MED441
KING SAUD UNIVERSITY

Bioavailability and Distribution

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

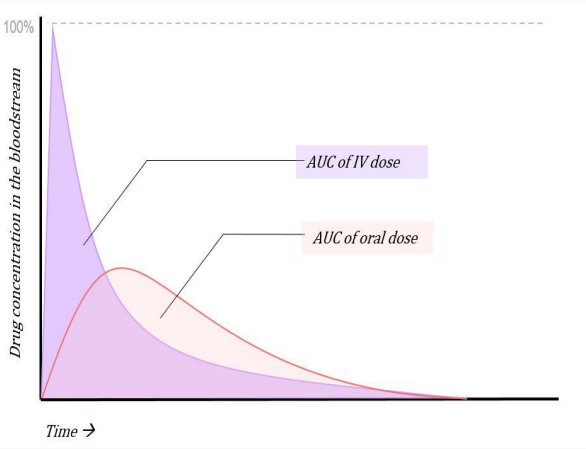
For any future corrections Editing file

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

Objectives

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

رغم كل الصعوبات والحواجز في ممارسة مهنة الطب ، إلّا أن إرتداء المعطف الأبيض ومساعدة الناس يستحق كل هذا العناء



Bioavailability

is?

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

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.

equation

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

AUC = Area Under the Curve

Notes:

Bioavailability= توافر الدواء في الدورة الدموية

unchanged= (دواء لم يتغير بشكل عام ، بعد ما مرّ بالكبد ماتغير)

Intravenous = (I.V)= Bioavailability دائماً ال

١٠٠٪ لانه يُحقن في الدم مباشرةً عكس الطُرق الاخرى

systemic circulation = blood systemic circulation

Notes

الريليتف مُقارنة بين نفس الادوية ولكن من شركات تجارية مختلفة عشان نعرف اي الدوائين افضل

Bioavailability

Absolute

The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation. the equation in the previous slide

Relative

is determined when two products are compared to each other, not to an intravenous standard. It has to be the same route , it cannot be I.V

This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation.
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.

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dosage adjustment is required when changing formulations or routes of administration.

Bioequivalence

Two pharmaceutically products are bioequivalent when the rate and extent of bioavailability of active ingredients in two products are the same.

Bioequivalence = bioavailability التساوي من حيث

What are the Factors that affect bioavailability?

factors that controlling drug absorption "Dosage forms,Molecular weight,Food" Lecture 1 Slide 20

First pass effect

Distribution

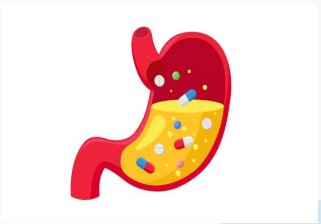
Is the process by which drugs leave blood circulation and enters the interstitium and/or the cells of the tissues.

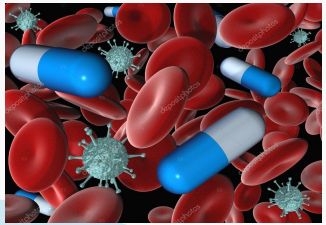
- **Lipid** soluble drugs are distributed in the **intracellular** region. Because they can cross the cell membrane
- **Water** soluble drugs are distributed in the **extracellular** region. Because they can not cross the cell membrane . Med439

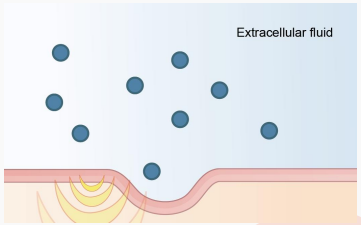
Notes

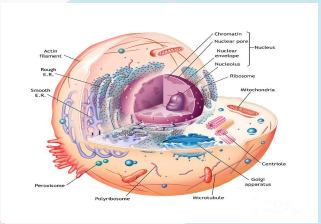
Not necessary to pass through all stages may stop at the stage of blood only

