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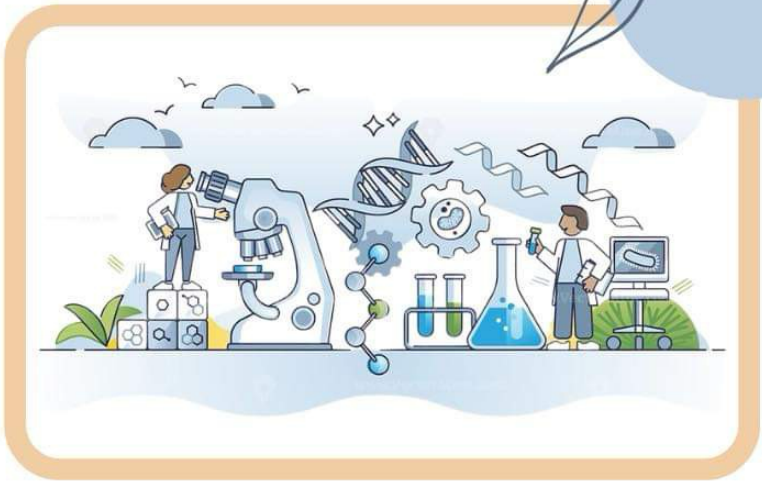

اسم الموضوع: Drug Distribution and Protein Binding

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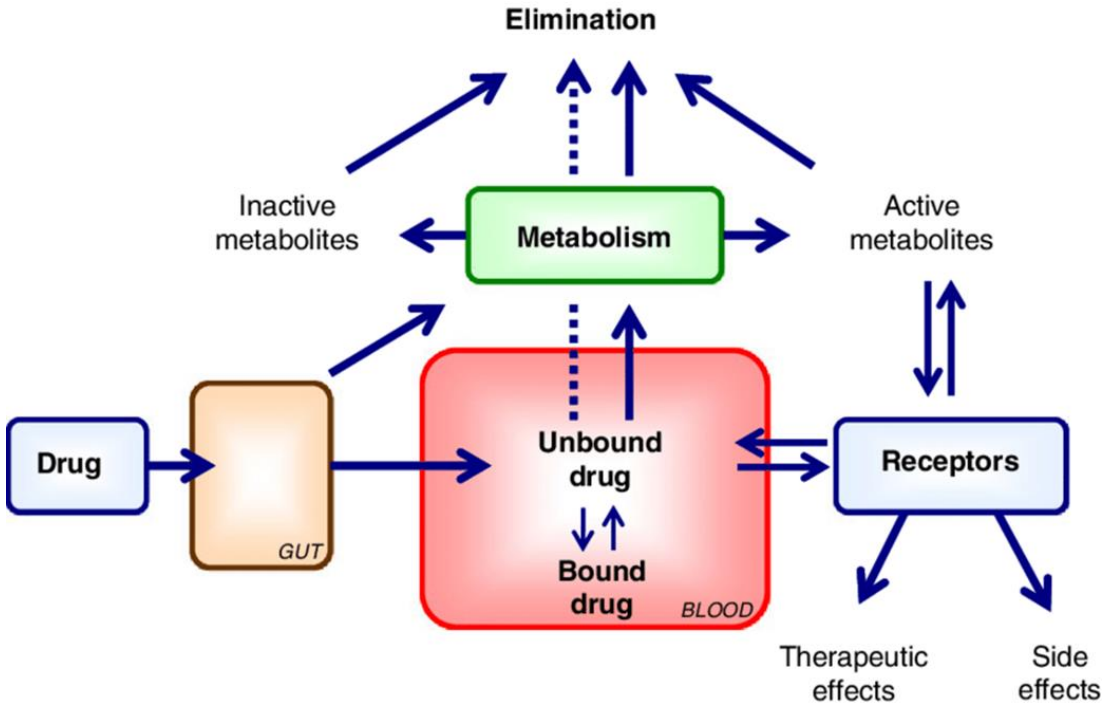
Soul Academy

