Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Bioavailability and distribution

Objectives:

By the end of the lectures, you should be able to define the following:

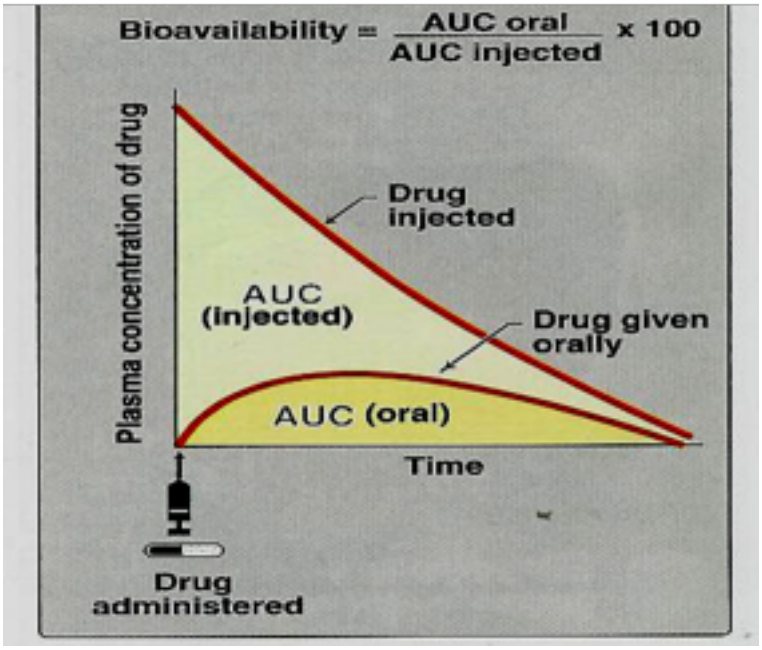
- Major body fluid compartments
- Concept of compartments.
- Apparent volume of distribution (vd).
- Plasma protein binding.
- Tissue binding.

Titles Very important Terms Extra informations

Success Doesn't Come To You, You Go To It!

Bioavailability

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



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

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

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

Absolute bioavailability:

-Comparing between the I.V bioavailability as a standard formulation and the bioavailability of the same drug taken by any other route.

Relative bioavailability:

- Determined when two products are compared to each other, not to an intravenous standard.

e.g Tylenol (paracetamol 500 mg) compared to Panadol (paracetamol 500 mg).

❖ Dosage adjustment is required when changing formulation or routs of administration.

The importance of the relative bioavailability:

1- To determine that the generic formulation is bioequivalent to another formulation .

2- To get an idea of how different formulations or a different routes of administration could change the bioavailability.

Bioequivalence:

We use this term when the rate and the extent of bioavailability of active ingredients in two products are the same.

Factors affecting Bioequivalence:

1- Same factors controlling drug absorption.

2- First pass effect.

You should now the difference and the meaning of absolute bioavailability and relative and bioequivalence

The major fluid compartments :

Extra cellular (1/3of TBW):

- Plasma (20% of ECF)
- Interstitial fluid (80 %of ECF)

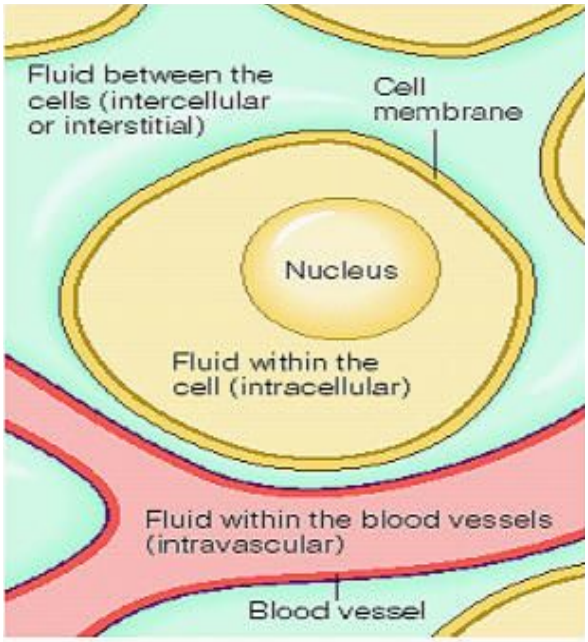
Intracellular(2/3 of TBW):