Drug Administration → Absorption → Blood → Extracellular → Intracellular

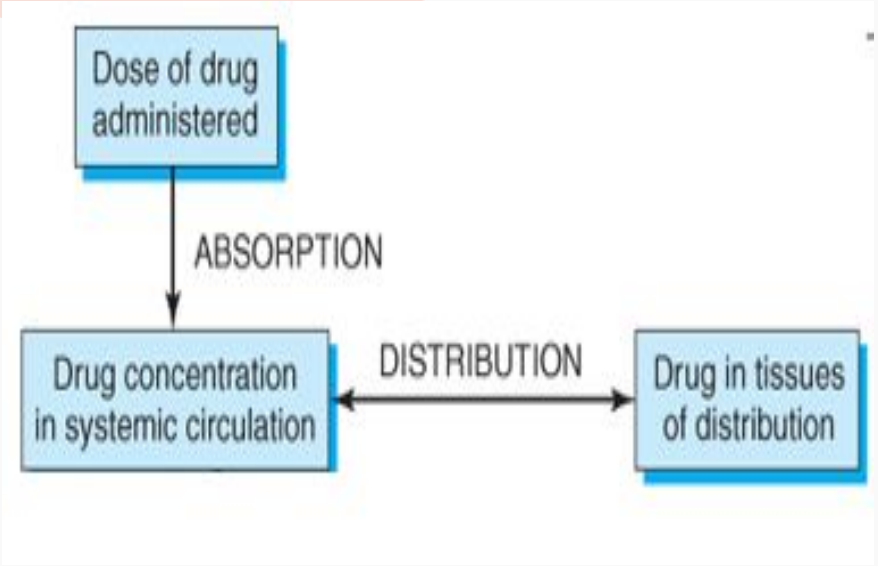








Apparent Volume of Distribution (Vd)



(VD) : is the ratio of drug amount in body (dose) to the concentration of drug in blood (plasma concentration)

$$VD\ (L) = \frac{\text{Dose (mg)}}{\text{Plasma concentration (mg/L)}}$$

Why is Vd important?

1. To calculate loading dose
2. Large Vd = means long duration of action

Loading dose is the large initial dose that is given to achieve rapid therapeutic plasma level

The major body fluid compartments

Extracellular Fluid(22%)

*** In male slides (21%)**

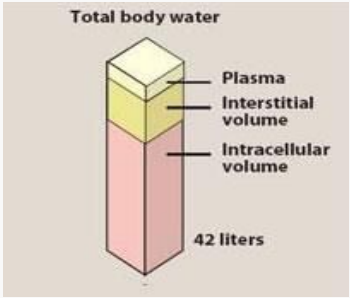
1-Plasma
(5% of body weight =4L)
2-Interstitial fluid
(16%=10L)

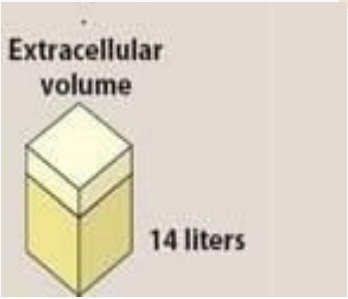
Intracellular Fluid (35%)

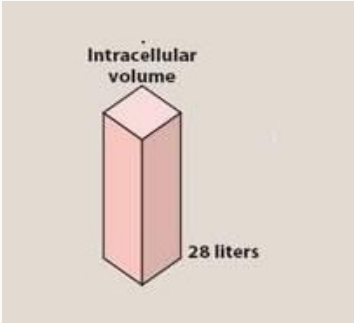
fluid present inside all cells in the body (28 L).

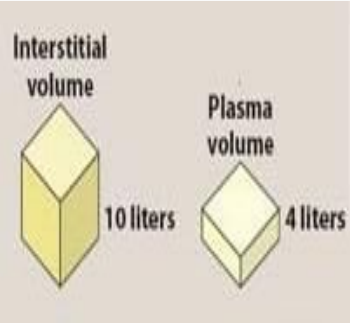
Extra information : ECF is 22% of the body fluids
the plasma(5%) and interstitial fluids(16%) = 21% (drugاللي ياصلها)
The remaining 1% is for TCF (Transcellular fluids)

volume of distribution (vd)









Drugs may distribute through

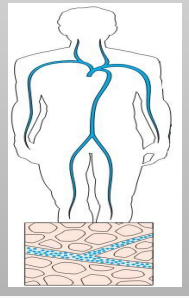
Plasma compartment

(one compartment)

