Pharmacokinetics II: Distribution

PHC 721

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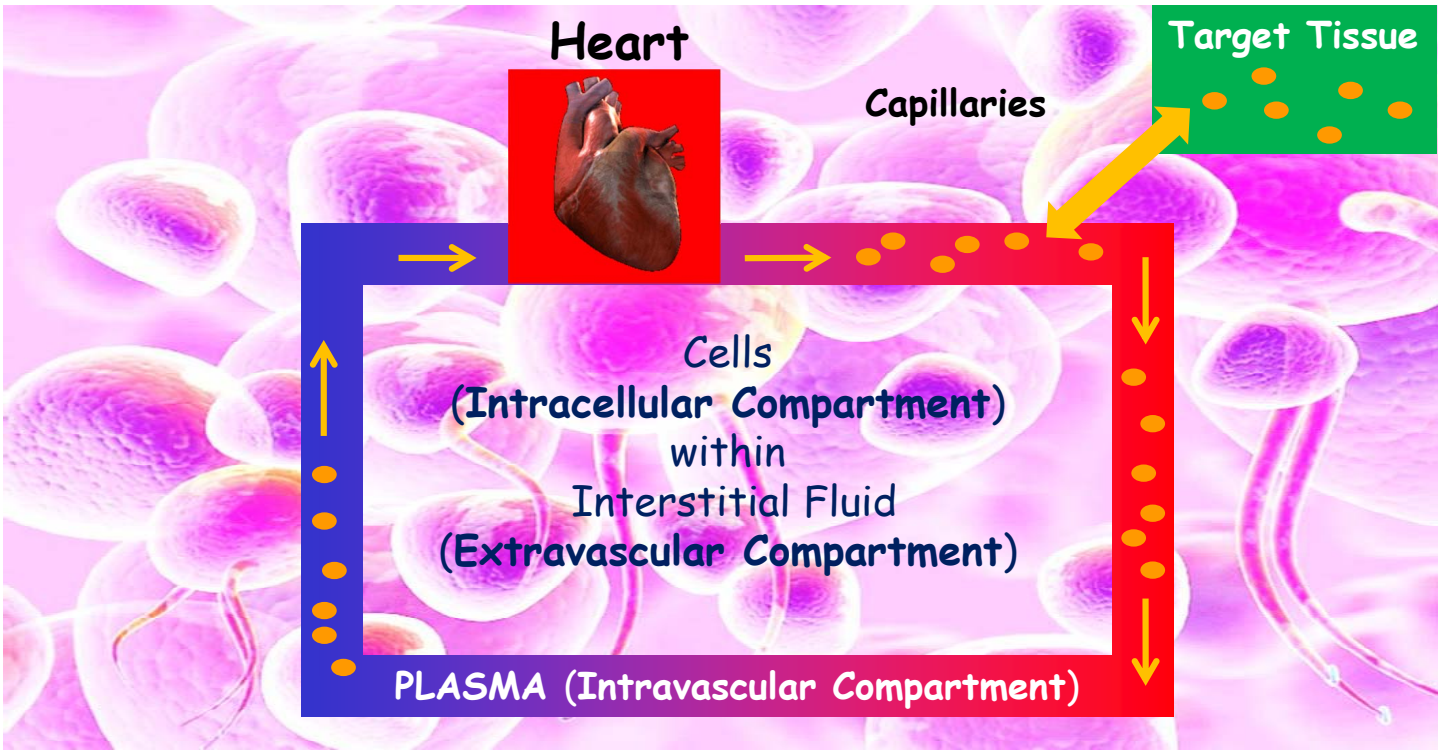
Distribution

The movement of drugs throughout the body.
Concentration gradient in the direction: Plasma 〉 Tissues
Drug movement until equilibrium between 'Free $Drug_{PLASMA}$' & 'Free $Drug_{TISSUE}$'.



What is distribution?
As the name suggests, it is a movement of drugs throughout the body. Distribution of drugs throughout the body. Because we are talking about the whole body, how the drugs are distributed?

I wanted to start with the big picture. What is the body? what are the main compartments? divisions of the body?
We consist of cells that are embedded in the interstitial fluid. The environment inside the cells is the intracellular compartment. Everything outside the cells is the extracellular compartment. The extracellular compartment is divided in relation to the circulation to the vascular system. It's the extravascular, which is the interstitial fluid and the intravascular compartment plasma. We have also well emphasize system, but for the purpose of the pharmacology here, **most of the drugs are absorbed to the vascular system.** I wanted to show you this type of cartoon.

We realize basically what are the options for the drugs? where do they go? As we said, they could be taken, but as oral forms. They get absorbed through the GI tract, then absorb to the blood vessels to the intravascular compartment. Or we inject the drug directly to the intravascular compartment, could be intramuscular injection, that also eventually gets the drug to the intravascular to the circulation. Then, **once the drug is in the circulation, it travels the same way as the blood travels. It basically gets within the blood vessels to every single part of the body. We have the heart that's pumping the blood and letting the drug to be distributed.**

This is what happens. First, we have the drug in the intravascular compartment, but most drugs that we will be talking about act outside of blood. So, except for the drugs that have their targets that are blood constituents, **most drugs act outside the blood vessels**, some peripheral target tissue.

How do drugs get to the target tissue services? Review of cardiovascular as well because you have hopefully remember when we talked about the cardiovascular system. We said that **the only part of the cardiovascular system that it's open to the outside world is the capillaries. Capillary is the only part of the vascular system that is enable exchange of everything. It is supposed to be exchanged with metabolize nutrients, gases…everything goes through capillaries. We have the capillaries as part of the cardiovascular system and the target tissue. Now, the drugs will go directly through the endothelial cells, through the membrane. They pass through the membrane that dissolve in lipids, or hydrophilic drugs**. They are more likely to go through different means. They are transported through active way or passive way of filtration, through those large peri cellular spaces that actually most capillaries in the bodies are characterized by. Again, capillary is the only place of exchange with the cardiovascular system, and between the cardiovascular and outside world. This is first piece of information.

How the distribution occurs? It depends on the properties of the drug.
What are additional factors? What are the drivers?

Drugs go according to the concentration gradient. We have higher concentration in plasma. When we put the drug there at the tissue level, the drug diffuses to the tissue. The process of diffusion is in the direction of that issue until there is a equilibration in the concentration. **When the equilibrium is reached between the plasma and that issue, it's not the movement stops, but net movement is zero.** This is an important piece we will talk today about drugs bound to plasma proteins.
As far as exchange of drugs with tissues, it's only about **free drugs, not bound to proteins**. Drugs bound to proteins, we will talk later, are actually protected from being used. You can put it this way. In most cases, **drugs bound to proteins has prolonged action, because this pool that is bound is not available for actually distribution to tissues**.

This is my big picture for you. We'll talk today about volume of distribution, based on where the drugs go, how far they go, and how widely they get distributed. We'll talk about specific systems where the capillaries are very tight that don't allow the drug movement. We'll talk about protein binding and so on. Let's start.