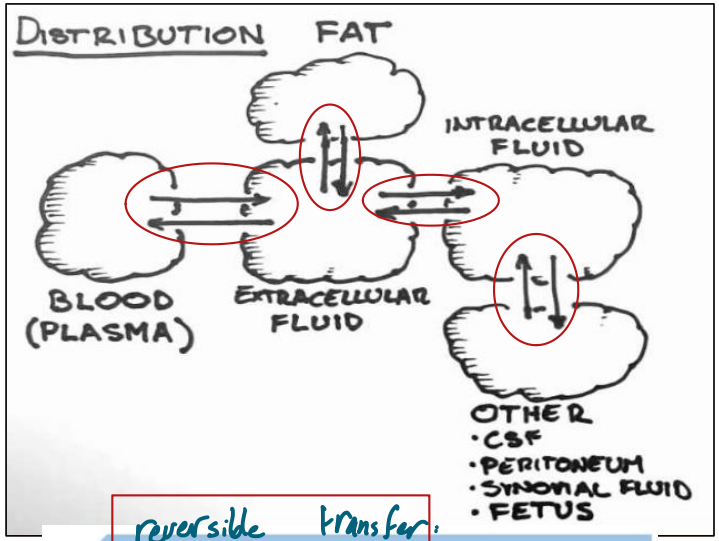
لجان الدُّفعات

Drug Distribution and Protein Binding



Distribution

- Distribution of the drug is the reversible transfer of drug from one location to another within the body which determines the concentration of the drug at the site of action (drug action) and other tissues (drug adverse effects)
- Drug also distributes to the eliminating organs (kidney and liver) and non-eliminating tissues such as skin, brain and muscles.
- In pregnancy, it may distribute to the placenta to reach the fetus
- In lactating mother: may be secreted by mammary glands with milk
- May bind to plasma proteins Or may deposit in the fat to be released slowly

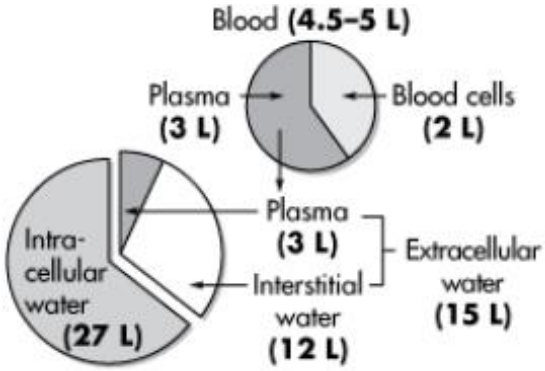


Distribution

Drug distribution in the body depends on:

1. Its lipophilicity
2. Blood flow
3. Protein/tissue binding.

- Low plasma binding, high tissue binding, high blood flow or high lipophilicity usually means an extensive tissue distribution.



Major water volumes (L) in average 70 kg human.

Summary :-

- High plasma binding = low distribution
- High tissues binding = high distribution

extra cellular fluids = 15 L
- Plasma = 3L
- Interstitial = 12L

Intra cellular = 27L

The total body = 42 L

- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution. →

$V_d = 42L$ هاي الحجم تحت الدواء وليس الجسم، يعني دواء بعرف رح يظل في الدم، أما بده 1000L مثلاً وأصلاً الجسم ما فيه أكثر من 42L فـ بنفهم إنه رح يتوزع على كل أنحاء الجسم.

- At equilibrium, V will theoretically not be lower than 7 L in a 70-kg person, but it has no upper limit. → Cause it apparent volume of distribution

الدم والسوائل المحيطة به

- The extent to which a drug distributes affects the half-life of the drug and the fluctuation of the concentration at steady state. مرحلة ثبات

عمر النصف للدواء (عمر الدواء داخل الجسم وفيه تستهلك فعاليته للنصف)

The amount of drug that entering the body = the amount that excreted

absorption = elimination

any drug has V_d higher than 42L, this means:

The drug will distributes among the body [plasma + tissues]

Drug Distribution Patterns

أنماط

The pattern of drug distribution can be one of the four following types:

1. The drug may remain largely within the vascular system. Mannitol and plasma substitutes such as dextran are examples of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.