- fluid present inside all cells in the body (24_28 L)

Volumes of some compartments of the adult human body in relation to Vd:

- ***Total body water 0.6 L/Kg Body Weight***
- ***Intracellular water 0.4 L/Kg Body Weight***
- ***Extracellular water 0.2 L/Kg Body Weight***
- ***Plasma 0.04 L/Kg Body Weight***

Total Body Water = 0.6 x Weight



Drugs maybe distributed through :

One compartment	*2 compartments*	*Multiple compartments*
Plasma: blood inside capillary	***Extracellular : plasma + interstitial fluid***	***Extra cellular + intracellular : total body water***

Apparent Volume of Distribution (VD)

Objective 3:define the Apparent volume of distribution (vd).

It is the ratio of drug amount in the body (dose) to the concentration of drug in blood.

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

Vd is important in:

calculate loading dose

-Prediction of the duration of action:

1-High VD means long duration of action

2- Low VD means short duration of action

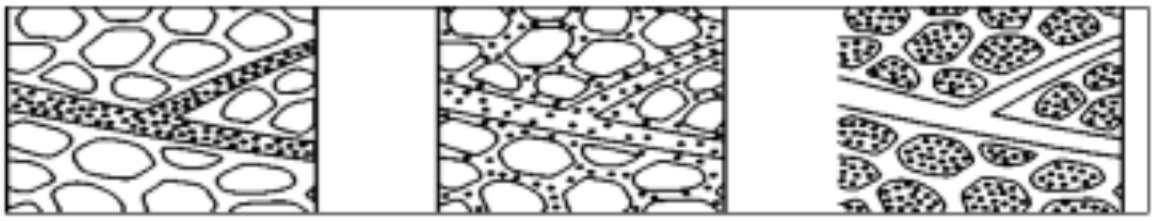
-The major body fluid compartments:

The major body fluid compartments:

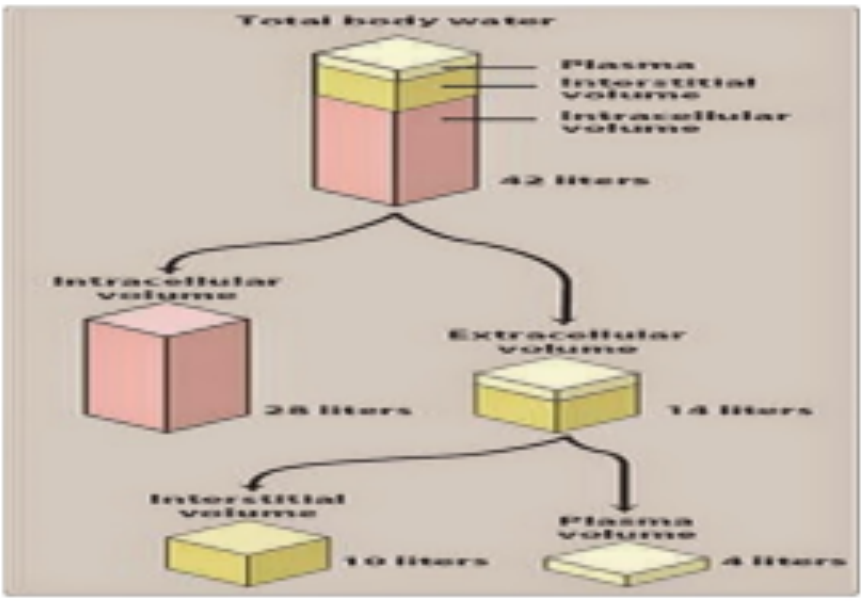
- Intracellular fluid : (35 %) fluid present inside all cells in the body (28 L)
- Extracellular fluid (22%):-
  - -plasma(5% of body weight=4liters)
  - -Interstitial fluid (16 % = 10 liters)

Total body fluids
(70% of body weight in 70-kg individual)

Plasma volume(4L) + Interstitial volume (10 L) + Intracellular volume (28 L) = Total body fluid (42L)



Volume of distribution:



ميم جدًا ان نفهم ان:
Intracellular have much volume than Extracellular

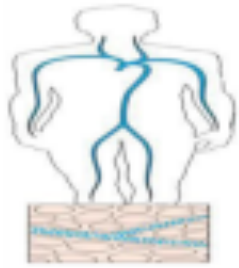
Volumes of some compartments of the adult human body in relation to Vd:

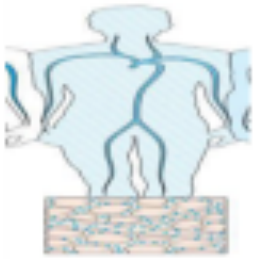
- **Total body water:**
  0.6L/Kg Body Weight
- **Intracellular water:**
  0.4 L/Kg Body Weight
- **Extracellular water:**
  0.2 L/Kg Body Weight
- **Plasma:**
  0.04 L/Kg Body Weight

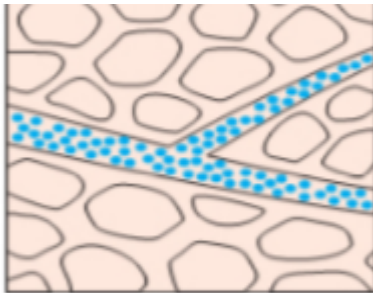
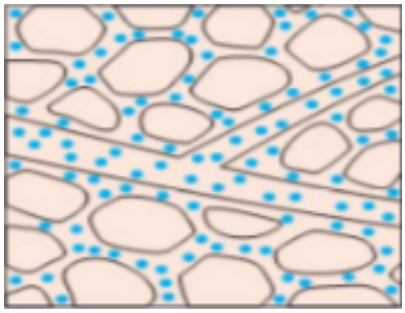
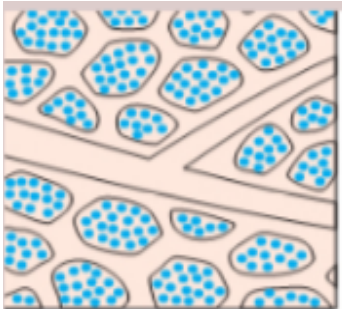
Total Body Water =0.6xWeight

Drugs may distribute through:

One compartment
Plasma compartment
Two compartment
Extracellulr compartment
Multiple compartment
Intracellular compartment

