Bioavailability and Distribution

Lecture no. 2

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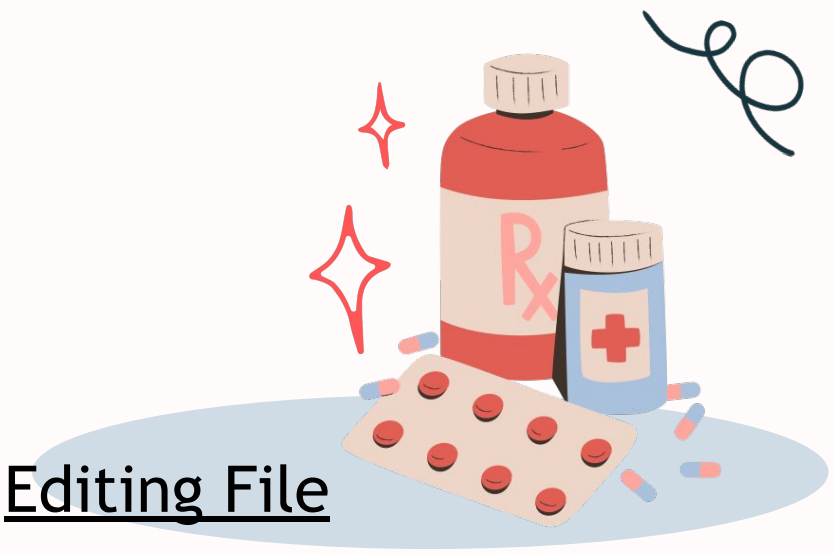

Editing File

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Objectives

- Bioavailability
- Major body fluid compartments
- Concept of compartments
- Plasma protein binding
- Apparent volume of distribution (VD)
- Tissue binding

Bioavailability

- The amount of unchanged drug that enters systemic circulation after administration and becomes available to produce pharmacological actions (treatment).

Rate and extent of active reaching systemic circulation

Note439:
For drugs administered orally: Bioavailability may be less than 100% for 2 main reasons: incomplete absorption & first pass metabolism

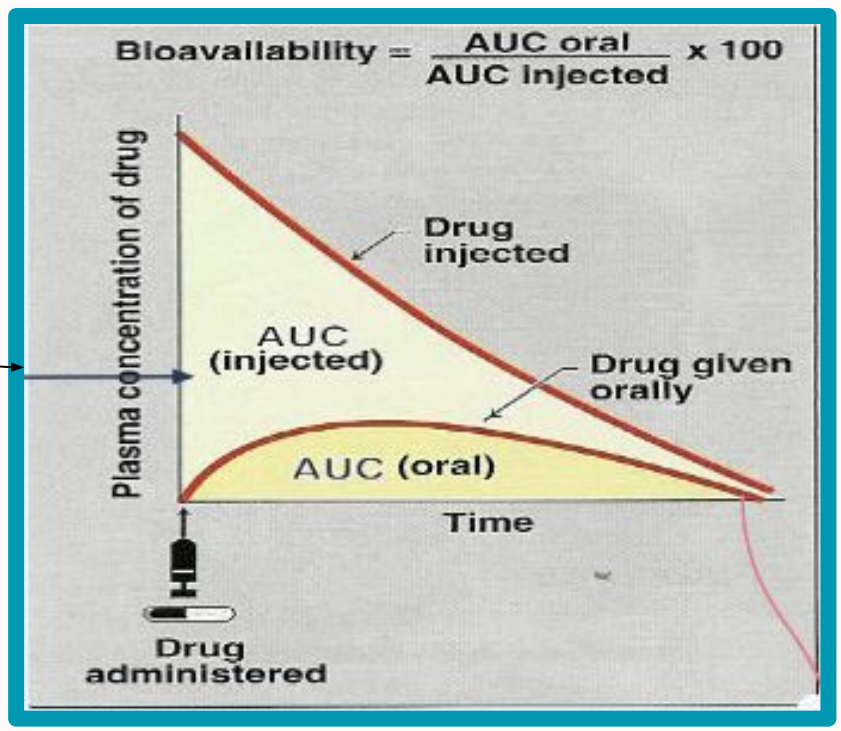
Equation

$$\text{Bioavailability (F)} = \frac{\text{AUC (oral) X 100}}{\text{AUC (I.V)}}$$

I.V. provides 100% bioavailability i.e. F= 1.

Subcutaneous, intramuscular, oral, rectal, and other extravascular routes of administration require that the drug be absorbed first, which can reduce bioavailability.

