
للوصول الى guidance الفارما و تفاريغ المادة كاملة :

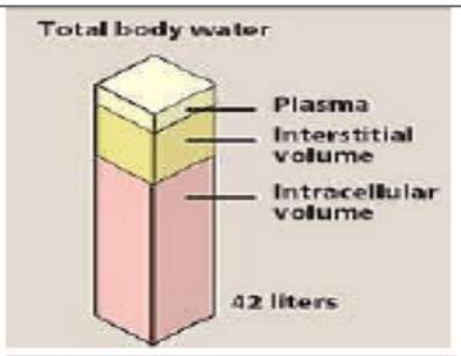
كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

# DISTRIBUTION OF DRUGS

❖ It is the passage of drug through body compartments which are separated by capillary walls and cell membranes. Leaving the blood , entering the tissues

❖ Body fluid compartments:




(plasma) ← Normal adult weight

1- intravascular volume = 4 L/70 Kg

2- interstitial volume = 10 L/70 Kg

(Extracellular volume)

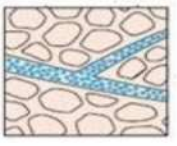
3- intracellular volume = 28 L/70 Kg

*Total body fluid = 42 L/70 Kg

**The Fluids in our body helps the drug to be distributed into the cells by 4 patterns**

**1. Plasma compartment (one compartmental model):**

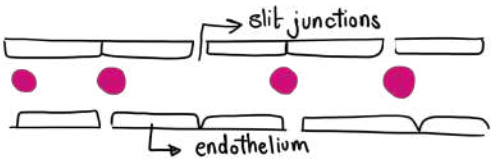
- If a drug:
  - has a **high molecular weight** or
  - **binds strongly to plasma proteins**



4L

- It is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment.
- e.g. Heparin , Dextran. Heparin injection is an anticoagulant.

Increase blood volume and blood pressure

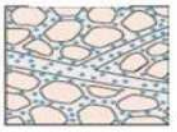



ظو ال drug اكبر من size تبع ال junction حيفل موجود بالبلازما ، السبب يا إما طبيعة الدواء هيك أو انه مرتبط مع plasma proteins .

**2. Extracellular fluid (two compartmental models):**

Water soluble

- If a drug has a **low molecular weight** and is **hydrophilic**



14L

- It can move through the endothelial slit junctions of the capillaries into the interstitial fluid BUT cannot move across the lipid membranes of cells
- e.g. Aminoglycoside antibiotics, Mannitol.

هدول ال drugs حجمهم حغير فبعدوا ال junctions . وكمان Hydrophilic

بكون متوزع بمكانين (interstitial fluid+ intravascular)

The aminoglycosides include gentamicin, amikacin, tobramycin, neomycin, and streptomycin.

Mannitol is Indicated for reduction of intracranial pressure associated with cerebral edema and/or brain mass.

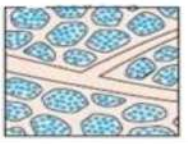
### 3. Extra & intracellular fluid (multi-compartmental model)

- If a drug has a **low molecular weight** and is **lipophilic** → يبعدوا ال cell membrane
- It moves into the interstitium through the slit junctions and also moves through the cell membranes into the intracellular fluid.
- Some drugs uniformly distribute throughout whole body water e.g. Ethanol, sulphonamides.

42L

بكون متوزع ب 3 أماكن ( **intracellular fluid+ iterstitial fluid+ plasma**)
بس في ادوية ما بتتوزع على الثلاث أماكن بالزبط ممكن تكون مركزة على ال **tissue** اكتر من باقي الأماكن.

- the majority of drugs distribute into several compartments, often binding cellular components for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells)



لو مسك بأجزاء جوا الخلية بكون بالأكثر جوا ال cellular components

بتروح عمكان معين و بتكون فيه بكمية كبيرة

### 4. Tissue reservoir: Drugs concentrated in certain tissues

steroid gland

- **Iodine** in thyroid & salivary glands
- **Calcium & tetracyclines** in bone & teeth
- **Chloroquine** in liver → It is used to treat Malaria , its parasite lives in the liver
- **Thiopental** in fat (Redistribution ??)