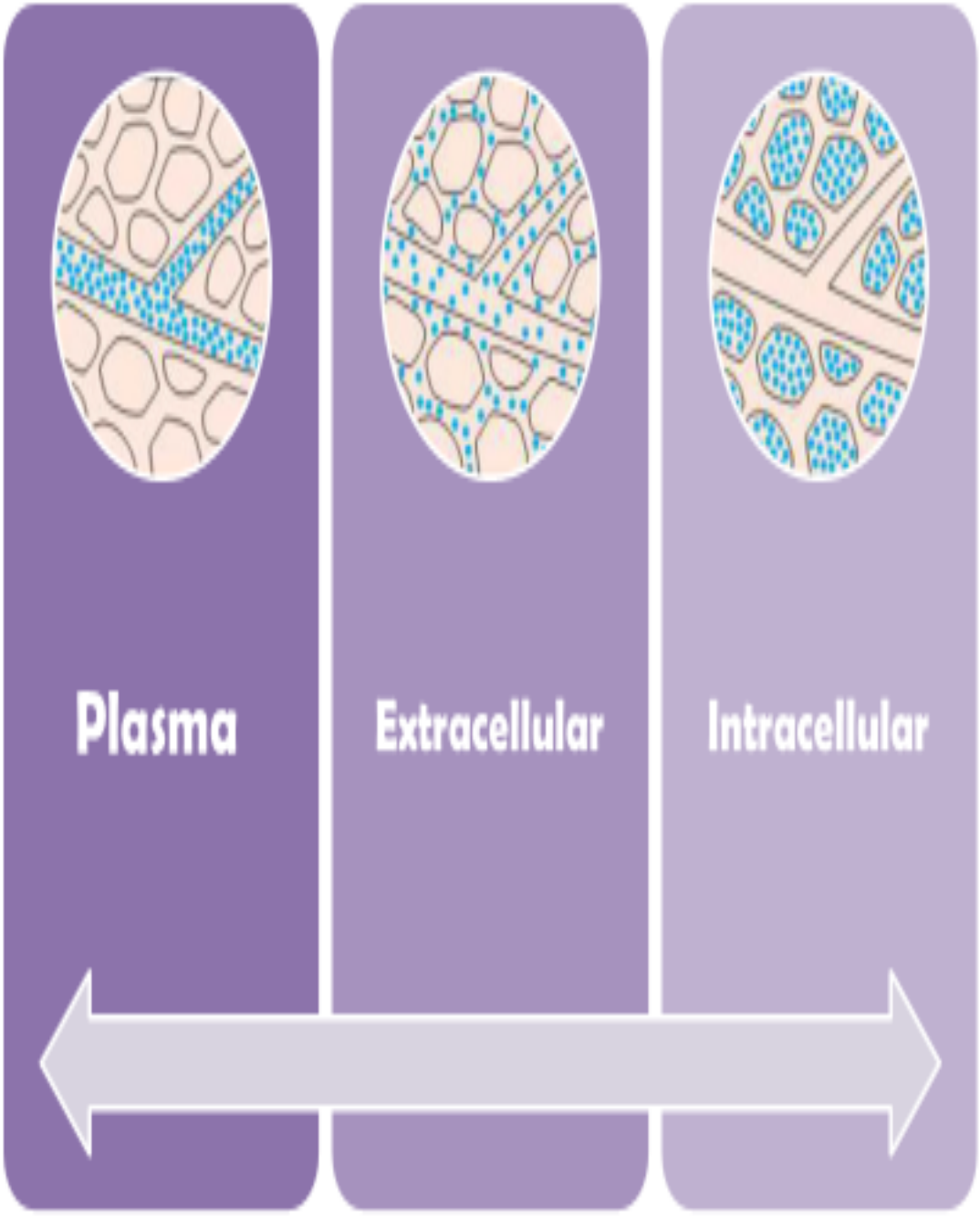




	Plasma (one compartment)	Extracellar (Two compartments)	Intracellular (Multi-compartments)	
VD	• 4L	• 4-14L • (10+4)	VD > Total body water (42)	**VD=Total body water (42)**
Characteristics of the drug	**Very high molecular weight** drugs Or Drugs that bind to plasm proteins (البروتين يقيد حركته)	Drugs that have a **low molecular weight** But Are **hydrophilic**	**Lipid soluble drugs.**	**Drug that binds strongly To tissues**
Distribution	Can not moves across endothelial cells (lining layer) of capillaries So Drugs are trapped in blood	Pass endothelium into interstitial fluids But can not cross cell membranes to intracellular fluids	Pass the cell membrane And enters the cell	
Examples	Heparin: (Anticoagulant) 4L	Atracurium: 11L	Ethanol: 38 L (34-41)	**Digoxin 385L**
Pictures				

Note: Digoxin binds strongly to tissues so that it's volume of distribution is higher than TBW

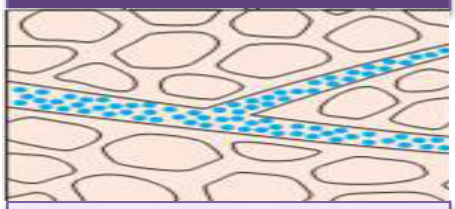
Main Body Fluid Compartments



Distribution through the compartments

One compartment (Plasma)

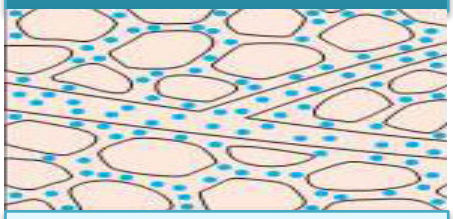
High molecular weight or **High plasma protein binding drugs**



Vd = 4L (amount of blood)
They can **NOT** pass endothelial cells of capillaries. *So they are trapped in the blood*
*Molecules with low molecular weight can pass, but when they are bound to plasma proteins, their weight increases.
Example: Heparin 4L

Two compartments (ECF)