AUC means "Area Under Curve"



Note 442: Its the standard because IV rate is (1 or 100%)

Bioavailability

Note439: *Generic formulation is the actual name of a drug e.g Paracetamol

Absolute

The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation .

Relative

- Is determined when two products are compared to each other not to an intravenous standard.
- This is commonly calculated in the drug industry to determine that the *generic formulation is bioequivalent to another formulation

Bioequivalent = Same bioavailability
e.g Tylenol (paracetamol 500 mg) compared to Panadol (paracetamol 500 mg).

- is important to get an idea of how different formulations or routes of administration differ in their bioavailability.
- dosage adjustment is required when changing formulations or routes of administration.

Bioequivalence

➔ Two pharmaceutical products are bioequivalent when the rate and extent of bioavailability of active ingredients in two products are the same.
They have same effect

Factors affecting Bioavailability

1. Factors controlling drug absorption
2. First pass effect (decrease bioavailability)

Factors affecting absorption

1-Route of administration

2-Dosage forms

(depending on particle size and disintegration (ease of dissolution)).
(suspension > capsule > tablet)

3-Molecular weight of drugs

low mm > high mm

4-Lipid solubility

5- Degree of ionization

(non ionized absorbs easily)

6-Drug solubility

(aqueous preparation better than oily,suspension preparations)
Oily drugs have a long duration of action

7-Chemical instability in gastric pH

(Penicillin & insulin)

8-Surface area available for absorption.

small intestine has large surface area than stomach due to intestinal microvilli.

9-Blood flow to absorptive site

- greater blood flow increases bioavailability

-Intestine has greater blood flow than stomach

10-Intestinal motility (transit time)

-Diarrhea reduces absorption

11- Gastric emptying

- drugs that increase gastric emptying enhances absorption (metoclopramide).

12-Drug interactions

13-Food

- Slow gastric emptying
- generally slow absorption
- Tetracycline, aspirin, penicillin

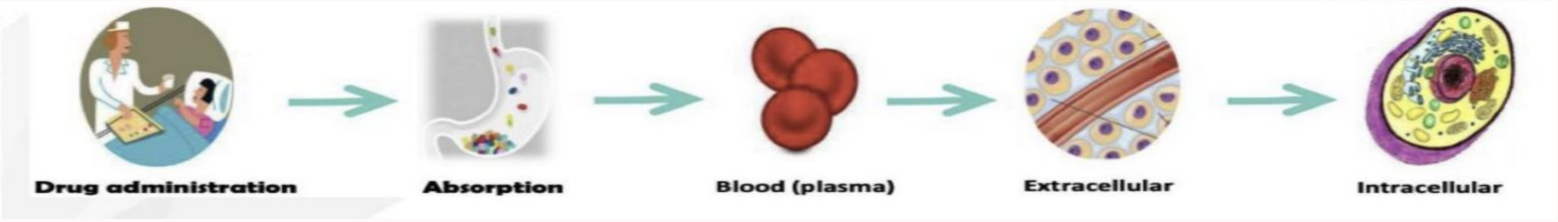
- A fatty meal increase the absorption of fat soluble antifungal drug (e.g. griseofulvin)

Distribution

– Is the process by which drugs leave blood circulation and enters the interstitium/ interstitial and/or the cells of the tissues.

– Distributed either intracellular or extracellular

- Lipid soluble drugs are distributed in the intracellular region. Because they can cross the cell membrane (Med439).
- Water soluble drugs are distributed in the extracellular region. Because they can not cross the cell membrane (Med439).



Note 442: Not necessary to pass through all stages may stop at the stage of blood only

Apparent Volume of Distribution (Vd)

Apparent Volume of Distribution (Vd): is the ratio of drug amount in the body (dose) to the concentration of drug in the blood

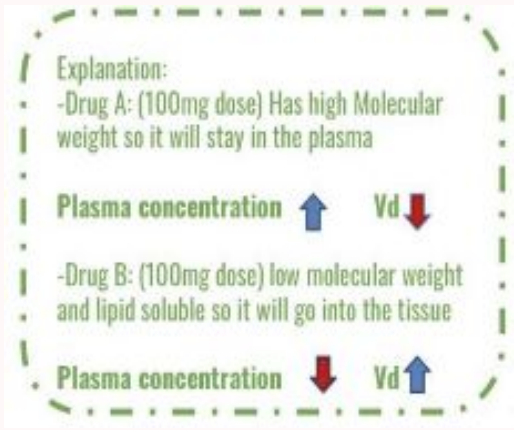
$$Vd\ (L) = \frac{\text{Dose (mg)}}{\text{plasma concentration (mg/L)}}$$

note 439: when (Vd) is inside the plasma blood it will decrease due to metabolic reactions, but (Vd) will be high inside cells and organs.

