drug in the body would be eliminated readily by the liver or kidneys, thus bringing down the concentration of the unbound drugs.

Selective Accumulation of Drugs in Tissues

There are various ways by which drugs may accumulate selectively in certain tissues. Below are some examples of selective drug accumulation.

1. Binding to specific tissue components

The broad spectrum antibiotic tetracycline binds with cations such as calcium to form tetracycline-calcium complexes that irreversibly deposit in the bones and teeth of developing fetus or young children (below 8 years old). This results in the retardation of bone growth and discoloration of teeth.

2. Presence of active transport

Following ingestion (accidental or intentional), the herbicide paraquat is actively taken up into the lungs from the plasma by a selective transport system meant for
polyamines. Consequently, the herbicide selectively accumulates in the lungs where it may attain concentration which is several times higher than that in the plasma, even when the plasma concentration is falling. This selective distribution results in organ-specific toxicity (lung fibrosis) typical of paraquat poisoning.

3. Very high lipid solubility

The intravenous anesthetic thiopental is highly lipid soluble and passes into the brain easily. Since the brain is highly perfused, the drug reaches its target site very rapidly and produces a very fast induction of anesthesia. However, as the drug is progressively taken up by the less well perfused tissues such as muscle and then eventually by the poorly perfused adipose tissues, it results in a decrease in the plasma drug concentration. The change in the concentration gradient between plasma and brain now favors the back diffusion of the anesthetic drug from the brain into the plasma and then to other tissues. This redistribution of thiopental from brain to other less well perfused tissues is mainly responsible for the rapid termination and short duration of its anesthetic action.

4. Ion-trapping effect

Trimethoprim is a lipophilic weak base (pKₘ = 7.3) and readily diffuses across cell membranes. Once it enters the prostate gland it would become more ionized in the relatively more acidic prostatic fluid (pH ~6.5) environment, compared to the pH 7.4 of plasma. This prevents the antibiotic from diffusing back into plasma. Such ion-trapping effect helps to concentrate the antibiotic at the target site and contributes to its effectiveness in treating bacterial prostatitis.

Physiological Barriers to Drug Distribution

Besides the simple capillary endothelial barrier mentioned above, there are some more specialized physiological barriers which restrict the permeability of drugs into specific tissues.

1. Blood–brain barrier

In many tissues, the capillary wall forms a continuous sheet with no intercellular clefts or intracellular pores (Fig. 4.2). In the brain, the capillary endothelial cells are joined by tight junctions and pericapillary glial cells are present, making this blood–tissue barrier impermeable to many drugs, including many antineoplastic drugs given for treating brain tumor or antibiotics for treating central nervous system infection. In addition, efflux carriers like P-glycoproteins and organic anion-transporting polypeptides (OATP) transport drugs out of the brain and other tissues which express these transporters. However, the permeability of this blood–brain barrier increases somewhat during inflammation (e.g., meningitis) and it allows sufficient amount of penicillin to enter to produce its bactericidal effect.
Although dopamine cannot permeate blood–brain barrier due to poor lipid solubility, its precursor levodopa is able to do so because of the presence of amino acid transporters which can also carry levodopa into the brain. Once in the brain, levodopa is converted to its active drug dopamine. Some enzymes (e.g., monoamine oxidase) are also present in the capillary walls of the brain and these would destroy drugs such as catecholamine (e.g., epinephrine and norepinephrine) from entering the brain.

Clinical Correlation—Importance of “Continuous” Capillaries (Fig. 4.2) in the brain

The brain is impermeable to the catecholamines as these would have been destroyed by enzymes such as monoamine oxidase present in the capillary walls. This prevents the blood vessel of the brain from vasoconstriction and compromising oxygen delivery each time we administer these drugs or when it is produced endogenously by the adrenals in times of stress.