- Vd: around 4 L
- Very high molecular weight drugs, or drugs that bind(محبوس او مرتبط) to plasma proteins
- Can not moves across endothelial cells of capillaries
- Drugs are trapped in blood

- Example: heparin 4L

يستخدم مانع لتجلط يعطي تأثيره بس لدم(anticoagulant)



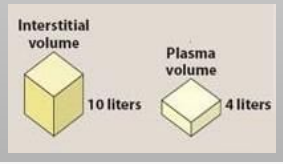
Extracellular fluid

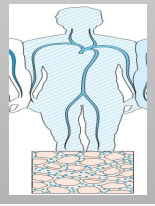
(two compartment)

- Distribute through extracellular fluids.

- Pass endothelium into interstitial fluids BUT **can not cross** cell membranes to intracellular fluids.(but they can cross the endothelial cells)
- Drugs that have a **low molecular weight** but are hydrophilic.
- Vd: between 4 and 14 L.
- E.g. atracuronium 11 L

يستخدم مع عقاقير أخرى للقيام بارخاء العضلات خلال العمليات الجراحية



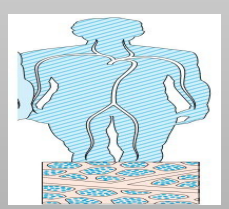


Total body water =extracellular and intracellular

(multi-compartments)

- Diffusion to **intracellular** fluid
- For **lipid soluble** drugs
- Vd **equal** to total body water.
- Ethanol 38 L (34-41)
- Drug that **binds** strongly to **tissues**. Vd higher than total body water.
- Digoxin:385 L

يستخدم لعدد كبير من الأمراض القلبية مثل الرجفان الأذيني وفشل القلب الاحتقاني



Volume of Distribution (vd)

Drugs with low Vd

•distributed in **extracellular** compartments
(plasma & interstitial fluid).
•Polar comp or lipid **insoluble** drugs.
e.g.
gentamycin, atracurium
•High MW e.g. heparin – insulin.
•High plasma protein binding e.g. warfarin (anticoagulant).
•Do not cross **BBB** (Blood Brain Barrier)or **placental barriers.**

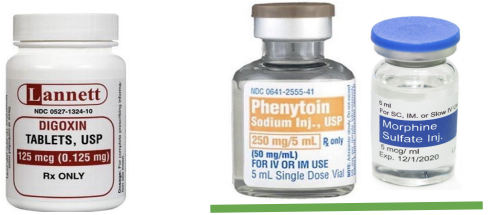
These types of drugs are safe for pregnant women to use because they can not cross to placental barrier

Drugs with high Vd

•Have **higher** concentrations in **tissues** than in **plasma**.
•Lipid soluble.
•Distributed intracellularly

e.g. digoxin, phenytion, morphine
(يستخدمونهم لعلاج الصرع والتشنجات)

They have an effect on the central nervous system



FACTORS AFFECTING DISTRIBUTION

Cardiac output and blood flow

علاقة طردية بينه وبين distribution

Physical and chemical properties of the drug

Capillary Permeability

Plasma protein binding

the highest plasma protein binding the least distribution

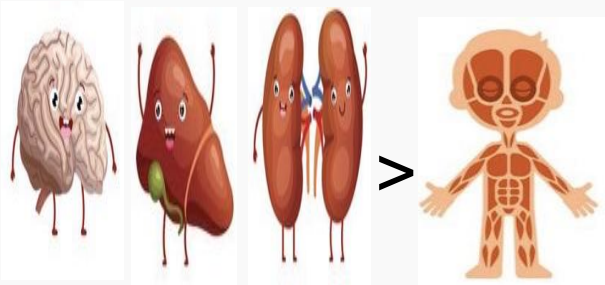
Tissue binding

علاقة طردية بينه وبين distribution

Factors affecting Distribution

1-Cardiac output and blood flow

•Drugs distribute **more rapidly** to Brian -liver -kidney > more than skeletal muscles - fat.



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

2- Physical and chemical properties of the drug

◦ Molecular weight(علاقه عكسيه مع distribution)
◦ Pka.
◦ Lipid solubility(علاقه طرديه)

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

•Hydrophilic drugs (**ionized, charged, polar**) do not readily cross membranes but go through slit junctions in endothelial cells of capillaries.