Distribution

Factors that determine the rate, sequence and extent of drug distribution:

- **Physicochemical properties of the drug**
  - **Lipid solubility** ($\uparrow$ Log*P* $\Rightarrow$ faster equilibrium w/ interstitial fluid)
  - **Ionization at physiological pH** (pK_a value of the drug)

- **Fat : Lean Body Mass Ratio** ($\uparrow$ BMI $\Rightarrow$ $\uparrow$ accumulation in the adipose tissue)

- **Cardiac Output and Regional Blood Flow** (the determinant of lipophilic drug uptake rate)

- **Binding to Plasma Proteins and Tissue Reservoirs** (affinity for different tissues)

- **Pathological conditions, e.g., Congestive Heart Failure, Uremia, Liver Cirrhosis**, with altered: distribution of body water, membrane permeability, protein levels, accumulation of metabolites that displace the drug from binding sites, etc.

DILUTION, BINDING, SEQUESTRATION

What are the factors that determine the drug distribution? There are several factors. We will briefly discuss them here and come back to some of them on the following slides.

W will not be coming back to the first one, the **physical chemical properties of the drug**, because we discussed it already in the absorption portion in the first hour. Some of the factors that are determining absorption are also determining distribution. This is because we have two membranes for the drug to challenge. First, the group of membranes when the drug is getting to the systemic circulation. Then, when it's leaving the systemic. As I said, even intravenously applied drugs, they have to pass through the membranes to get to the site of action. The same physical chemical properties that determine absorption of the drug. For the drugs that are not administered directly to the circulation, the same properties determined drug distribution, meaning leaving the group, how the drug leaves the circulation and gets to the peripheral tissues.

The next very important factor is the **ratio of the fat to lean body mass, basically, the BMI body mass index**. To make it short, more fat, more chance that the drug is accumulated in this fat adipose tissue. We will come back to this later in the session when we talk about drug distribution. This will also be emphasized in our clinical case scenario that we'll discuss next Wednesday.

The next factor is the **cardiac output and the regional blood flow**. Cardiac output is the amount of blood ejected in one minute. The amount of blood determines how much blood gets to peripheral tissues, how efficiently it is distributed there. The drug is distributed with the blood, so the cardiac output is critical for drug distribution. Cardiac output is actually that the determinant of drug uptake by peripheral tissues for lipophilic drugs. This is because lipophilic drugs move through the membranes instantaneously. As I was discussing during the first session about absorption, **the faster the blood flow, the quicker the concentration of the drug drops in the circulation at the site of the drug absorption. Same is here. The faster the drug is delivered to the tissues, the faster distribution to the peripheral tissues because more drug is delivered to the end organ.** There will be higher concentration of the drug, their instantaneous concentration, faster movement to the final place where the drug is supposed to act or where the drug is accumulating and so on…

Besides the cardiac output, **regional blood flow** also has an important role because sometimes we need to consider this when you apply a drug, when the regional blood flow is changed. If the blood flow is changed through the organ where you want the drug to act, you need to consider the decreased blood flow, when you think about whether the drug can actually work.

The next one, **binding to plasma proteins and tissue reservoirs.** We'll come back to this. We'll have the slide devoted to plasma proteins. They play critical role in distribution or preventing distribution of drugs to peripheral tissues. We'll talk about tissue reservoirs as well.

Finally, **pathological conditions** are actually conditions that are related to some of the points made about that such as congestive heart failure, directly related to the effect of cardiac output on drug distribution. There's another aspect of congestive heart failure that also affects distribution. This is when with congestive heart failure, we are dealing with edema or liver cirrhosis. There is also decreased level of protein made by the liver. Now you have the play of hydro osmotic, osmotic pressures. When you have the water accumulating outside of the circulatory system, we'll have additional water there that provides constitutes that barrier for the drug distribution. This is same for the absorption in the GI tract and then the distribution. Uremia also changes the membrane permeability and so on. We will be coming back to those points in the following sessions. This is just an overview.

As far as the distribution goes in general, we'll talk about 3 aspects: one is the effects of **dilution**, the effects of **binding**, and effect of **separation**.

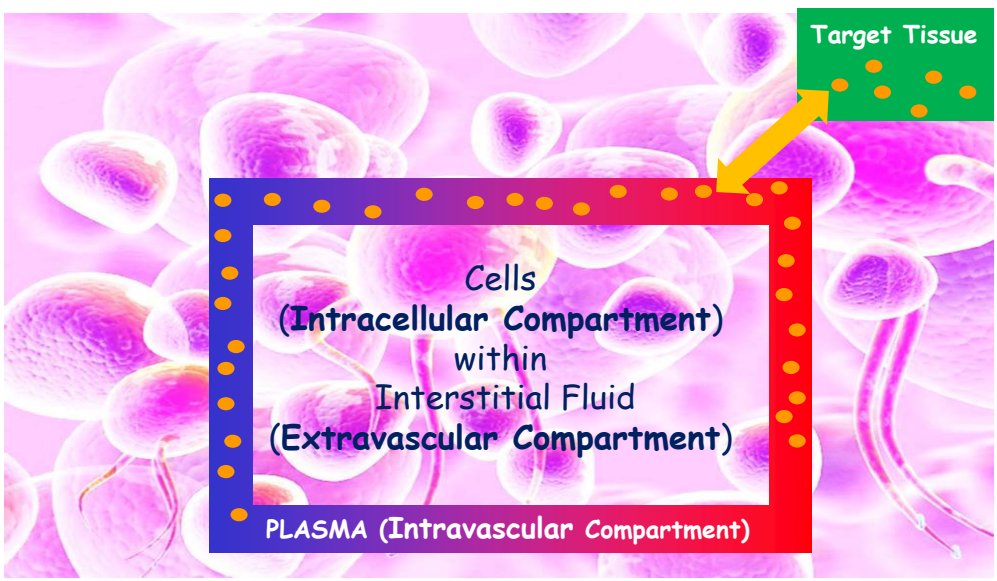
Distribution

Volume of Distribution (V_d)

The hypothetical amount of water by which a particular dose (all the drug in the body) would have to be diluted to produce a given plasma concentration, assuming that no drug amount has been lost through incomplete absorption, metabolism, or excretion.

$$Cp_0 = \frac{D}{Vd} \Longrightarrow Vd = \frac{D}{Cp_0}$$

Cp_0, drug concentration in plasma at time 0;
D, drug quantity administered in a single dose



Vd is a useful indicator of how drugs are dispersed among the various body compartments and, together with Drug Clearance, important Pharmacokinetic Parameter.

Now we are going to talk about a pharmacokinetic parameter that it's not real. I don't know how you are feeling about me taking your time talking about something that's not real, but I am going to tell you why I call it not real. It's apparent volume of distribution. All joking aside, this is a very important pharmacokinetics parameter. From my experience, it actually gives some people trouble in comprehending it understanding the concept because it is a theoretical volume. You may be remember from the my first introductory session, when I gave examples of pharmacokinetic properties. Pharmacodynamic properties of Propranolol you had there on the list was just an example. Propranolol had volume of distribution of 280 liters, sounds like a lot. This is definitely not a real volume for anybody. No matter how large human body, it's not real 280L. This is why I wanted to spend some time giving you on the subsequent slides, different examples of different drugs, with different types of distribution to hopefully make the concept bring it closer and make it really well understood by everybody. Let me start with a definition. Maybe for some of you, this will be sufficient. By definition, I just tried to try to come up with the most easy explanation of definition of what the volume of distribution is.