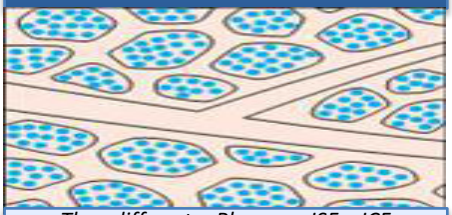
Low molecular weight, but are *hydrophilic*
Why hydrophilic? Because they can not pass the cell membrane



Vd= 4-14L (Plasma + ISF)
They **CAN** pass the endothelium but **NOT** cross cell membranes
*Lipid solubility increases Vd
Example: Atracurium 11L

Multi compartments (ICF)

Lipid soluble drugs



They diffuse to: Plasma > ISF > ICF
Therefore, they distribute to the whole body fluids.
Vd = Total Body Water (42L)
Drugs that bind strongly to tissues have higher Vd than TBW
Examples: Ethanol 38L (34-41)
Digoxin 385L
**Alcohols bind strongly to tissues, that's why large amounts of it causes problems in tissues*

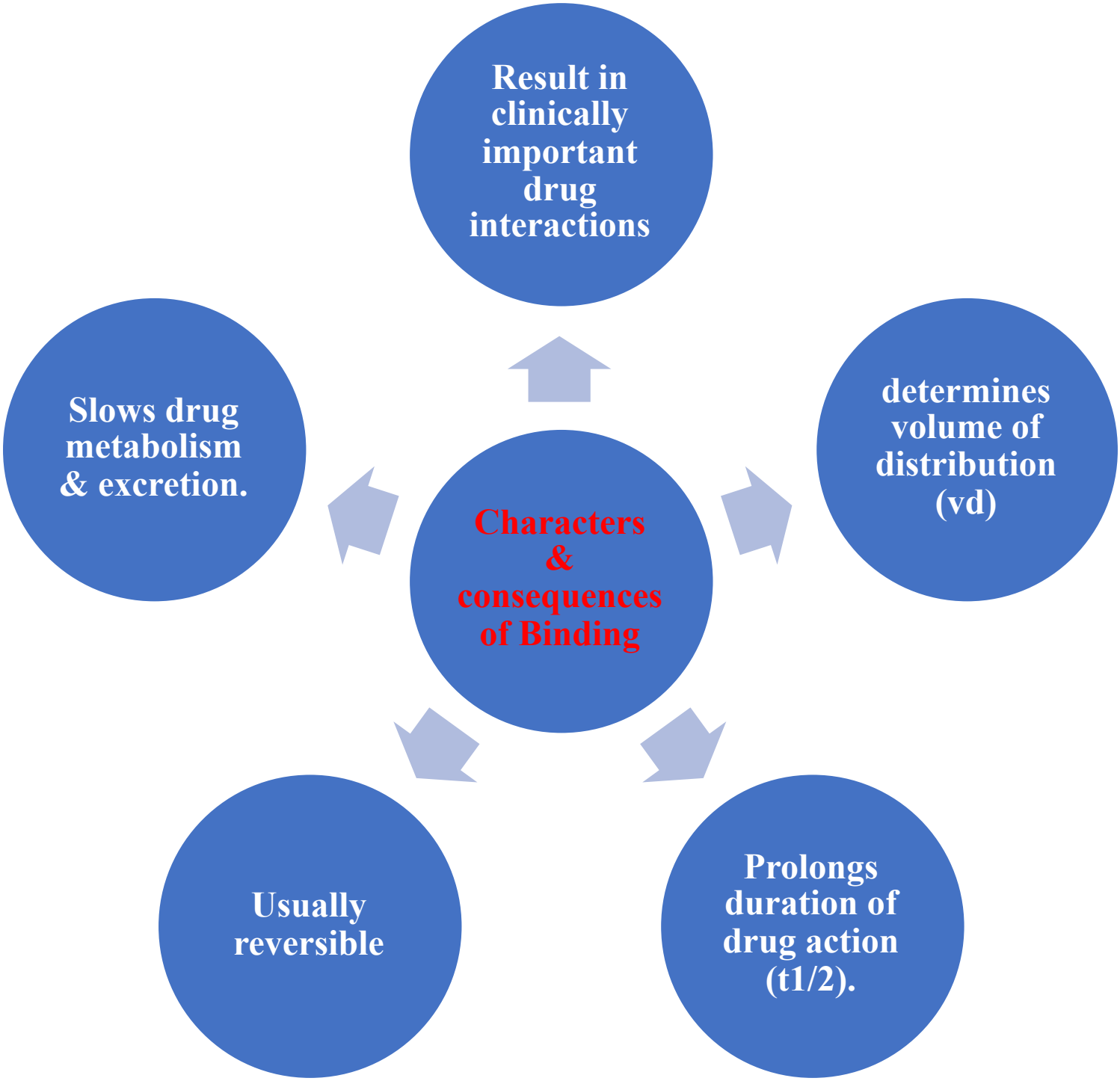
Example: Heparin (Anticoagulant)