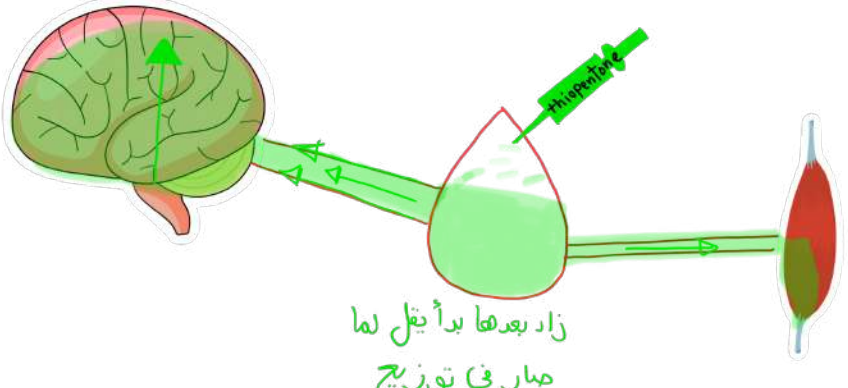
لـ مخدر عام على CNS

**Redistribution of drugs :**

* it means when you give a drug it is first distributed somewhere and then it is redistributed to somewhere else.
* this is seen with highly lipid soluble drugs such as thiopental , because these drugs cross the biological membrans easily.
* the drug first get distributed to organs with high blood supply (ex: brain, heart, kidney) and because they are lipid soluble they diffuse back and gets redistributed into less vascular but more bulky organs (ex: muscles and adipose tissue)
* now lets talk about thiopental :if i give it to the patient by IV injection -> it first will increse in the blood From here it will enter the brain very rapidly due to high blood supply this result in rapid induction of general anesthesia (تخدير)

At the same time thiopental starts entering the fat and muscles

Because of this the concentration of thiopentone in blood falls down




زاد بعدها برأ يقل لما صار في توزيع

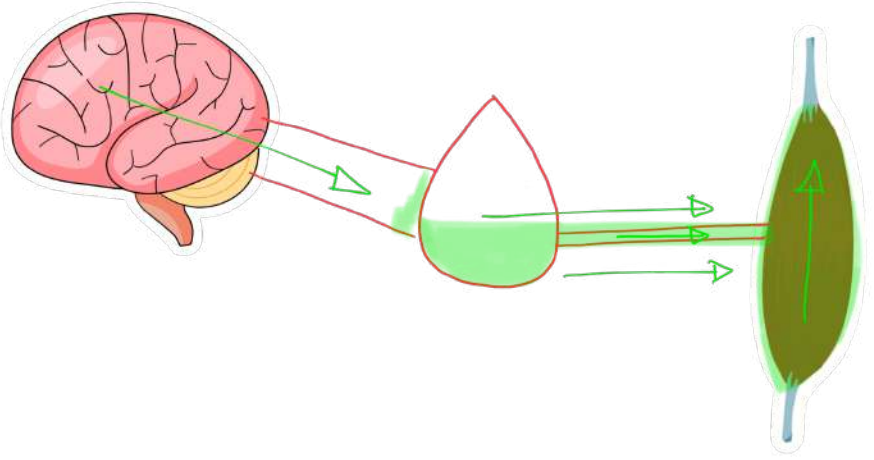
رسم توضيحي :-

**And it doesnt take Very long for concentration to drop to a level where the drug starts diffusing back from the brain**

**As concentration in brain falls,  the anesthesia disappears…**

**At this point the drug is largerly taken by fat and muscles because they are more bulky**

**NOTE THAT : the thiopentone is not eliminated from the body but its action has disappeared due to redistribution**



## ❖ Volume of Distribution ($V_d$) حجم الإنتشار

- Definition: the **apparent** volume of fluid required to accommodate the entire amount of the drug in the body in the same concentration as that present in plasma (i.e. when the drug is equally distributed between plasma and tissues).