   Mannitol + dextran = have low Vd + stay in the blood

   في أدوية بتفضل موجودة في الـ blood circulation و إلها Vd قليلة

   بيقى بالدم لأنه أهلًا بشتغل في الدم (صدرين)

2. Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.

   low M.w means high Vd = حجمها صغير

   مع إنها ذائبة في الماء بس لأنه M.w إلها قليل بالتالي بتقدر تعبر عشا و تخلا

3. Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility.

   غط تسلك أغلب الأدوية

   الأدوية تختار أماكن التوزع حسب هل هي lipo/hydrophilic

   + حجمها هل كبير أو صغير + M.w ...

   مثل أن BBB صعب يوصله الأدوية، بس liver + kidneys سهل يوصلهم الدواء سواء محب أو كاره الماء

Drug Distribution Patterns

4. A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action.

- **Iodine** is concentrated by the thyroid gland.
- The antimalarial drug **chloroquine** may be present in the liver at concentrations 1000 times those present in plasma.
- **Tetracycline** is almost irreversibly bound to bone and developing teeth, consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth.
- Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.
- Note that, the highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

Drug Distribution Patterns

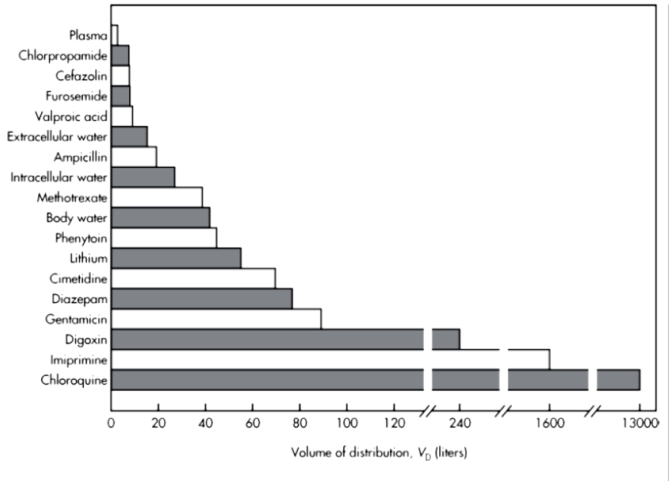
Other examples

- Flutamide, antiandrogen drug, is highly concentrated in prostate (20 times that of plasma)
- Digoxin (Polar) is highly bound to the myocardial tissue leading to long distribution half life.
- The chlorinated hydrocarbon, DTT (dichlorophenyltrichloroethane), is highly lipid soluble and remains in fat tissue for years.
- Phenothiazine, used in chronic schizophrenia, is bound to melanin in skin and eye after long term of administration.
- Purine and pyrimidine analogues that treat cancer binds irreversibly to macromolecules and cause destruction of the cell.