Factors affecting Distribution

3-Capillary permeability

4-Tissue binding

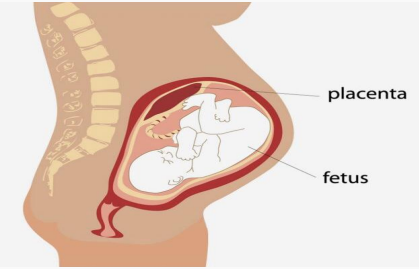
5-Plasma protein binding

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

- Drugs can bind to specific tissues and will have high volume of distribution (Vd)
- Tetracycline bind to bone

Placental barrier

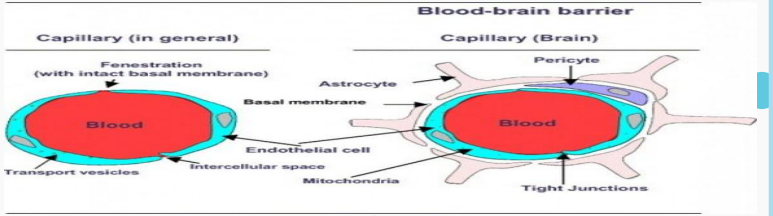
Lipid soluble drugs can cross placental barrier
and enter the fetal blood.

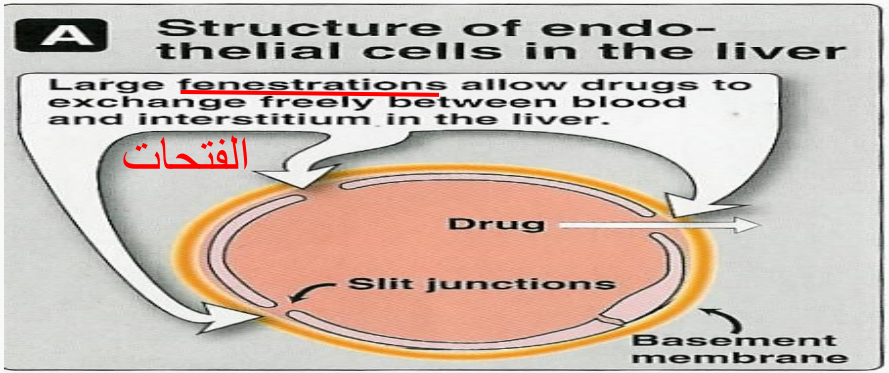


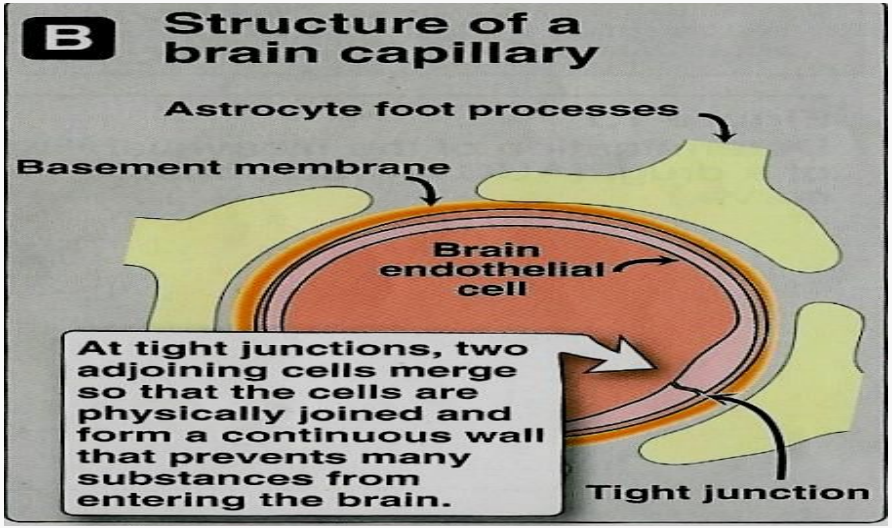
Blood brain barrier (BBB)