$$V_d\ (L) = \frac{\text{Amount of drug in the body}}{\text{Plasma concentration}} \quad \frac{A}{C}$$

$$(V_d = A/C \text{ or } Q/C)$$

- The apparent volume of distribution does not describe a real, physical volume, but rather, reflects the **ratio of drug in the extraplasmic spaces relative to the plasma space** as it assumes that the drug distributes uniformly, in a single compartment, e.g. the Vd for digoxin is 6 **L/Kg** (in adult 70 Kg) or 420 **L.**

$\frac{420\ L}{70\ KG} = 6\ L/KG$

* لو السؤال ما حدد النا وزن ، بدنا نفرض انه 70Kg

* لو أعطاني بوحدة L/KG والسؤال طالب Vd ، بهالحالة بضرب بـ وزن الجسم *

كلما كان الدواء small volume بكون رايح ع الplasma... بينما لو كان الدواء lerge volume بكون رايح ع الtissue
لو كان ال volume= 3 رح يكون بالplasma ولو كان =12 رح يكون الدواء بال plasma and interstitial ولو كان =20 رح يكون بال3 أماكن ولو كان =400 رح يكون متركز كتير بال tissue.

### • Importance of $V_d$

**1.** It is an estimate of the extent of **tissue uptake** of drugs:

- Small $V_d$ (e.g. frusemide) indicates that tissue uptake is limited.
  ال frusemide هو دواء مدر للبول
- Large $V_d$ (e.g. digoxin) indicates extensive tissue distribution.

**2. In cases of drug toxicity:**

- Dialysis is **not useful** for **high $V_d$** drugs (most of drug is in the tissues). ↓Vd → ↑ [drug] in blood → effective
- Dialysis is **useful** for **low $V_d$** drugs (most of drug is in the blood).

**3.** $V_d$ can be used to calculate the **loading dose (LD):** لحساب الجرعة الأولية التي يريد الطبيب اعطاءها للمريض

$$[LD = V_d \times C_{ss} \text{ (Steady State plasma Concentration)}]$$

**4.** $V_d$ can be used to calculate the **total amount of drug** in the body:

$$[A = V_d \times C_p]$$

مثلاً شو هي الكمية الي تناولها المنتحر لمعرفة اذا بثير اعمله Dialysis او لا

عملت ضرب تبادلي بالقانون وغيرت الأسماء

## ❖ Factors Affecting Distribution of Drugs:

التروية **1) Perfusion:** the amount of the drug which is delivered to a particular organ depends on the ***blood flow*** to that organ: ↑ blood flow → ↑ distribution.

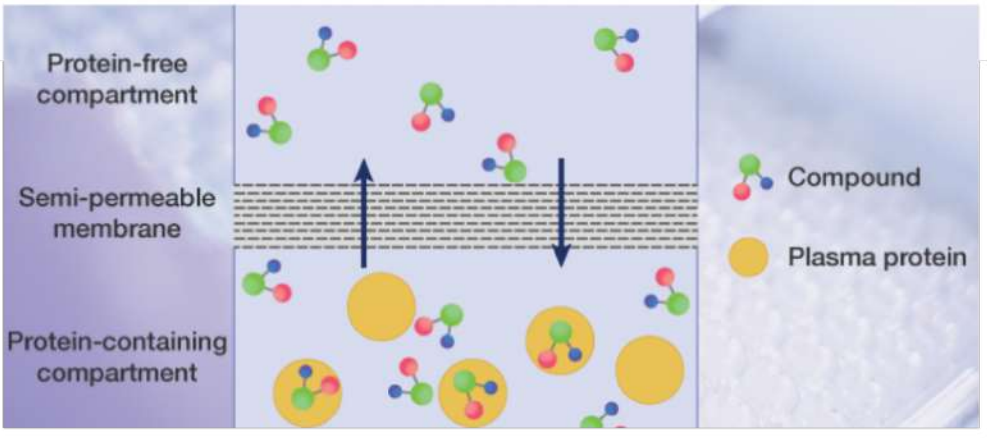
**2) Diffusion:** the ability of the drug to diffuse across the cell membranes is governed by its ***lipophilicity***, ***ionization*** & ***molecular weight***: (as absorption)

**3) Binding to plasma proteins (PPs):**

- Most of drugs when introduced into the body are bound to plasma proteins (pp) e.g.