Volume of distribution is a hypothetical amount of water by which a particular dose (the dose here is all drug in the body) would have to be diluted to produce a given plasma concentration. This is with the assumption that no drug is lost. Whatever dose we think we are giving to the individual, this is the dose that getting. If it's through oral oral administration, the absorption is complete. There is no metabolism, no excretion. The entire volume, entire dose of the drug, is there.

Again, the hypothetical amount of water by which a particular dose would have to be diluted to produce a given plasma concentration. I know by repeating the same thing I'm not going making it easier for you to understand. So let me start with this.

Let's take the first scenario. You inject the drug (make it more straightforward, this is not oral administration). You know a dose, how much you injected to the circulation. You injected the certain volume, a certain amount of the drug, you get a certain plasma concentration. This is at the very beginning when you just inject it, right? You get the set on plasma concentration. The volume of distribution of the drug when you just inject that into the circulation is the volume of plasma, because this is a situation before the drug had the chance to escape to go outside of the circulation. When the whole amount of the drug is in the circulation, the volume of distribution of the drug is the same as the volume of plasma. Again, if you inject it, you let it mix well with entire plasma, collect the sample, measure the concentration. From the concentration and the dose you put in, you know what the volume of plasma. This would be the volume of distribution for the drug at the time when the entire drug is in the in plasma. But very few drugs work as I said earlier within the circulation that the targets are in the blood constituents. They leave the circulation. Depending on how much of the drug leaves, the drug plasma concentration decreases. When the concentration is lower, you had this hypothetical greater volume that you would have to use in order to get the specific plasma concentration. Now, the volume is greater, but some of the drugs escaped the circulation, the plasma concentration got down. When you calculated how much volume of water you would need to add to the given dose of the drug to obtain the concentration in plasma, this is basically the volume of distribution. It's a very important factor because it actually tells you how is the drug distribute, is it mostly in the blood, is it mostly somewhere else… We will go through specific examples. Those examples will give you maybe a better sense of what I was just talking about.

Formula of how you measure plasma concentration is a dose of the substance over volume. This will be g/L, or whatever unit, or mg or ng/mL or per L. This will be a concentration. If we solve it for volume of distribution, volume of distribution is D, the dose, over the drug concentration in plasma.

This is how you can calculate the the volume of distribution because it has to be the entire dose of the drug. We don't know exactly where the drug is, but it escaped the circulation. The amount of the drug and the circulation is lower. This caused the plasma concentration of the drug to decrease. We assume that this is the new volume that the drug is present in one big compartment where the drug is now dissolved in. This is a critical indicator. You will have this parameter volume of distribution presented in all pharmacokinetic data for a drug. The clearance is another one that both together as you will see as at our last session of pharmacokinetics series. We will use those tool to make some calculations.

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NEXT SLIDE

Scenario #1 is that the drug remains in the intravascular compartment. You can imagine what type of drugs are those. I mentioned about the plasma binding to plasma proteins. I gave you some examples of some drugs, but you don't need to remember the names of the drugs. **They are drugs that are extensively bound to plasma proteins**. They are mostly in the plasma bound to proteins. Sometimes, a lot of them, they stay in the circulation. In this case, if **most of the drug stays in the circulation, volume of distribution of the drug is distributed in plasma. So the volume of distribution will be the volume of plasma.**

I am presenting those three different scenarios with hopes that they will help you grasp the concept of the volume of distribution.

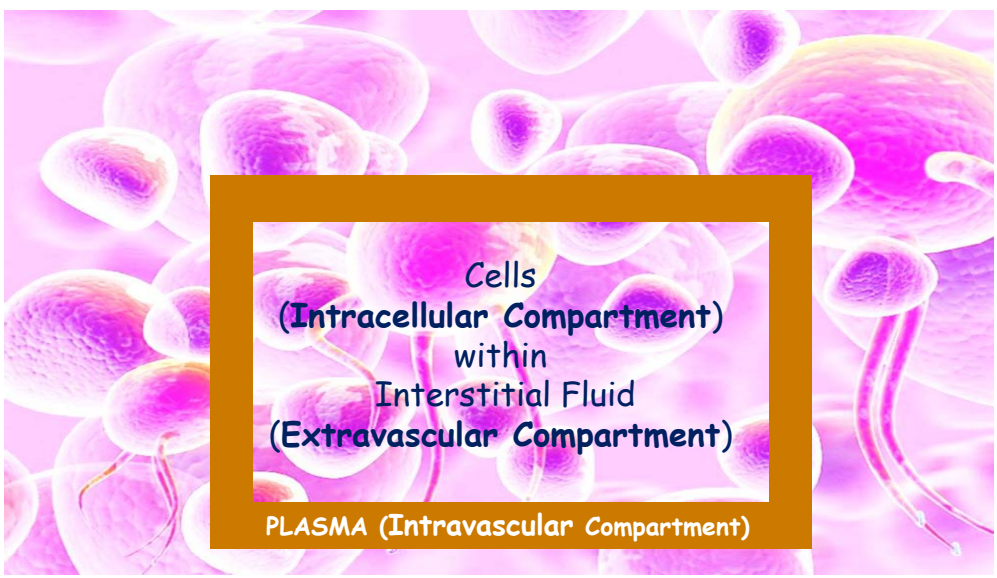
Distribution

Volume of Distribution (V_d) – Scenario 1

The hypothetical amount of water by which a particular dose (all the drug in the body) would have to be diluted to produce a given plasma concentration, assuming that no drug amount has been lost through incomplete absorption, metabolism, or excretion.

$$Cp_0 = \frac{D}{Vd} \Longrightarrow Vd = \frac{D}{Cp_0}$$

Cp_0, drug concentration in plasma at time 0;
D, drug quantity administered in a single dose



Drug remains in Intravascular Compartment (drugs extensively bound to plasma proteins, e.g., Diclofenac, Warfarin)

⇓

V_d = Volume of Plasma (~3 L)