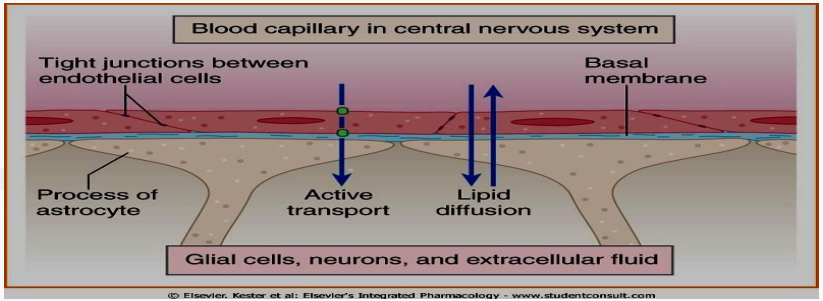
- Brain has tight junction
  Brain Barrier (BBB)
- **Only lipid soluble** drugs or **actively transported** drugs can cross BBB.
- Hydrophilic drugs (ionized or polar drugs) can not cross BBB.
- Inflammation as in meningitis **increase** permeability to hydrophilic drugs
- e.g. penicillin & gentamycin

If these medicines are given to a healthy person can not cross BBB but in the inflammation can cross

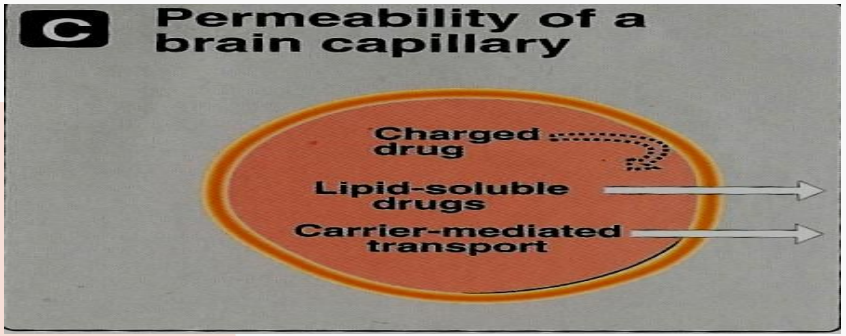








Tight junction they are similar to soldiers because they do not allow anything to enter the brain but some specific things



Plasma protein binding

◦ 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).
بيكون الدواء محبوس وممسوك داخل الدورة الدموية واللي بتكون حابسة البروتين

Examples of plasma proteins

Albumin

Has affinity for acidic drugs as warfarin, phenytoin, aspirin

Alpha 1- acid glycoprotein

Has affinity for basic drugs (cationic) as diazepam, quinidine.

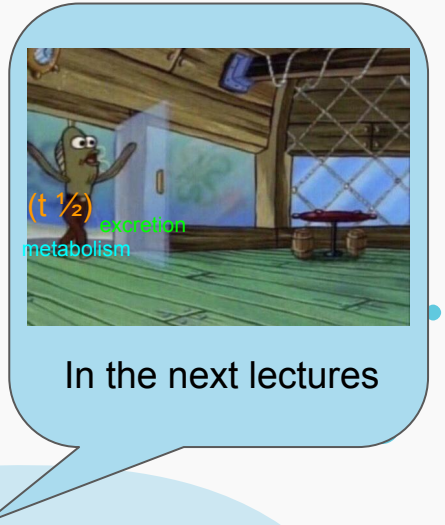
•drugs which bind strongly to plasma protein tend to have lower distribution (Vd).
• In blood, drugs exist in two forms bound and unbound forms in equilibrium