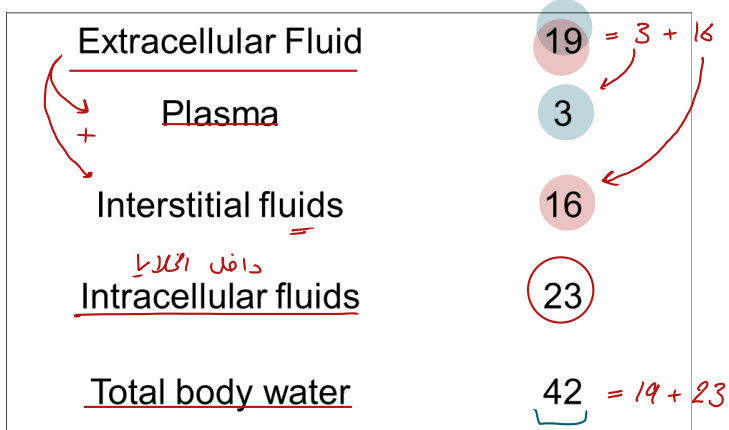
تدمير الخلايا

Drug Distribution Patterns

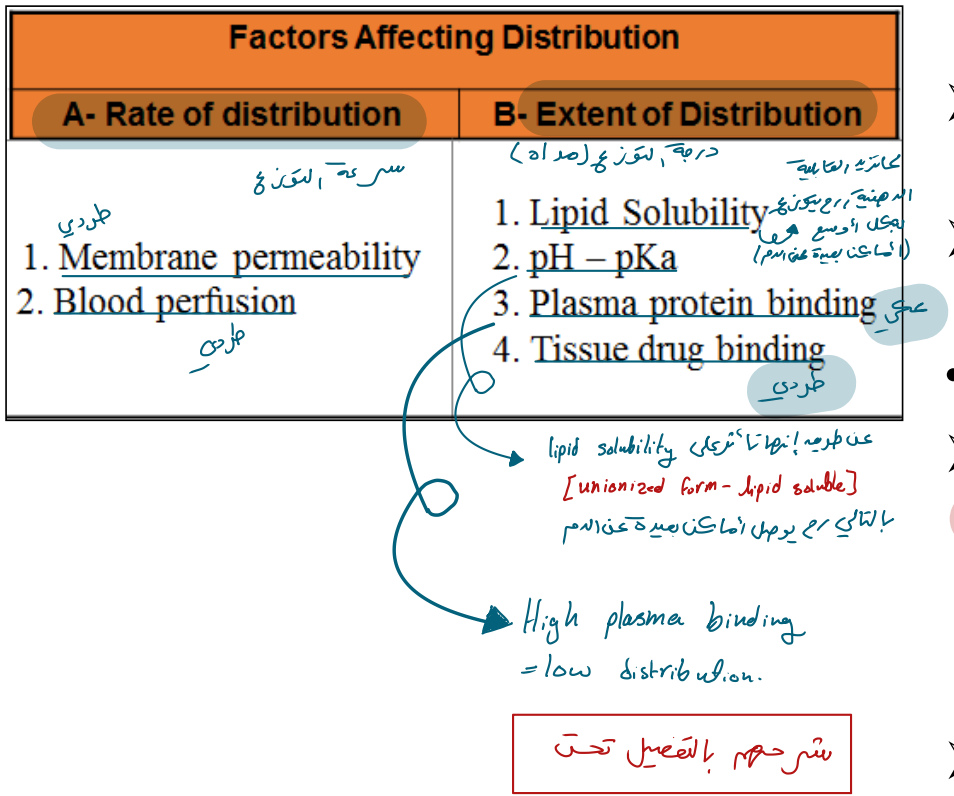
- **Apparent volume of distribution (V) is a useful indicator of the type of pattern that characterizes a particular drug.**
- **A value of V in the region of 3-5 liter (in an adult) would be compatible with pattern 1. This is approximately the volume of plasma.**
- **Pattern 2 would be expected to produce a V value of 30 to 50 liter, corresponding to total body water.**
- **Agents or drugs exhibiting pattern 3 would exhibit very large values of V. Chloroquine has a V value of approximately 115 L/kg.**
- **Drugs following pattern 4 may have a V value within a wide range of values.**



Volumes of body fluids	
Fluid substances	**Volume (liter)**



Factors Affecting Drug Distribution



- **Permeability of the drug through the capillary membrane which depends on two factors:**

➢ Passive diffusion: described by Fick's law of diffusion

➢ Hydrostatic pressure: presents by the pressure gradient between arterial and venous capillaries

- **Permeability of drug can be affected by:**

➢ Diffusional factor: as membrane thickness, diffusion coefficient of the drug and concentration gradient across the capillary membrane which is affected by some diseases as inflammation (increase permeability).