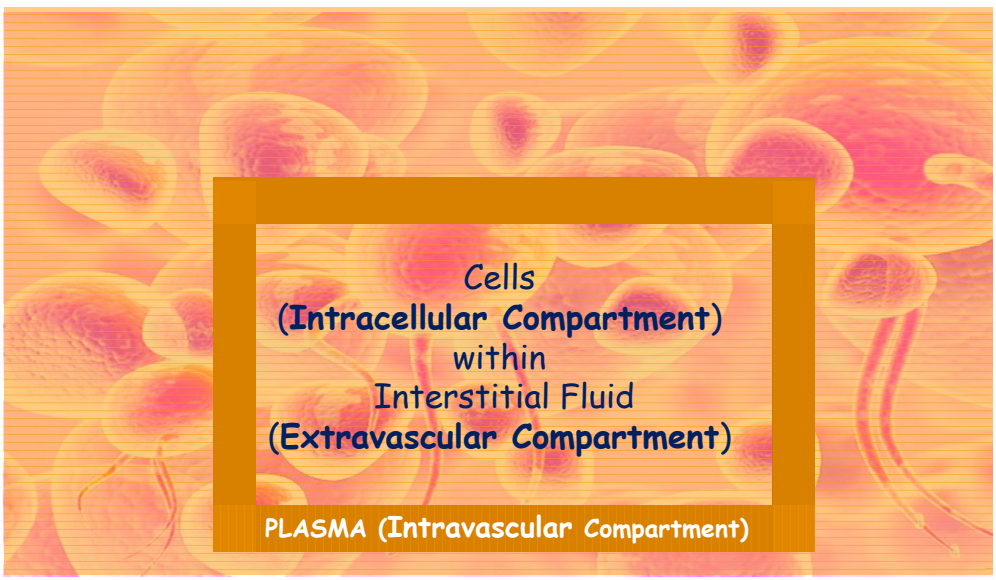
Distribution

Volume of Distribution (V_d) – Scenario 2

The hypothetical amount of water by which a particular dose (all the drug in the body) would have to be diluted to produce a given plasma concentration, assuming that no drug amount has been lost through incomplete absorption, metabolism, or excretion.

$$Cp_0 = \frac{D}{Vd} \Longrightarrow Vd = \frac{D}{Cp_0}$$

Cp_0, drug concentration in plasma at time 0;
D, drug quantity administered in a single dose



Drug evenly distributed in
All Fluid Compartments
⇓
Vd = Volume of Body Fluids (~41 L)

Scenario #2 is where the drug is evenly distributed in all fluid compartments. For an average individual of 70 kilograms body weight, the volume of body fluids is approximately 41 liters. In this situation we start again with the drug being present only in the circulation, in the intravascular compartment. The drug gets distributed to all fluid compartments, so the drug leaves the circulation and present everywhere. Everywhere meaning all body fluids, including the plasma and intravascular compartment. Now, **the volume of distribution of the drug is the volume of all body fluids.** In this case, it's not the same as the scenario #1, it's the real volume of distribution. **This is a theoretical situation.** Very few drugs, if any, distribute exactly to all body fluids. With some approximation, we can say that. In this case, the volume of distribution is 41L. The plasma concentration of the drug reflects the actual concentration everywhere in the body.

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NEXT SLIDE

Scenario #3 demonstrates the hypothetical nature of the volume of distribution. We have a situation where the drug is sequestered in a selected tissue or target. It's actively transported against the concentration gradient. Here, I gave examples of some drugs that actually do that, meaning drugs do to the body or what the body does to the drugs, right? In this situation, we are starting with a scenario where the drug stays everywhere like we discussed on the previous case. But now, when the drug leaves the circulation, it actually accumulates in one specific tissue. **The drug is definitely not distributed around the body. It is just in one place, but the volume of distribution that power and volume of distribution is really high.** This is because most of the drug left the systemic circulation. It means that the drug is accumulated somewhere, has accumulated in some place. Very little of it is actually in the plasma. The plasma concentration of the drug is very low. So we need to imagine a really large volume that would dissolve the drug (~dilute the drug) to the amount that would correspond to the actual concentration in the plasma. This is why this demonstrates is the **only apparent volume of distribution**. If you have the drug information like I said earlier for Propranolol, really high volume of distribution, it means that the drug is accumulated somewhere, has accumulated in someplace. Very little of it is actually in the plasma.

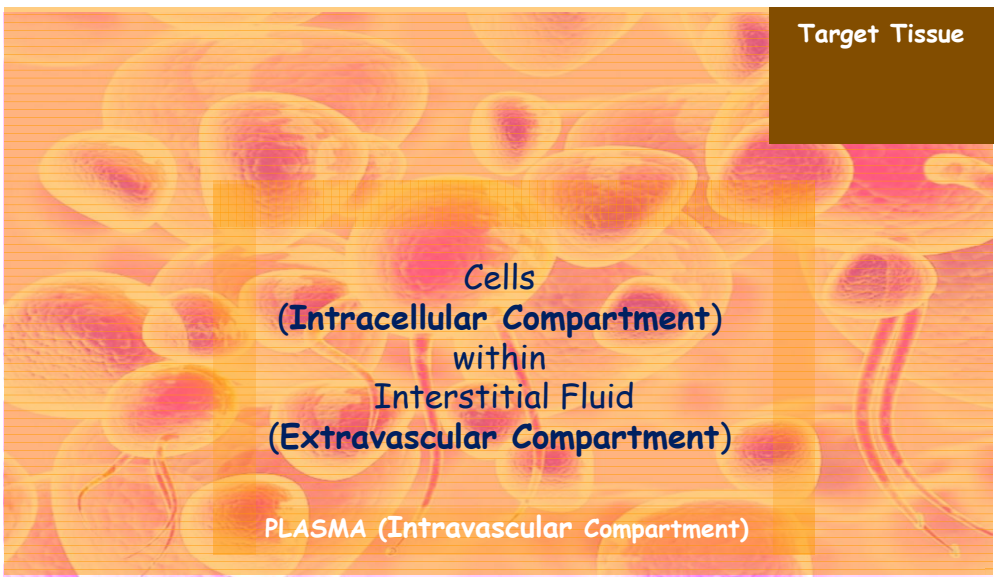
Distribution

Volume of Distribution (V_d) – Scenario 3

The hypothetical amount of water by which a particular dose (all the drug in the body) would have to be diluted to produce a given plasma concentration, assuming that no drug amount has been lost through incomplete absorption, metabolism, or excretion.

$$Cp_0 = \frac{D}{Vd} \Rightarrow Vd = \frac{D}{Cp_0}$$

Cp_0, drug concentration in plasma at time 0;
D, drug quantity administered in a single dose



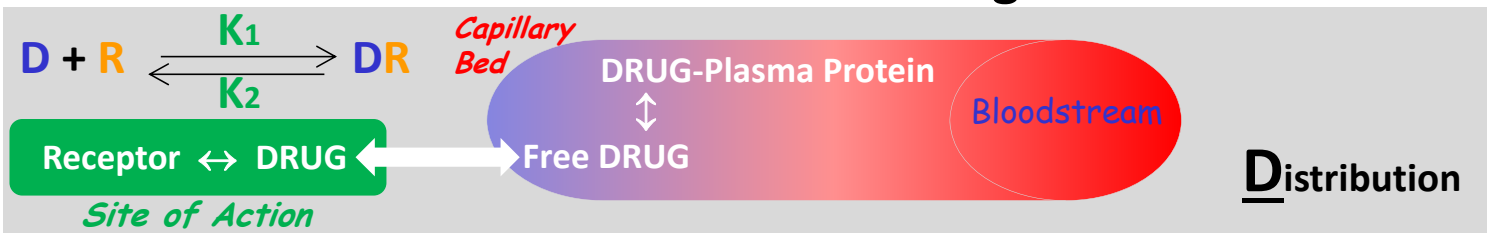
Drug sequestrated in Selected Tissue/Target (actively transported against concentration gradient, e.g., Lidocaine, Tetracycline, Atropine, Morphine)

⇓

V_d » Plasma Volume or even Total Body Fluids (>41 L ⇒ Apparent V_d)

Distribution

Plasma Protein Binding



Albumin – Acidic Drugs; α1-Acid Glycoprotein – Basic/Cationic Drugs;

Drugs differ in their affinity for plasma proteins (0%-~100% binding at therapeutic concentrations)

No generalization for pharmacological/chemical class, e.g. Flurazepam 10%, Diazepam 99%)

↑Drug concentration ⇒ Progressive saturation of the plasma protein binding sites.