Unbound drug (free) ⇄ bound drug

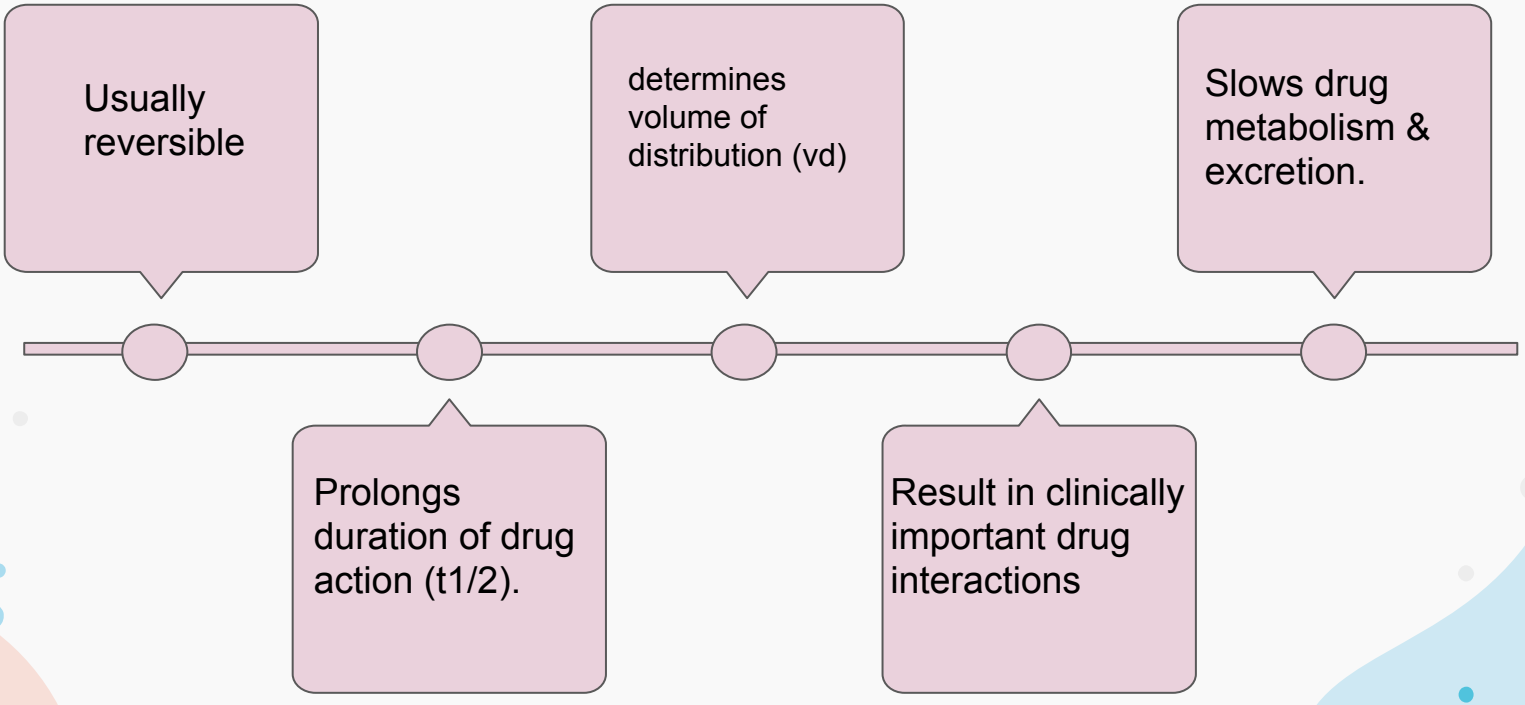
Unbound drug
اذا أثر على الجسم وخلص بتختفي هذي الجهة وبتعطيه الجهة الثانية(bound drug)

bound drug
يكون مثل المخزن كل ماتخلص الجهة الثانية بتاخذ منه بدون ما يأثر على الجسم :

Bound form of drug	Unbound form of drug(free)
non diffusible form	diffusible form
can not cross endothelial barrier	cross endothelial barrier
can not combine with receptors يعني مايعطي اي تأثير	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



Example of Drug-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.

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 instead Med439

MCQs

Q1. Which one of these drugs does not require to be absorbed ?

A)Oral B)intravenous C)rectal

Q2. A drug is distributed through 2 compartments is found in

A)Plasma B)ICF C)ECF

Q3. A drug with large Vd mean that the drug has ?

A)Short duration of action B)Long duration of action C)No action

Answer

Q1=B
Q2=C
Q3=B

SAQ

1. When the rate and extent of bioavailability of active ingredients in two products are the same the two pharmaceutically products called ?

2. Drug exists in blood in two forms, what are they?

3. Name 3 factors affecting distribution.

4. In what compartment do lipid soluble drugs get absorbed in?

Answers

1-Bioequivalent
2-Bound & unbound
3-capillary permeability , plasma protein binding & tissue binding
4-in the intracellular compartment

Thank you

كل آتٍ قريب وكل همٍّ يلقى فرج

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