PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

Pharmacokinetics II: Bioavailability and Distribution

If you didn't understand any part from this lecture Click here!

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

Objectives

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

Any Future corrections will be posted on the editing file.
make sure to check it frequently

Click Here

Bioavailability

Unchanged = Not metabolized

Is the amount of **unchanged** drug that enters systemic circulation after administration and becomes available to produce pharmacological action .

Bioavailability can also be defined as the amount of **active** drug in the blood

- **IV 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 .

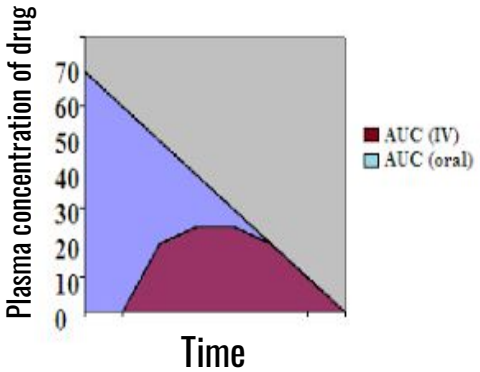
$$\text{Bioavailability} = \frac{\text{AUC (oral)}_{\text{or rectal or sublingual or I.M etc..}}}{\text{AUC(IV)}} \times 100$$

AUC = Area Under The curve

Factor affecting bioavailability :

1- factor controlling **drug absorption** MW, dosage forms, drug solubility, etc. 'in lecture 1" '

2- **First pass effect**



- **For Drugs administered orally**

Bioavailability may be less than 100% for two main reasons, **incomplete absorption** And **first pass metabolism**.

Note: The first pass effect affects the Bioavailability by decreasing it.

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

Bioavailability

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)

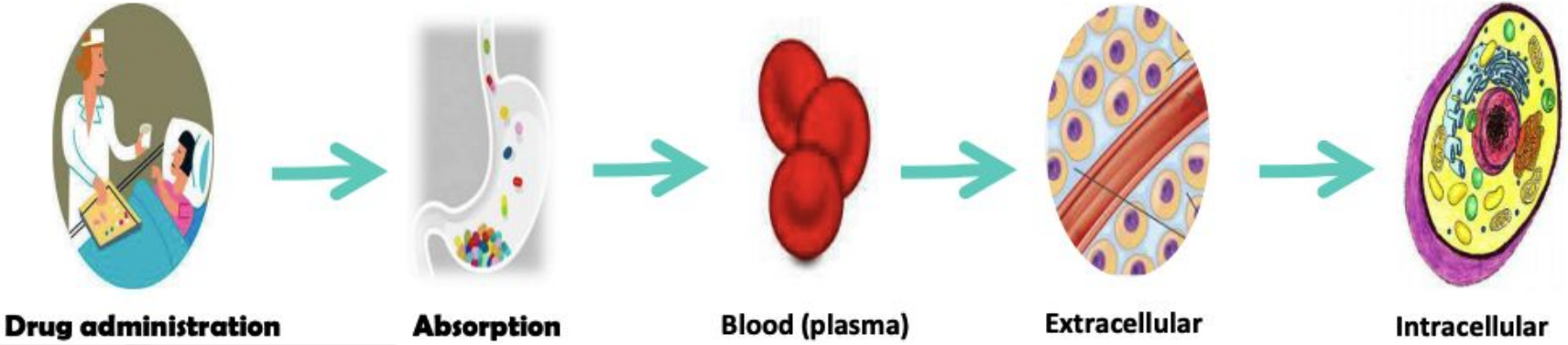
Relative bioavailability Is important to get an idea of how different formulation or routes of administration differ in their bioavailability .

- two pharmaceutical products are Bioequivalent when the rate and extent of bioavailability of active ingredients in two product are the same
- Dosage adjustment is required when changing formulation or routes of administration .

Distribution

Is the process by which drugs leave blood circulation and enter interstitium and/or the cells of the tissue .

- Lipid soluble drugs are distributed in the intracellular region. Because they can cross the cell membrane
- Water soluble drugs are distributed in the extracellular region.



Distribution & Apparent Volume of Distribution (Vd)

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

$$Vd(L) = \frac{\text{dose (mg)}}{\text{Plasma concentration (mg/L)}}$$

Why is Vd important ?

- To calculate loading dose
- Large Vd mean long duration of action .