Why is Vd important?

➢ To calculate loading dose

➢ Large Vd = means long duration of action



Note 442: drugs which are in other compartments (extracellular or intracellular) are not available for metabolism, they should come in the plasma to be metabolized by the liver and excreted by the kidney

Drugs may distribute through:

One compartment (Plasma) 4l

Two compartments (Extracellular fluids) 10l

Multi-compartme -nts (total body water) 28l

Major Body Compartments

Don't forget

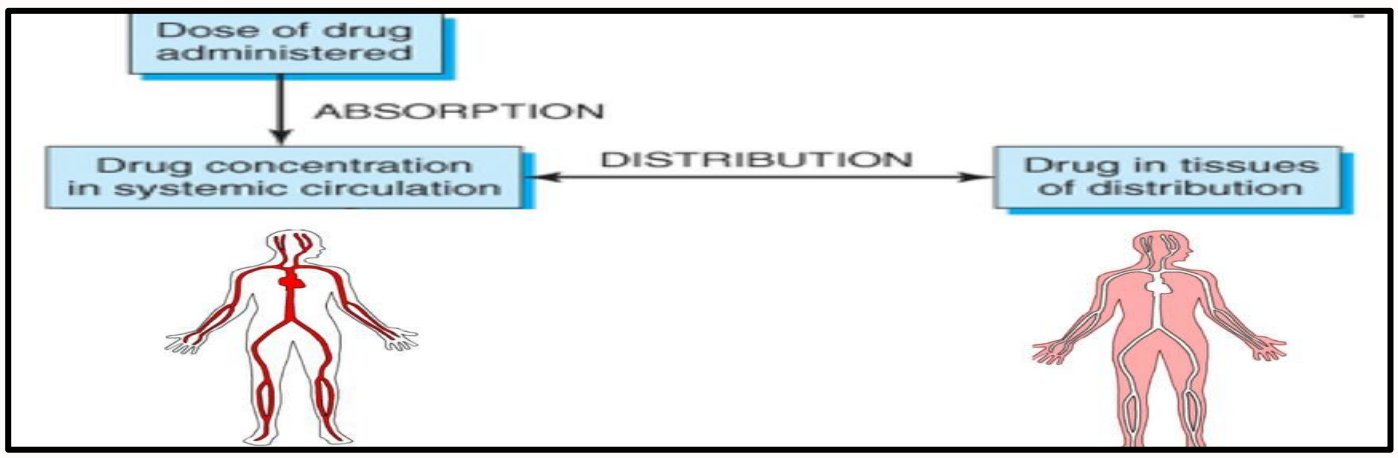
Extracellular fluid (22%)

Intracellular fluid (35 %)

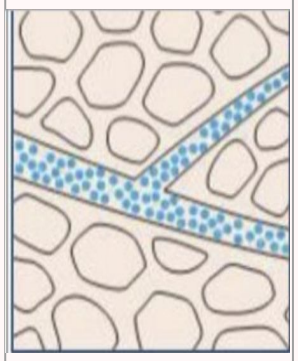
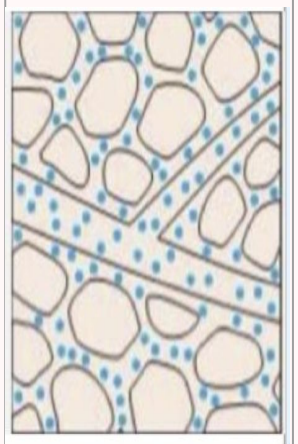
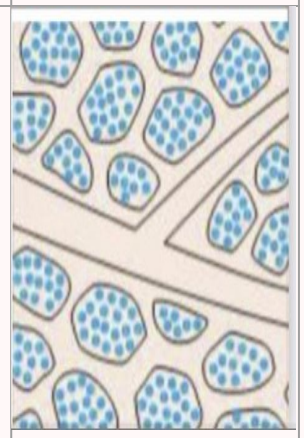
Plasma
(5 % of body weight = 4 liters).