- **Albumin:** - the most important pp
  - Acidic & lipophilic drugs bind mainly with it
- **Other:** globulin, glycoprotein…etc

- Drug in blood exists in 2 forms: **free form** & **plasma protein bound form** which exist in equilibrium; when the free form is metabolized and/or excreted, another part is released from plasma proteins




| Free fraction | Bound fraction |
|---|---|
| • Active Produce action<br>• Diffusible<br>• Can be Metabolized<br>• Can be Excreted | • **In**active<br>• **Non**diffusible<br>• Can**not** be metabolized<br>• Can**not** be excreted<br>• Act as a reservoir for drug |

مكان لتخزين الدواء يعني كلما قل ال free بصير ال bound يرجعه للكمية الطبيعية

- **Significance of Binding to Plasma Proteins**

1. The binding of drug to plasma proteins **limits its tissue penetration & decreases its $V_d$.** كلما زاد الارتباط مع pp كلما قل tissue uptake وقل ال distribution والعكس صحيح

2. The bound drug cannot be eliminated → **prolongs the t½** of the drug → **prolongs the effect** of drug.

Half-life (t1/2) refers to the time required for plasma concentration of a drug to decrease by 50%

3. **Hyboalbuminemia** e.g. starvation, malnutrition → **↑ free drug** → therapeutic dose changes to **toxic dose** e.g. phenytoin.

liver failure or kidney failure :سبب

لو كان الدواء 40% free و 60% bound... قل عندي albumin فقل عندي الbound وزاد ال free يعني زاد ال effect of drug وهيك ممكن يعمل toxicity

4. Competition for binding sites between drugs → **displacement of each other** → **clinically-significant drug interactions** e.g.

examples

high affinity

anticoagulant

- Aspirin, sulphonamide displace warfarin → bleeding.

أطفال الخداج مبكري الولادة أطلاع صفراء

- Sulphonamide displaces bilirubin → kernicterus in premature neonates.

ال pp بيحمل عدد كبير من الأدوية فممكن يصير interaction بينهم بحيث انه واحد يضل bound والتاني يصير free

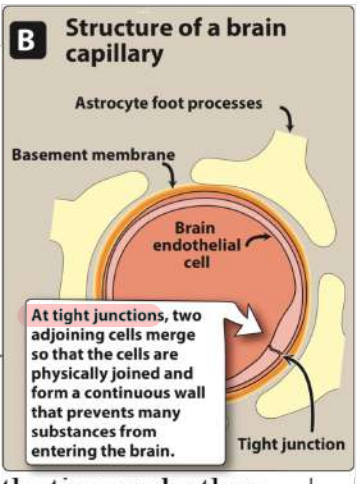
**Kernicterus is a type of brain damage that can result from high levels of bilirubin in a baby's blood.**

**The plasma proteins are bounded with sulphonamide except bilirubin , so bilirubin is free in the blood it will reach the CNS and beause the premature does not have a blood brain barrier the bilirubin will enter the CNS.**

بتسببلي jaundice

## 4) Binding to cell and tissue constituents:

- Drugs concentrated in certain tissues **(Tissue reservoir)**.