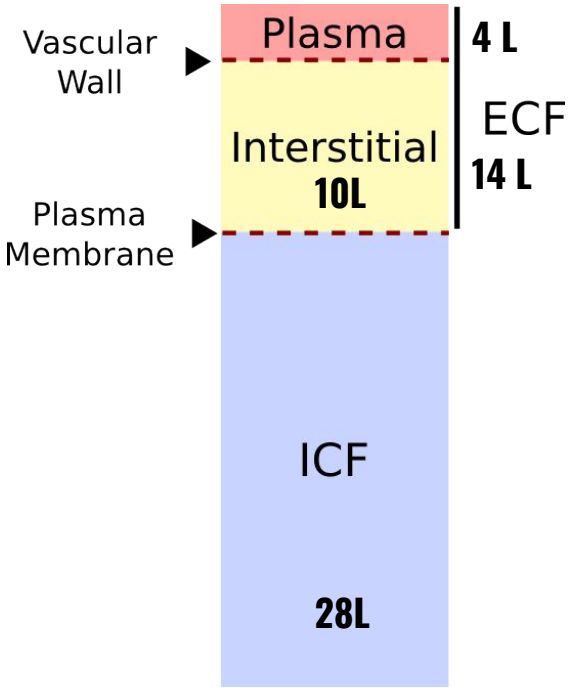
Explanation:

-Drug A: (100mg dose) Has high Molecular weight so it will stay in the plasma

Plasma concentration ↑ **Vd** ↓

-Drug B: (100mg dose) low molecular weight and lipid soluble so it will go into the tissue

Plasma concentration ↓ **Vd** ↑



The major body fluid compartment are	
extracellular fluid(22%)	intracellular fluid (35%)
1-Plasma (5% of body weight =4L) 2-Interstitial fluid (16%=10L)	Fluid present inside all cells in the body (28L)

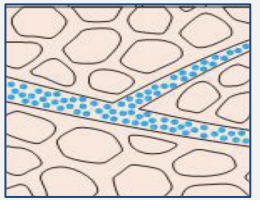
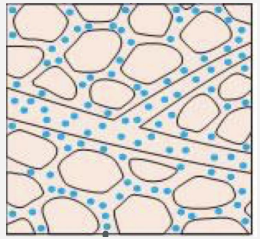
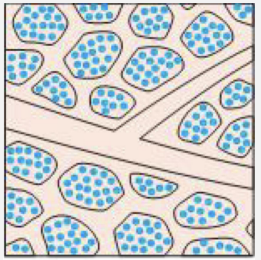
Note: when (Vd) is inside the plasma blood it will decrease due to metabolic reactions, but (Vd) will be high inside cells and organs.

Drugs may distribute through :

One compartment:
Plasma

Two compartments:
Plasma
↓
Intersitial fluid

Multi compartment:
Plasma
↓
Interstitial fluid
↓
Intracellular fluid

Compartment	Volume of distribution	Drug characteristic	Crossing	Example	Distribute in	Picture
One	4 L	1* High molecular weight 2* bind with plasma protein	**CAN Not** cross the endothelium (Due to high molecular weight)	4L Heparin (Anticoagulant)	Trapped in blood **(Plasma)**	
Two	4-14L (14):* plasma * Interstitial fluid	1* Low Molecular weight ↓ <u>But</u> 2* Hydrophilic (cannot pass through cellular membranes)	**Can pass through endothelium** to the interstitial fluid BUT **Can't cross cell membrane** (because its hydrophilic)	11 L Atracuronium (muscle relaxant)	**Extracellular Fluid**	
Multi	Equal to the total body water(42) or might be **higher**	Lipid soluble drugs will bind strongly with tissue **Vd > TBW**	**Diffusion** to intracellular fluid (can pass through membranes because its lipid soluble)	385 L > TBW -Digoxin (Cardiac glycoside) -Ethanol (34-41)=TBW	**Intracellular Fluid**	

Volume of distribution (Vd)

The characteristics are usually opposites

Low Vd

distributed in extracellular compartments (plasma & interstitial fluid).

Polar comp or lipid insoluble drugs.
E.g. 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.

High Vd

Low is Molecular weight
-Free drugs (not bounded to plasma proteins

Have higher concentrations in tissues than in plasma.

Lipid soluble

Distributed intracellularly

For example: digoxin, phenytoin, morphine

Note: Drugs that cross the blood brain barrier, will cross placental barrier and vice versa.

Factors affecting distribution

Cardiac output and blood flow

The **greater the blood flow** to tissues, the **more distribution that occurs** from plasma to interstitial fluids.

Drugs distribute more rapidly to **brain**,
liver & kidney > more than skeletal muscles & fat.