The percentage of bound drug usually does not change over the dosage ranges used clinically.

DRUGS HIGHLY BOUND TO:

ALBUMIN	α1-ACID GLYCOPROTEIN
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine, Lidocaine
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Imipramine
Phenytoin, Valproic Acid	Methadone
Warfarin	Prazosin
Penicillins, Sulfonamides, Tetracyclines	Quinidine
	Verapamil

Distribution of drug
First, **binding to plasma proteins**. This is part of the big picture cartoon of pharmacokinetic processes where we talked about the distribution. To remind you, only free drug can leave the circulation. In the context of plasma protein binding, drug that is bound to plasma proteins is not involved in the drug action. Here we have the site of action interaction of the drug and the receptor. The receptor and drug interaction is not the permanent bond. We have two dissociation constants there that is binding and unbinding of the receptor. In this process, the critical role is the concentration of the drug in the vicinity of the receptor. This concentration is ermined by the concentration of the free drug in the bloodstream. The concentration of the free drug is determined partially by the amount of drug that is bound to plasma. We'll talk about conditions when the plasma protein binding decreases, then you have higher level of free drug, meaning higher concentration available for binding. Then, we have this stronger binding of the drug to the receptor, meaning the probability of binding increases.

As far as plasma protein binding, we have **2 major types of proteins: Albumin and alpha1- acid glycoprotein. Both are important.** Although albumin binds more drugs in general compared to the alpha1- acid, like protein. Both are important. It depends on the drug. **Acidic drugs bind to albumin.** Important piece: the drugs differ in their affinity for plasma protein. Some drugs such as warfarin shown in the first example of first scenario for distribution, warfarin is bound 99%. Other drugs have very low binding to proteins. This information is also included in the pharmacokinetic data sheet for each drug. There is no general rule. You can have a drug from the same class. As I gave examples of two benzodiazepine's: flurazepam is only 10% protein binding, and diazepam 99% protein binding, with clinical consequences that I will discuss on the next slide.

When you increase the drug concentration, the availability for plasma protein binding decreases because you basically have the saturation of the binding sites. In addition, we'll talk about this on the next slide. There is a competition. If you give a patient two drugs, both are highly protein bound, then you have to consider that one of the drugs might be at higher concentration or both of them at higher concentration of the free drug. Meaning active form of the drug is at higher levels because of the competition. One of the drugs might lose the competition. Higher level is available for action, which could be dangerous if we are talking about drugs with a narrow therapeutic window ~low therapeutic index. That percentage of bound drug usually does not change their ranges used clinically. When I put here, increase drug concentration saturates the binding side. When the drug is developed, this part is always considered. But even though the percentage of drug doesn't change over the range of the concentration, this can change, if you have another drug that's competing. You have like doubling the concentration of the drug. You have another one that is also using the binding site.

Here I'm giving the list of drugs that highly bound to protein. Here is for albumin and alpha1-acid glycoprotein. You don't need to remember the drugs. Obviously, we haven't talked about any of them. I wouldn't expect you to remember the names but wanted you to the just have a first look at sells drugs like warfarin 99%. We will talk about the clinical consequences of plasma protein binding. And on drug availability and so on.

Distribution

Plasma Protein Binding

Clinical Implications

I. Plasma drug concentrations refer to bound+free drug ⇒ consider the degree of protein binding

II. High plasma protein binding ⇒ Drug largely restricted to Vascular Compartment (Low V_d)

III. The bound fraction not available for action, but in equilibrium with free drug

IV. High plasma protein binding ⇒ Drug long acting (the bound fraction not available for metabolism or excretion), unless the drug is actively taken by organs (plasma protein as a carrier), e.g. Lidocaine by the liver, Penicillin G by renal tubules

V. Hypoalbuminemia⇒ ↓ binding ⇒ ↑ concentration of free drug (e.g., Diazepam)

VI. Pregnancy & Inflammatory Disease ⇒ ↑ α1-acid glycoprotein ⇒ ↑ drug binding

VII. More than one drug can bind to the same site(s) on Albumin ⇒ displacement of drugs bound with lower affinity. Significant for:

⇒ **highly bound drugs** with **small Vd** (Albumin-bound acidic drugs),
⇒ administered in **large doses**,
⇒ characterized by **a narrow margin of safety**, or
⇒ when **metabolism/excretion are decreased**.

EXAMPLES: **Aspirin** displaces **Sulfonylureas / Methotrexate**

Indomethacin / Phenytoin displace **Warfarin**

Here are the **clinical implications of plasma protein binding**. It looks like I've covered most of them in narration to previous slides only briefly.

1. **Plasma drug concentration**: whenever you have a given you are given plasma drug concentration, which refers to both bound and free drug, you need to consider this meaning the degree of protein binding. If the drug is highly protein bound, that fraction available for action would be only a fraction of the plasma drug concentration that is given or recommended.

2. **High plasma protein binding**: the second point it was actually indirectly presented in the first case scenario here for the drug distribution. I gave example of warfarin is 99% protein bound. This drug would be highly largely restricted to the vascular compartment. That means low volume of distribution, basically, equal or close to the plasma volume.

3. **The bound fraction is not available for action but in equilibrium with free drug.**

4. **Drug that has the high plasma protein binding:** this would be associated with longer duration of action. This is because the fraction that is bound to protein is not available for metabolism. The drug is not seen because it's staying in the circulation. It's not distributed or goes to the liver. It's not metabolized and not excreted. This prolongs that fraction of action going back to the point of equilibrium of both free and protein bound drugs. If you now have the drug that is highly protein bound, the fraction that's not bound to proteins gets metabolized. The fraction of free drug decreases the concentration because of the equilibrium. Once the free drug concentration drops, the more drug gets unbound from the protein. It's basically slowly being released to the circulation from the binding sites. This extends the action with one exception after that, unless some drugs actually use the proteins as vehicles for delivery, or the body uses the protein for delivery of drugs to the liver or to the kidney.

    - One classic example is actually lidocaine. The plasma is the carrier of the lidocaine to the liver. Actually, the metabolism in the liver is determined by the blood flow through the liver. It's a blood flow limited. There're a lot of enzymes in the liver that metabolize like pain and the metabolism is limited by the blood flow. The blood flow is associated with amount of lidocaine and the plasma protein carriers there. If the drug is actively taken by organs, higher protein binding, means actually increased metabolism and shorter duration of action.

5. **Hypoalbuminemia** means **decrease binding**. Basically, in the context of the liver cirrhosis or so, when you have less proteins, less binding, this would increase the concentration of the free drug.

6. **Pregnancy & inflammatory disease:** there is no known association with the increased levels of alpha1-acid glycoprotein, so increase drug binding obviously for drugs that are bound to the specific protein.