## ❖ Passage across barriers:

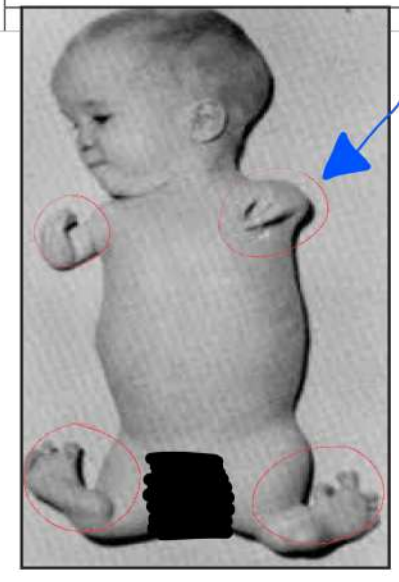
### Passage of Drugs to CNS

Because of tight junctions

1. **Lipid-soluble** drugs pass freely through BBB (Blood → Barrier → Brain), e.g. general anesthetics and other CNS depressants.
2. **3ry amines** (unionized) can pass while 4ry $NH_4^+$ compounds (ionized) cannot. دريناها بالبيوكيمز
3. **Some hydrophilic** antibiotics e.g. penicillin can pass **inflamed BBB** only

### Passage of Drugs to the Fetus

- Many drugs cross placental barrier by simple diffusion (depending on their lipid solubility & their degree of ionization) and can **harm the fetus:**
  - Drugs given in **3rd to 10th week** (هي أخطر مرحلة — مرحلة تكون الأعضاء) of pregnancy → **teratogenicity** e.g. thalidomide (مُسكن) → phocomelia The foots and the hands are directly attached to the trunk
  - Oral anticoagulants (ميوعة الدم) → fatal hemorrhage in the newborn.
  - Oral hypoglycemics (sulfonylureas) → prolonged neonatal hypoglycemia.
  - Aminoglycosides → 8th cranial nerve damage. It is resposible for hearing + balance
  - During labor, Morphine → respiratory depression (asphyxia neonatorum). (اختناق)



## Passage of drugs to breast milk

- Most of drugs administrated to lactating women are detectable in breast milk.
- pH of milk is more acidic (7.0) than that of plasma (7.4) → **basic drugs** accumulate in milk (ion trapping).
- Milk contains more fat than plasma → retention of **lipid soluble** drugs.

- **Drugs are contraindicated during lactation**:
  - Sedatives, hypnotics and narcotics → CNS depression in baby. (المهدئات المنومات — كمل بالقفل ، نايم طول اليوم)
  - Oral penicillins and purgatives → diarrhea in baby. (مضاد حيوي — المليينات)
  - Anticancer drugs → decrease growth of baby.
  - Bromocriptine & sex hormones → suppress lactation. (بشتغل مثل الـ dopamin)

# QUIZ TIME ⏰

1) NN610 is an investigational cholesterol-lowering agent. N610 has a high molecular weight and is extensively bound to albumin. NN610 will have a ..... apparent volume of distribution (Vd).

A. High

B. Low

C. Extremely high

D. Normal

2) Which of the following is true about the blood–brain barrier?

A. Endothelial cells of the blood–brain barrier have slit junctions.

B. Ionized or polar drugs can cross the blood–brain barrier easily.

C. Drugs cannot cross the blood–brain barrier through specific transporters.

D. Lipid-soluble drugs readily cross the blood–brain barrier.

E. The capillary structure of the blood–brain barrier is similar to that of the liver and spleen.

3) A 40-year-old male patient (70 kg) was recently diagnosed with infection involving methicillin-resistant S. aureus. He received 2000 mg of vancomycin as an IV loading dose. The peak plasma concentration of vancomycin was reported to be 28.5 mg/L. The apparent volume of distribution is:

A. 1 L/kg. B. 10 L/kg. C. 7 L/kg.

D. 70 L/kg. E. 14 L/kg.

4) A 55-year-old male patient (70 kg) is going to be treated with an experimental drug, Drug X, for an irregular heart rhythm. If the V is 1 L/kg and the desired steady-state plasma concentration is 2.5 mg/L, which of the following is the most appropriate intravenous loading dose for Drug X?

A. 175 mg. B. 70 mg.

C. 28 mg. D. 10 mg. E. 1 mg.