Physical and chemical properties of the drug

Most lipid soluble drugs (unionized, uncharged, nonpolar) cross biological membranes

Hydrophilic drugs (Ionized, Charged, Polar) go through slit junctions in endothelial cells of capillaries

- molecular weight
- PKa
- Lipid solubility

Capillary permeability

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

*Blood brain barrier (BBB):

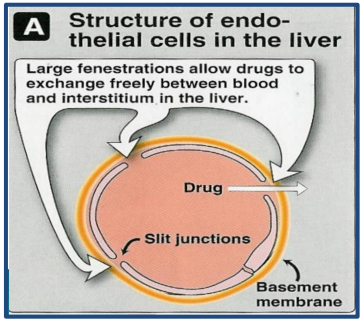
Brain has tight junction called Blood Brain Barrier

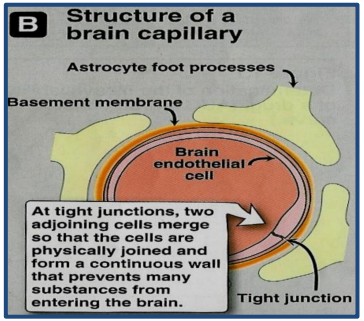
-Only lipid soluble drugs or actively transported drugs can cross BBB.
-Hydrophilic drugs (ionized or polar drugs) can not cross BBB.
-Inflammation as in meningitis increase permeability to hydrophilic drugs e.g. penicillin & gentamysin

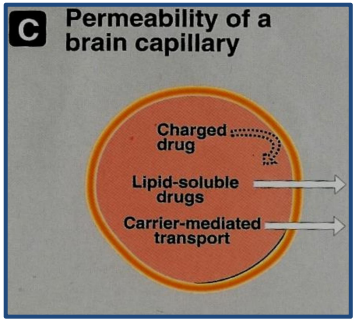
*Placental barrier

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

Slit junctions are seen in this pic







No slit junctions.
The molecule has to **diffuse** through the membrane (has to be hydrophobic) or it has to be transported **through carriers**

Factors affecting distribution	Plasma protein binding (VD عكسية مع)	Albumin	Has affinity for **acidic** drugs as warfarin, phenytoin, aspirin.	• Extensive & **strong plasma protein binding** will cause more drug to stay in the blood compartment.Therefore,they tend to have **lower distribution (Vd).** • 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
		Alpha 1- acid glycoprotein	Has affinity for **basic** drugs (cationic) as diazepam, quinidine.	
	Tissue binding (VD طردية مع)	• Drugs can bind to specific tissues and will have high volume of distribution (Vd). (because the plasma concentration will be low therefor Vd will be high) E.g. Tetracycline binds to bone		

Opposites

Bound form of drug	Unbound form of drug
non diffusible	diffusible
can't cross endothelial barrier	cross endothelial barrier
can't combine with receptors	combine with receptors
inactive	active
not available for metabolism & excretion	available for metabolism & excretion
has long duration of action (t ½).	has short duration of action (t ½).

Characters & consequences of Binding

- Usually reversible.
- determines volume of distribution (vd).
- Slows drug metabolism & excretion.
- Prolongs duration of drug action (t1/2).
- Result in clinically important drug interactions.