7. The **competition for a drug for protein binding sites**. I already talked about this so I can leave it that way. This actually competition would be significant for those drugs that are highly bound because when you think of …

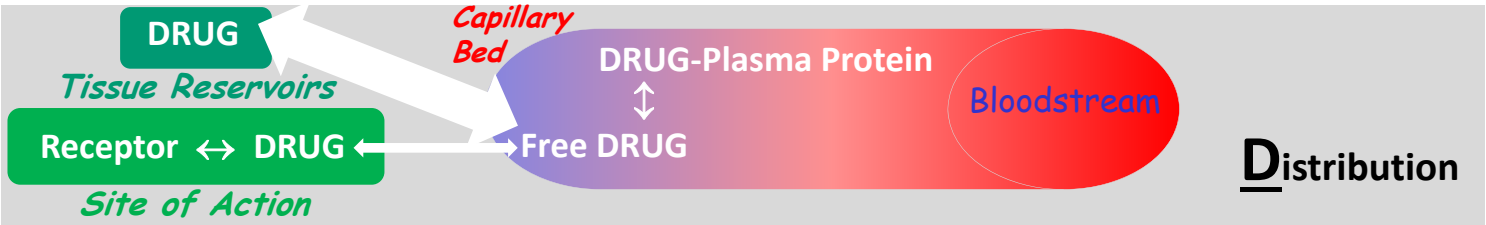
    - **warfarin**, for example, 99% of the drug is bound. If you don't have enough protein in there to bind all the drug, because of the competition, even if only binding drops from 99 to 98%, it means that the free drug increases from 1% to 2%. Meaning you double the amount of free warfarin, meaning warfarin available to decrease blood calculation. This could be sometimes dangerous. It's important. You will see warfarin, one of the drugs critical for you to know, as far as drug interactions with other drugs. You need to know because of the drugs you use. Also, because of the increased risk of bleeding in patients who have increased levels of warfarin. We'll talk about all this. This is from the perspective of plasma protein binding.
    - Also, for **drugs that are administered in large doses** because then we are talking about the fraction of the drug not being available for binding so dramatically increasing.
    - And very significant when the **drug has narrow margin of safety** because then even small change in concentration can be dangerous
    - If the **metabolism is decreased** because you have higher level of free drug. If metabolism excretion are compromised, then this higher level of drug stays longer in the body. This can be dangerous especially when you combine the narrow partition of safety and the patient with compromised metabolism.

So you will need to consider all of these when you plan your pharmacotherapies. I gave some examples of drugs that displays and here in red.

- You have **aspirin** that actually is the one that you will be prescribing to your patients. With the patient treated with **sulfonylureas** (this is antidiabetic drug) or methotrexate that came out therapeutic cancer/chemotherapeutic, basically levels of those drugs increase. This is dangerous because sulfonylureas will potentially result in hypoglycemia. **Methotrexate** is also toxicity of the drug.
- The second example is **indomethacin/phenytoin**. They displace warfarin. Again, with warfarin, increased risk of bleeding as I just discussed.

Distribution

Tissue Binding and Storage



Drugs may accumulate in specific organs or get bound to specific tissue constituents.

High concentration ⇒ Local toxicity:

Bone & Teeth:

Tetracyclines
Fluoride
Lead
Bisphosphonates /Zoledronic Acid
(extended anti-osteoporotic action)

Sequestration:
When that drug leaves the circulation it has pretty much two choices:

1. One is to **get to the site of action**. Meaning when it leaves the circulation at a place where the site of its action is, it binds to the receptor.
2. In addition to this, there are other tissues that we together call tissue reservoirs. In those reservoirs, the drug is bound there too.

It seems that most of the drug is actually bound to the receptor site of action. Meaning receptor through which that drug acts, but it's not the case. Actually, the proportion of the drug that's bound to the receptor, the site of action, called tissue reservoirs, the difference is big. Meaning **most of the drug content is actually bound to tissue reservoirs, not to the specific receptors at the site of the drug action. Different drugs can bind to different tissues as tissue reservoirs and get accumulated there.** I only decided to give you the most prominent dentistry related examples.

The consequence of this accumulation is that **you have high concentration of the drug. This can lead to drug toxicity**, the local toxicity. For the bone and teeth, Here are the drugs that are known to accumulate in the tissues. Tetracyclines- they actually cause discoloration of teeth (we'll talk about those later when we talk about antibiotics). Fluoride, lead and biphosphonates, specifically zoledronic acid~ those are drugs used to treat osteoporosis. In this case, Presence of the drug in the tissue extends the anti-osteoporotic action.

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NEXT 2 SLIDES

Distribution
It's actually redistribution of highly lipid soluble drugs. This topic is highly clinically relevant.
So we are talking about drugs, with specific examples of drugs acting on the central nervous system. This is just an example where you can very quickly see the outcome of the action. You can basically demonstrate the principle. The same occurs for other organs that I will be listing here. It's just harder to catch the phenomenon. This phenomenon for hypnotics and general anesthetics has actually clinical relevance.

So **you inject a highly lipid soluble drug to the circulation**. Where does the drug go first? When it's in the circulation, **first it gets to the organs that are characterized by a high vascularization, organs that get the highest blood flow**. What are these organs? It's the **HEART, KIDNEYS, LIVER, LUNGS** and the most irrelevant for the type of drugs that we'll be discussing here is the **BRAIN**. The drug gets to the brain very quickly.

As I mentioned at the very beginning, the cardiac output actually determines the rate of the uptake of highly lipid soluble drugs because the diffusion passing through the membranes is almost instantaneous. Higher the flow, more drug gets taken up by the tissue versus the first ways that the highly vascularized organs get the drugs. You notice the rectangle in the center (her picture), **rising the circulation gets lighter because the drug gets redistributed to highly vascularized organs.** This is first stage, but obviously the blood flows to other organs, too.

Some of them, because this is highly lipid soluble drug, will bind the drug as well. **With time, the drug actually gets taken up by other organs that have low perfusion. The bulky organs that there is high capacity can take a lot of drugs. Even though the perfusion is not high, the total volume and the mass of those organs is high.** So we have the **MUSCLE, SKIN and FAT**. Because the blood flows through all of them, all other organs, the drug gets taken from the circulation and deposited in those high capacity organs.