Interstitial fluid
(16 % = 10 liters).

fluid present inside all cells in the body **(28 L).**



Drugs may distribute through

Compartment	Distribution	Volume of distribution (VD)	Drug characteristics	Crossing	Example	Picture
One compartment	Plasma (Trapped in blood)	around 4 L (Very low because of high molecular weight)	Very high molecular weight drugs, or drugs that bind to plasma proteins	Can not move across endothelial cells of capillaries (due to high molecular weight)	Heparin 4 L (Anticoagulant)	
Two compartments (Inside capillary)	Extracellular fluid	between 4 and 14 L	Drugs that have a low molecular weight but are hydrophilic (Not lipid soluble)	can pass through endothelium into interstitial fluids BUT can not cross cell membranes to intracellular fluids. (because its hydrophilic)	Atracurium 11 L (muscle relaxant)	
Multi compartment	Total Body Water (Extracellular & intracellular fluid) Diffusion to intracellular fluid	-For Lipid soluble drugs: Vd = Total Body Water -Drugs that bind strongly to tissues : Vd > Total Body Water	Difusion to intracellular fluid (can pass through membranes because it's lipid soluble)	a) Ethanol 38 L b) Digoxin 385 L	

Volume of Distribution (Vd)

Drugs with low Vd

- Distributed in extracellular compartments (plasma & interstitial fluid)
- **Polar compound** or lipid insoluble drugs eg, Gentamicin, Atracurium
- High MW (molecular weight) e.g. heparin-insulin
- High plasma protein binding e.g. Warfarin (anticoagulant)
- Do not cross BBB (Blood Brain Barrier) or placental barriers These types of drugs are safe for pregnant women, since they can't cross the placental barriers

Drugs with high Vd

- Distributed **intracellularly**
- Have **higher concentration in tissues** than in plasma (Lipid Soluble)
- Low MW (molecular weight)
- Free drug not bound to plasma proteins
- E.g. digoxin, phenytoin, morphine

Drugs that cross Blood brain barrier, will cross placental barrier and vice versa eg Hypnotic. (Med 439)

Factors Affecting Distribution

Cardiac output and blood flow

01

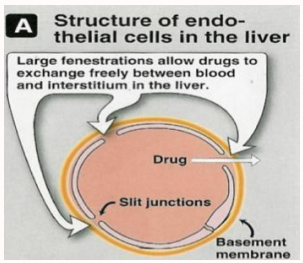
- The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids
- Drug distribute more rapidly to brain, liver, kidney > more than skeletal muscle & fat

Physical and Chemical properties of the drug

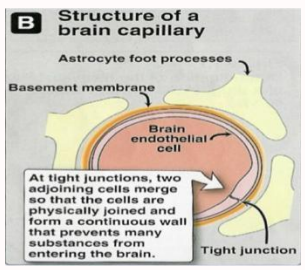
02

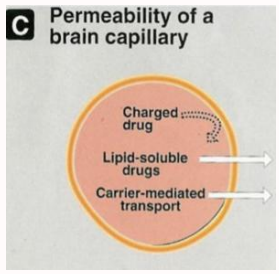
- Molecular Weight
- PKa
- Lipid Solubility
  -Hydrophilic drugs (Ionized, charged, Polar) do not readily cross cell membranes but go through slit junctions in endothelial cells of capillaries
  -Most lipids soluble drugs (Unionized, Uncharged, Nonpolar) cross biological Membranes

Capillary permeability



439: Slit Junctions are seen





439: No Slit Junctions. The molecule has to diffuse through the membrane (has to be hydrophobic) or it has to be transported through carriers

Capillary Permeability

03

Endothelial cells in tissues other than brain have wide slit junctions allowing easy movement, permeation and distribution.

Blood Brain Barrier (BBB):

-Brain has tight junction BBB
-Only lipid soluble drugs or actively transported drugs can cross BBB
-Hydrophilic drugs (Ionized and Polar) cannot cross BBB
-Inflammation as in meningitis increase permeability to hydrophilic drugs
-e.g. Penicillin & Gentamicin

Placental Barrier: Lipid soluble drugs can cross placental barrier and enter the fetal blood.

Tissue Binding (Directly Proportional)

04

Drugs can bind to specific tissues and will have high volume of distribution (Vd) (Because the plasma concentration will be low therefore Vd)
E.g Tetracycline binds to bone (teeth-ca)

Plasma Protein Binding

05

in next slide

05

Plasma Protein Binding

Albumin:
Has an affinity for acidic drugs as warfarin, phenytoin, aspirin
Extensive & Strong plasma protein binding e.g. Albumin will cause more to stay in the blood compartment. They tend to have lower distribution (Vd)
Alpha 1-Acid glycoprotein
Has an affinity for basic drugs (Cationic) as diazepam quindine
In blood, drugs exist in two forms bound and unbound forms in equilibrium. Bound drugs become free when the unbound drugs run out (so it's as if they are stored while bound to proteins, and they come out when there is a demand)

Unbound drug (free) ⇌ **Bound Drug**

-drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

-In blood, drugs exist in two forms bound and unbound forms in equilibrium

-Extensive plasma protein binding will cause more drug to stay in the blood compartment .