2. Placental barrier

The maternal blood supply is separated from the fetal blood supply by a layer of trophoblast cells which together constitute the so called placental barrier. It is worth noting that drug molecules permeate the placental barrier more easily than the blood–brain barrier. Restricted amounts of water soluble drugs, especially if present in high concentrations for a long period, may cross the placenta into the fetal circulation. Thus, the use of drugs during pregnancy must be with great caution as many of these drugs may cause harm to the fetus (i.e., teratogenic). For example, ingestion of thalidomide during pregnancy causes phocomelia in the newborn while maternal consumption of alcohol can lead to fetal alcohol syndrome.

Volume of Drug Distribution

It is practically impossible to measure the exact extent of distribution of a drug in the body. We can however estimate the extent of drug distribution mathematically assuming the body is a homogeneous compartment into which a drug distributes. Therefore the volume of distribution \((V_d)\) is the volume into which a drug appears to have distributed assuming the tissue concentrations equal to that of plasma. It is also a proportionality constant that relates the amount of drug in the body \((A_b)\) to its plasma concentration \((C_p)\) at any one time.

\[
A_b = V_d C_p
\]
Relationship Between Drug Distribution and Drug Elimination Half-life

Although drug distribution and elimination are described as two separate pharmacokinetic processes, and $V_d$ and CL are two independent pharmacokinetic parameters, yet the extent of drug distribution (whether extensive or restrictive) can have an effect on the elimination half-life of a drug, according to the equation $t_{\frac{1}{2}} = \frac{0.693V_d}{CL}$.

In the examples given in Table 4.2, a long elimination half-life can occur with both a drug with large $V_d$ (e.g., dirithromycin) as well as with a drug with small $V_d$ (e.g., tenoxicam). In the case of dirithromycin, the long elimination half-life is a result of the extensive distribution of the drug in tissues, despite its large total body clearance (CL). In contrast, the long elimination half-life of tenoxicam results more from restrictive drug clearance due to the binding of the drug to plasma protein, making it hard for the drug to be cleared rapidly, despite its small volume of distribution ($V_d$).

### Key Concepts

- The ability of a drug to distribute to specific tissues depends on both physiological factors (e.g., tissue perfusion, membrane permeability) and drug properties (e.g., molecular size, degree of ionization, lipid solubility, relative binding to plasma protein and tissue protein).
- Volume of distribution ($V_d$) is defined as the volume into which a drug appears to have distributed assuming the tissue concentrations equal to that of plasma.
- Polar drugs are confined to plasma and interstitial fluids (generally small $V_d$) and most do not enter the brain following acute dosing. Their distribution is generally permeability-limited.
- Lipid-soluble drugs reach all fluid compartments (generally large $V_d$) and may accumulate in adipose tissue with repeated dosing. Their distribution is generally perfusion-limited.
- For drugs that accumulate outside the plasma compartment, their $V_d$ may exceed total body volume.
- Both changes in $V_d$ and CL can influence the plasma half-life of a drug.

### Table 4.2 How the distribution and elimination of drugs affects their plasma half-lives

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Dirithromycin (macrolide antibiotic)</th>
<th>Tenoxicam (NSAID)</th>
</tr>
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<tbody>
<tr>
<td>$V_d$ (L)</td>
<td>800</td>
<td>9.6</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>38.0</td>
<td>0.106</td>
</tr>
<tr>
<td>t_{\frac{1}{2}} (h)</td>
<td>44</td>
<td>67</td>
</tr>
</tbody>
</table>
Summary

Distribution is the reversible transfer of substances between the blood and extravascular tissues. The ability of a drug to distribute to specific tissues depends on both physiological factors (e.g., tissue perfusion, membrane permeability) and drug properties (e.g., molecular size, degree of ionization, lipid solubility, relative binding to plasma protein and tissue protein). The volume of distribution (Vd) is the second most important pharmacokinetic parameter after plasma clearance (CL). It gives some idea as to the extent of distribution of a drug in the body. It also determines the loading dose (DL) to be given during multiple dosing in order to achieve plasma steady-state concentration (Css) faster. Factors that alter the distribution of a drug (e.g., edema, sepsis, pregnancy) may contribute to failure in achieving the expected clinical outcome.

Further Reading