If a pregnant woman gets thrombosis *(جلطة)* we don't want to give the anticoagulant to her, because it could reach the baby and cause hemophilia *(سيولة بالدم)*

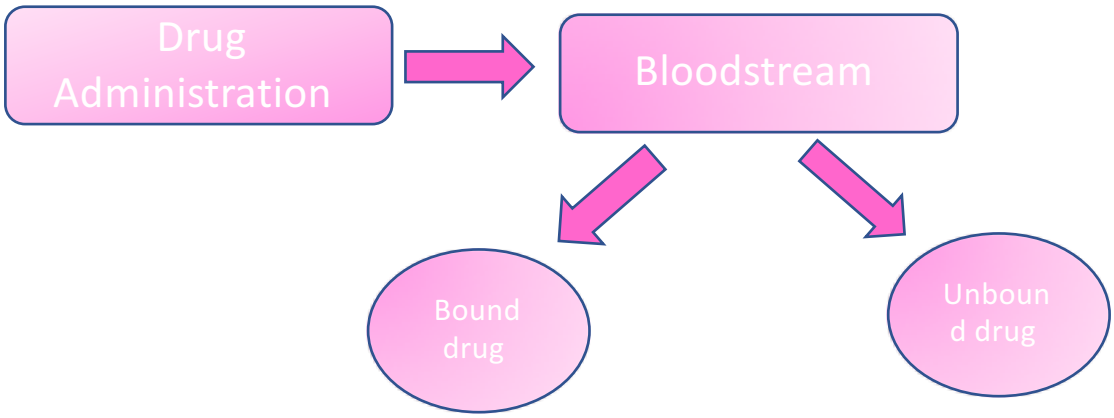
So when we pick a drug we check the kinetics of the drug to avoid problems.

For example we have Warfarin & Heparin.

Heparin is the better choice, Why? Because Heparin has higher molecular weight, therefore distribution will be less, which means that it will not pass the placental barrier thus won't reach the fetus. (Another note: Heparin works in the blood, so that means it doesn't need to move to another compartment in the mother)


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

Plasma protein binding



Displacement

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

Aspirin + Albumin-warfarin ⟶

Albumin-aspirin + free warfarin ⟶ bleeding

Tissues Binding

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

For example : Tetracycline bind to **bone**

Bound form of drug	Unbound form of drug
non diffusible form	diffusible form
can not cross endothelial barrier	cross endothelial barrier
can not 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).

MCQs

- **1. Which one of the following is a correct example of a multi-compartment distribution:**

A. Plasma > ICF > ISF
B. ICF > Plasma > ISF
C. Plasma > ISF > ICFvPlasma > ECF > ICF

2. If a drug is lipid soluble, which compartment would it most likely be found in?

A. In the plasma
B. In the interstitial fluid
C. In the blood
D. In the intracellular fluid

3. The Vd for Atracurium is:

A. 11L
B. 5L
C. 14L
D. 4L

4. Drugs with high molecular weight, but are not plasma protein bound can pass the endothelium?

A. True
B. False

5.A drug is distributed through 2 compartments is found in ?

A-Plasma b-ICF c- ECF D-Interstitial fluid

6.A drug is found in intracellular fluid is distributed through :

A- One compartment b-Two compartments c-Multiple compartments d-non of the above

Answers

1-C 2-D 3-B 4-A 5-C 6-C

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Useful videos:

Pharmacokinetics 3 - Distribution

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