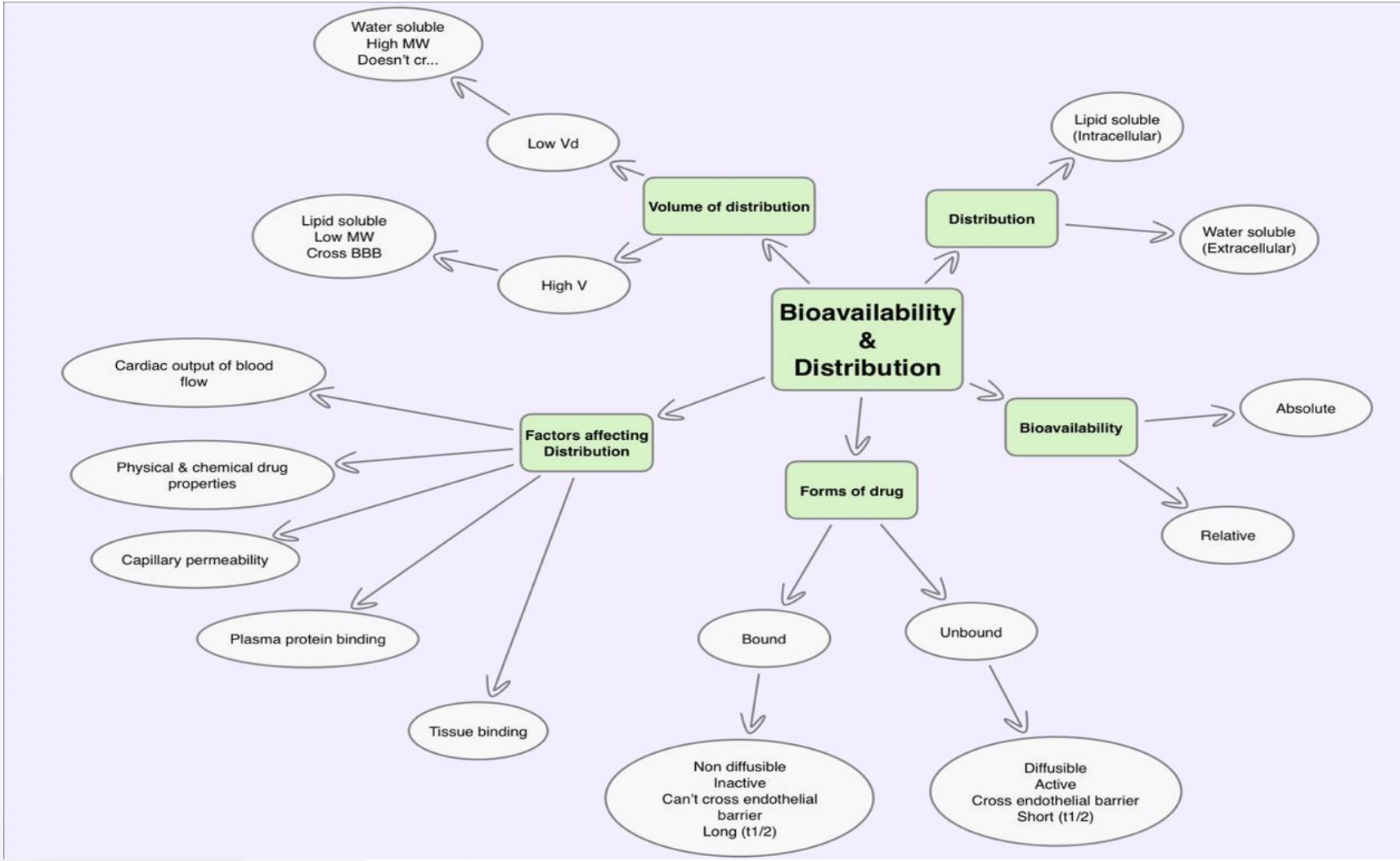
Displacement

Competition between two drugs for the same binding site on the plasma proteins may cause → displacement of one drug & increasing its concentrations & effects.

e.g.
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

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 instead


Bioavailability & Distribution
Volume of distribution
Low Vd
Water soluble High MW Doesn't cr...
High V
Lipid soluble Low MW Cross BBB
Distribution
Lipid soluble (Intracellular)
Water soluble (Extracellular)
Factors affecting Distribution
Cardiac output of blood flow
Physical & chemical drug properties
Capillary permeability
Plasma protein binding
Tissue binding
Forms of drug
Bound
Non diffusible Inactive Can't cross endothelial barrier Long (t1/2)
Unbound
Diffusible Active Cross endothelial barrier Short (t1/2)
Bioavailability
Absolute
Relative

MCQ

MQ team439 made awesome review questions
Check them out here!

1) Lipid soluble drugs are distributed in

A) Extracellular region.	B) Intracellular region.	C) Plasma	D) Interstitial fluid

2) Drugs distribute more rapidly to...

A) Skeletal muscles	B) Connective tissues.	C) Brain.	D) Stomach.

3) An unbound form of drug is...

A) Diffusible.	B) Inactive.	C) Non Diffusible.	D) Has long t(½)

4) If a root of administration has 100% Bioavailability. F would be...

A) F > 1	B) F <1	C) F = 100	D) F = 1

ANSWERS

1	B
2	C
3	A
4	D

SAQ

1) Drug exists in blood in two forms, what are they?

2) Name 3 factors affecting distribution.

3) In what compartment do lipid soluble drugs get absorbed in?

4) What are the characters of an unbound form of drug?

ANSWERS

A1) ~~Bound & unbound.~~

A2) ~~Capillary permeability, plasma protein binding & tissue binding.~~

A3 ~~In the intracellular compartment.~~

A4) ~~Diffusible, active, can cross endothelial barrier, has short (t1/2)~~

GOOD LUCK!

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