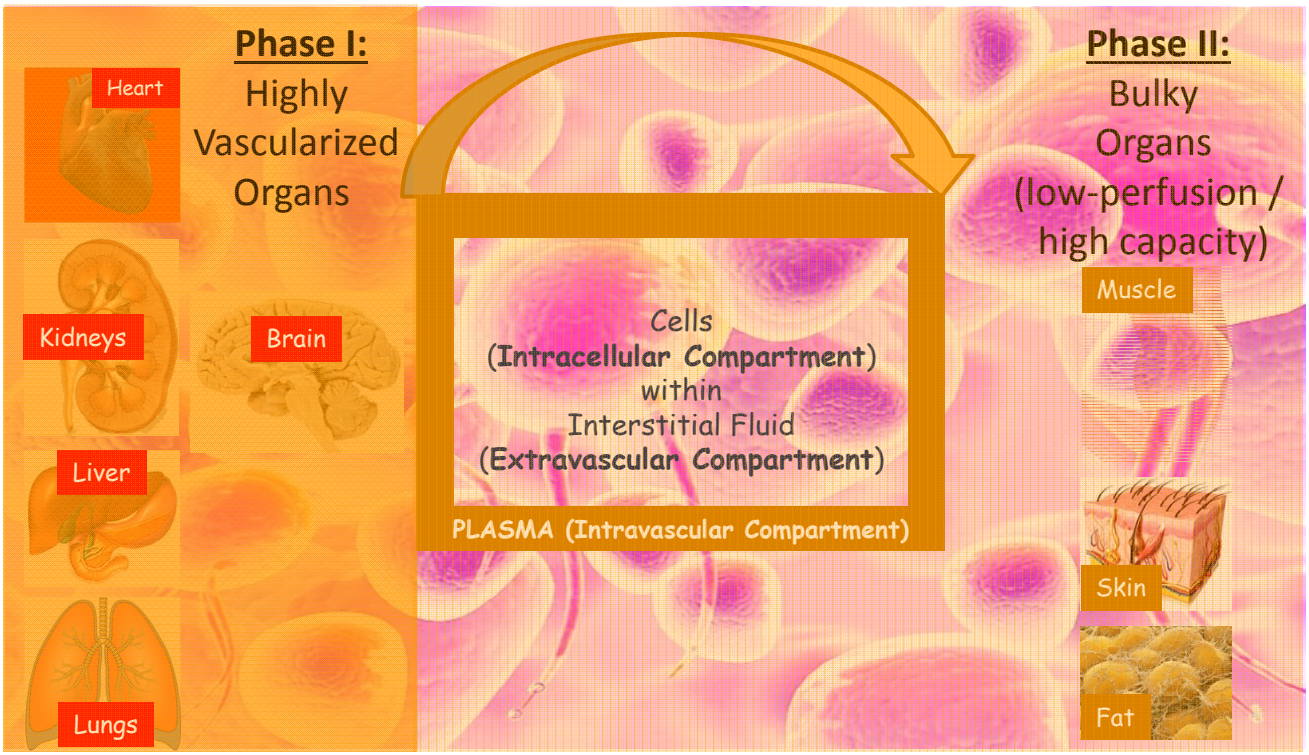
We have the redistribution of the concentration of the drug from the organs on the left to the organs on the right. Meaning, there's basically decrease in the concentration at highly perfused organs because that is drop in the plasma concentration of the drug. **If you're adding more drug, you eventually saturate those high capacity organs because they are high capacity, but limited capacity.** Once you said to raise them through subsequent injections or infusion, the original organ of interest, the brain will get the sufficient amount of the drug, for example, to keep the brain asleep (as with the case of the hypnotics).

We will actually talk about the redistribution phenomenon during your small group meeting because this phenomenon is part of the clinical case scenario. I know I'm helping you here but I think it's OK. I wanted you to think about this without giving you the connection, but just a little help never hurts, right?

Distribution

Redistribution of Highly Lipid-Soluble Drugs

(e.g., Hypnotics: Diazepam; General Anesthetics: Thiopental)



Distribution

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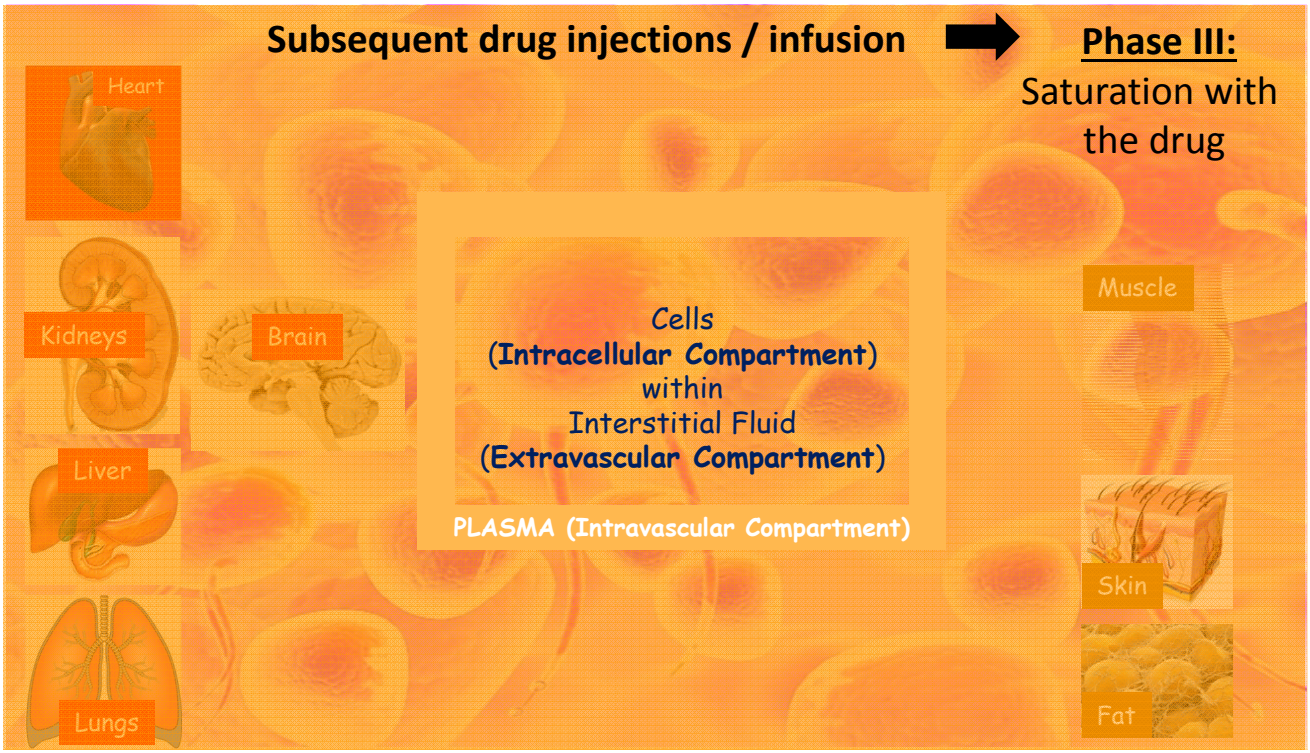

Distribution

Saliva

Systemic Circulation

⇓

Entry into Saliva through:

1) *Passive diffusion across the alveolar and ductal cells of salivary glands (primary route)*
2) *Active transport into saliva (e.g., P-glycoprotein; note: polymorphisms altering P-gp activity)*
3) *Passive diffusion across the oral epithelium*
4) *Bulk flow of fluid from the gingival crevice*

⇓

Swallowed Saliva

⇓

Reabsorption in the GI tract ⇒ Drug back in the Systemic Circulation

POTENTIAL APPLICATIONS:

1. Therapeutic:

Systemic administration of drugs to achieve a sustained therapeutic concentration in the saliva for a local effect ⇒ removing the need for intraoral application, e.g. fluoride & antiplaque agents for caries prevention.