➢ Blood flow: and this can be affected by some diseases as CHF

Congestive heart failure

Permeability through capillaries

Table 10.1 Permeability of Molecules of Various Sizes to Capillaries

	Molecular Weight	Radius of Equivalent Sphere *A* (0.1 mm)	Diffusion Coefficient In Water (cm^2/sec) x 10^5	Diffusion Coefficient Across Capillary (cm^2/sec x 100 g)
Water	18		3.20	3.7
Urea	60	1.6	1.95	1.83
Glucose	180	3.6	0.91	0.64
Sucrose	342	4.4	0.74	0.35
Raffinose	594	5.6	0.56	0.24
Inulin	5,500	15.2	0.21	0.036
Myoglobin	17,000	19	0.15	0.005
Hemoglobin	68,000	31	0.094	0.001
Serum albumin	69,000		0.085	<0.001

Factors affecting drug distribution

A. Rate of distribution

1. Membrane permeability:

- Cell membranes vary in their permeability characteristics, depending on the tissue.
- For example, capillary membranes in the liver and kidneys are more permeable to transmembrane drug movement than capillaries in the brain. The sinusoidal capillaries of the liver are very permeable and allow the passage of large-molecular-weight molecules.
- In the brain and spinal cord, the capillary endothelial cells are surrounded by a layer of glial cells, which have tight intercellular junctions. This added layer of cells around the capillary membranes acts effectively to slow the rate of drug diffusion into the brain by acting as a thicker lipid barrier.
- This lipid barrier, which slows the diffusion and penetration of water-soluble and polar drugs into the brain and spinal cord, is called the blood brain barrier (BBB).

Factors affecting drug distribution

A. Rate of distribution

1.Membrane permeability

- Under certain pathophysiologic conditions, the permeability of cell membranes, including capillary cell membranes, may be altered.
- For example, burns will alter the permeability of skin and allow drugs and larger molecules to permeate inward or outward.
- In meningitis, which involves inflammation of the membranes of the spinal cord or brain, drug uptake into the brain will be enhanced.
- The diameters of the capillaries are very small and the capillary membranes are very thin. The high blood flow within a capillary allows for intimate contact of the drug molecules with the cell membrane, providing for rapid drug diffusion.
- For capillaries that perfuse the brain and spinal cord, the layer of glial cells functions effectively to increase the thickness, thereby slowing the diffusion and penetration of water-soluble and polar drugs into the brain and spinal cord.

Factors Affecting Drug Distribution

A. Rate of distribution

1. Membrane permeability:

- Capillary walls are quite permeable.
- Lipid soluble drugs pass through very rapidly.
- Water soluble compounds penetrate more slowly at a rate more dependent on their size.
- Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.

- For drugs which can be ionized the drug's pKa and the pH of the blood will have a large effect on the transfer rate across the capillary membrane.
- On the other hand, brain capillaries seem to have impermeable walls restricting the transfer of molecules from blood to brain tissue.
- Lipid soluble compounds can be readily transferred but the transfer of polar substances is severely restricted.
- This is the basis of the "blood-brain" barrier.

Distribution to the tissues

2. Depends on the blood flow, tissue size and tissue storage.

- The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions.
- Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.
- Skin, bone, and depot fat equilibrate much more slowly.

Table 10.2 Blood Flow to Human Tissues

Tissue	Percent Body Weight	Percent Cardiac Output	Blood Flow (mL/100 g tissue/min)
Adrenals	0.02	1	550
Kidneys	0.4	24	450
Thyroid	0.04	2	400
Liver			
Hepatic	2.0	5	20
Portal		20	75
Portal-drained viscera	2.0	20	75
Heart (basal)	0.4	4	70
Brain	2.0	15	55
Skin	7.0	5	5
Muscle (basal)	40.0	15	3
Connective tissue	7.0	1	1
Fat	15.0	2	1

Factors Affecting Drug Distribution

B. Extent of Distribution

1.Lipid Solubility:

- Lipid solubility will affect the ability of the drug to bind to plasma proteins and to cross lipid membrane barriers.
- Very high lipid solubility can result in a drug partitioning into highly vascular lipid-rich areas. Subsequently these drugs slowly redistribute into body fat where they may remain for long periods of time.

رح يضلهم وقت طويل لأنهم مرتبطين مع الخلايا والجزيئات اللي مكونة من الدهون، ف بيأخذ وقت لحدا يقدر يطلع للدم وبعدين من الجسم.

2. Effects of pH:

تأثيرها على الدواء إذا ionized أو لا

- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.