-Therefore, drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

Bound Vs. Unbound Drug

Bound form of Drug (Eg. Heparin)	Unbound form of Drug
Non Diffusible form	Diffusible form
Cannot cross endothelial barrier	Cross endothelial barrier
Cannot combine with receptors	Combine with receptors
Inactive	Active (Cross any membrane)
Not available for metabolism & excretion	Available for metabolism (Liver) & Excretion(Kidney)
Long duration of action (T ½)	Short duration of action (T 1/2)

Characters & Consequences of Binding

-Usually Reversible

-Determines volume of distribution (vd)

-Slows drug metabolism & excretion

-Prolongs duration of drug action (t ½)

-Results in clinically important drug interactions

Displacement

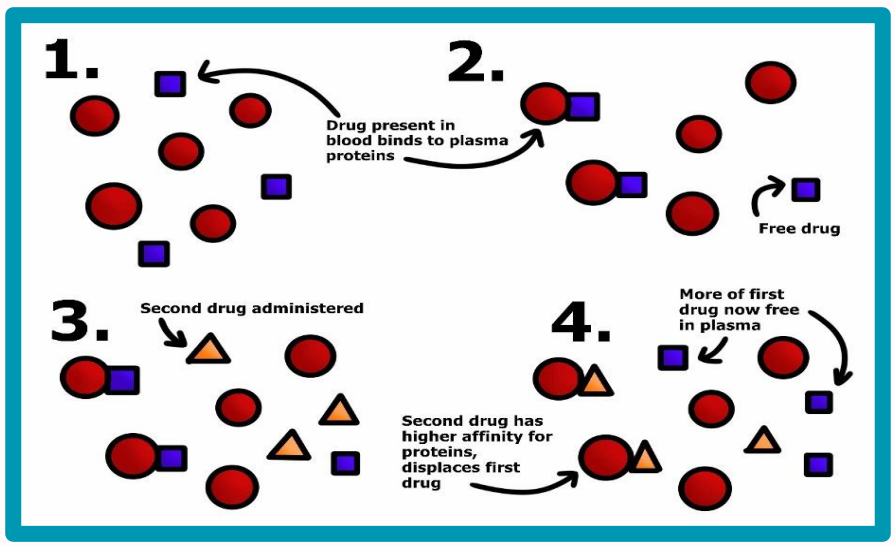
Competition for the same binding site of the plasma proteins may occur between two drugs, displacement of one drug & increasing its concentration & effects.

Aspirin + Albumin-Warfarin

Albumin-Aspirin +Free warfarin —> Bleeding

Explanation: Replacement of warfarin by aspirin will cause an abundance of free warfarin (anticoagulant) in the blood circulation and that will lead to bleeding. (Med439)

Extra info: The reason for displacement is the difference in protein affinity to drugs. The affinity of albumin to aspirin is higher than the affinity of albumin and warfarin. That's why when aspirin is freely present in the circulation. It throws warfarin out of albumin and binds to it. (Med439)



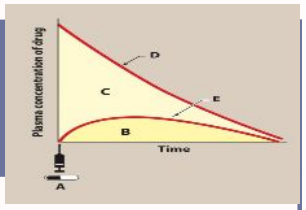
MCQs

Q1. Which compartment has 4 l ?			
a) one	b) two	c) three	d) multi

Q2. If a root of administration has 100% Bioavailability. F would be ? {from Med39}			
a) F > 1	b) F <1	c) F = 100	d) F = 1

Q3. Which of the following factors only affect Bioavailability ?			
a) Dosage forms	b) First pass effect	c) lipid solubility	d) food

Q4. A bound form of drug is ?			
a) Diffusible	b) inactive	c) active	d) has short t(1⁄2)

Q5. A novel medication designed to treat lymphoma can be administered via injection or orally. If the drug is given orally,an estimation of the area under the curve for this dose may be represented by which of the following letters in the following figure? 			
a) Letter A	b) Letter B	c) Letter C	d) Letter D

Answers:

1) A
2) D
3) B
4) B
5) B

SAQS

Q1.Name two factors affecting bioavailability:

1) Factors controlling drug absorption.
2) First pass effect.

Q2. What are the characters of an unbound form of drug?

Diffusible, active, can cross
endothelial barrier, has short (t1/2)

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