2. Diagnostic:

Measurement of drug levels in the saliva for a noninvasive determination of the free drug concentration in plasma.

Drugs differ in their levels in saliva: lipid-soluble or very small in size easily equilibrate with saliva.

3 quick topics:
First, close to your heart, SALIVA. Saliva is a target of drug redistribution. What I put here is the way that the drug gets from systemic circulation to the saliva. I will not be reading the slide. **You have the information how the drug gets to the saliva. Then, the saliva is swallowed. That drug gets reabsorbed in the GI tract and back to the systemic circulation.**

As far as applications, I wanted to have a slide and tell you about this because the salivary diagnostics specifically is rapidly developing field. Most likely by the time you graduate, you will be heavily involved in diagnostics of patients by taking samples of saliva. Actually, the 2 potential applications:

1. First, targeted **therapies** that you would basically administer the drug systemically, but to achieve the concentration in the saliva for the local effect in the mouth. So here I gave some examples.
2. The other is the **diagnostic** that you can measure drug levels. You can measure other biomarkers in the saliva. Basically, this is the saliva diagnostic. One is the biomarkers of diseases. The other is drug levels. You can determine the drug concentration from the saliva.

You need to basically remember that the **drugs differ in their levels in the saliva. This could be related to their lipid solubility or the size of the drug. When they are very lipid soluble or small in size, they would easily equilibrate with saliva**. This is all I wanted you to know as far as distribution to saliva.

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NEXT 2 SLIDES

Finally, I wanted to briefly mention **2 organs with restricted access of drugs**. The first one is the blood brain barrier. The second is placenta.

As far as the **BLOOD BRAIN BARRIER**, I already told you pretty much everything I wanted to say when we talked about drug absorption, when we talked about the passage through the membranes. I know I already mentioned the blood brain barrier that in the context of inflammation. Inflammation can increase drug access. **This is extremely important clinically featured because there's normally drugs like antibiotics would not cross the blood brain barrier**. This becomes extremely important in case of meningitis (=inflammation of the meninges) because thanks to the increased permeability during the state, **you can actually treat meningitis with antibiotic, e.g. penicillin G**. Other piece that I wanted to add because I presented here for you the components of the blood brain barrier. This is just to remind you for review: **The deficiency of the barrier at the level of the medulla**. This also is important clinically **because of the deficiency, many drugs and are emetic** ~cause the vomiting reflex because they basically activate the neurons in the medulla. That is possible for the reflex, even drugs that are lipid insoluble, because they can basically cross to the medulla, where the barrier is deficient.

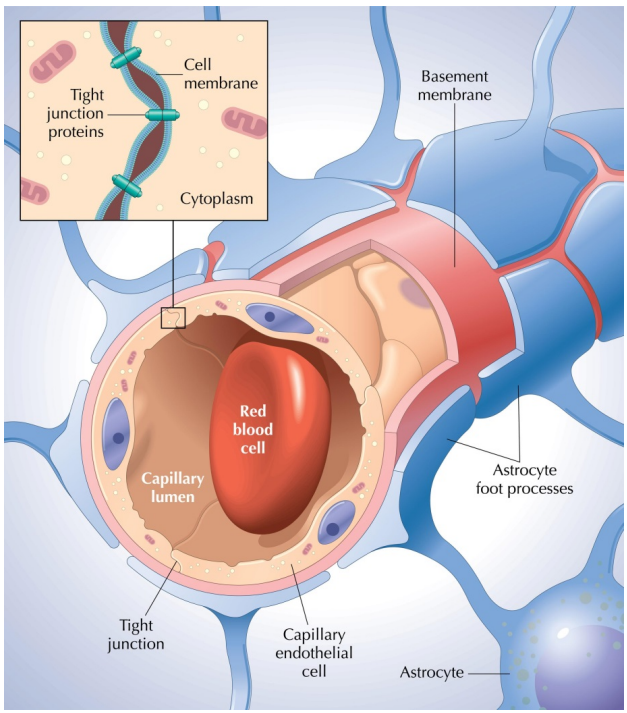
Pretty much the same general principles of the barrier applied to the other organ that I wanted to mention is the **PLACENTA**. First, lipid soluble drugs will use passive diffusion to cross the barrier. The barrier is that trophoblastic membrane. The membrane contains transporters, like a protein, the primary transporter will be preventing the drugs from entry, but lipid soluble drugs can diffuse. With a single injection, hydrophilic drugs cannot enter the placenta, but the lipophilic drugs (highly lipophilic). The mechanism here is very similar to what I mentioned at the beginning of this presentation was a cardiac output, when you had the effects of cardiac output on drug distribution. Greater the cardiac output, more drug can be taken up by the peripheral tissues, if the drug is highly lipophilic. Same here, highly lipophilic drugs penetrate easily in general. The distribution at the rate of the uptake is dependent on the rate of the flow. In this case, we're talking about maternal blood flow through the placenta.

- **Water soluble drugs with a single administration will not get to the fetus, to the placenta. Even drugs that are not lipid soluble can accumulate in the fetus if you administer it several times. For all those reasons, in general, you try to limit to the absolute minimum, any drug application to pregnant women, because of the risk of teratogenicity** (we'll talk about teratogenic effects of drugs later). General principles remain the same. Passive diffusion for lipid soluble drugs, water soluble don't pass with a single application, but all the matter of being consistent, persistent, and dose accumulation. With multiple applications, even though drugs that are not very lipid soluble will eventually get to the fetus. Again, you limit that application of drugs in pregnant women to the absolute minimum and whatever is only what's necessary.

Distribution

Restricted Access

I. Passage into the Central Nervous System - Brain & Cerebrospinal Fluid (CSF): Blood-Brain Barrier (BBB)



1. Tight junctions between endothelial cells of cerebral capillaries (lack large paracellular spaces).
2. Glial cell (astrocyte) processes cover cerebral capillaries.
3. Choroidal epithelium having tight junctions covers capillaries of the choroid plexus (pumping drugs out of the CSF).
4. Efflux transporters (e.g., P-glycoprotein) extrude many drugs that enter the brain.
5. Enzymatic BBB (in cells of the anatomical barrier): Monoamine oxidase (MAO), cholinesterase, etc, preventing catecholamines, 5-HT (serotonin), acetylcholine, etc, entrance in active forms.

Inflammation of the brain/meninges increases permeability of anatomical barriers (e.g., Penicillin G). The BBB is deficient in the Medulla (e.g., lipid-insoluble drugs are emetic) and in the anterior Hypothalamus.

Distribution

Restricted Access

II. Passage across the Placenta

1. The movement of drugs across the placenta is limited by the trophoblastic membrane, including the action of P-glycoprotein. The entry depends on **passive diffusion across the lipid barrier**.
2. Highly lipophilic drugs (e.g., Thiopental) penetrate easily, and distribution is dependent on the rate of maternal blood flow through the placenta (90% equilibration with maternal arterial drug concentration within 40 minutes).
3. Virtually no water-soluble drug from a single administration may gain access to the fetus.

Even sparingly lipid-soluble drugs accumulate in the fetus if administered to the mother in multiple doses (risk of developmental defects in the embryo and fetus - Teratogenicity).