مثلاً لو شخص اختنق وصار معه نقص O_2 بالتالي عاني اسمها Acidosis وترفع نسبة CO_2 عنده وحموضة الدم بتصير عالية بالتالي شو؟ رح تتأثر درجة تأيين الأدوية ورح يأثر على تفاعل الأدوية

- Changes in pH occurring in disease may also affect drug distribution. For example, blood becomes more acidic if respiration is inadequate.

غير كافي

Factors Affecting Drug Distribution

3.Plasma protein binding:

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (↑ protein binding = ↓ V)
- Albumin comprises 50 % of the total proteins binds the widest range of drugs. Acidic drugs commonly bind to albumin, while basic drugs often bind to α1-acid glycoproteins and lipoproteins.
- The functional groups on the protein molecules that are responsible for **electrostatic interactions** with drugs include:
  - NH_3^+ of lysine, N- terminal amino acids, NH_2^+ of histidine, S^- of cysteine , and COO^- of aspartic and glutamic acid residues.

- **Forces involved**:

In order to achieve stable complexes, the initial electrostatic attraction is reinforced by van der Waal's forces and hydrogen bonding.

Factors Affecting Drug Distribution

- **What is the effect of protein binding on drug action?**

A. Extensive plasma protein binding will decrease the amount of absorbed drug (decrease peak plasma level).

B. Elimination of a highly bound drug may be delayed. Since the concentration of free drug is low, drug elimination by metabolism and excretion may be delayed. This effect is responsible for prolonging the effect of the drug digoxin.

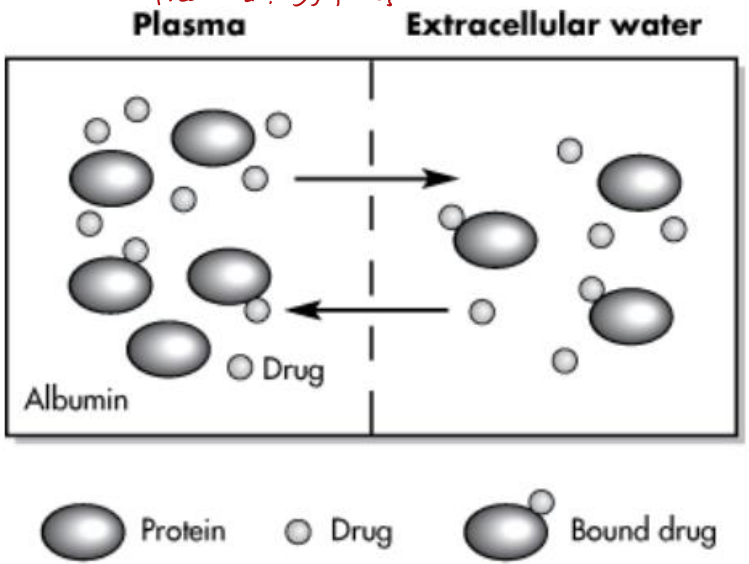


Diagram showing that bound drugs will not diffuse across membrane but free drug will diffuse freely between the plasma and extracellular water.

Factors Affecting Drug Distribution

C. Changes in the concentration of plasma proteins will influence the effect of a highly bound drug.

- A low plasma protein level may occur in: old age, malnutrition, illness such as liver disease (remember that most plasma proteins are made in the liver), or chronic renal failure where there is excessive excretion of albumin.
- In each case the result is a smaller proportion of drug in bound form and more free drug in the plasma. The greater amount of free drug is able to produce a greater therapeutic effect and reduced drug dosages may be indicated in these cases.

D. There may be competition between drugs.

- In which agents that are bound very tightly, such as coumarin anticoagulants, are able to displace less tightly bound compounds from their binding sites.

Factors Affecting Drug Distribution

- In general, plasma protein binding is reversible and obeys the law of mass action, where rate constants, respectively.

$$\text{(free drug)} + \text{(albumin)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{(drug-albumin complex)}$$

k_1 : association constants
k_2 : dissociation constants

- At equilibrium:

$$K_D = \frac{k_2}{k_1} = \frac{[\text{free drug}] \times [\text{albumin}]}{[\text{drug-albumin complex}]}$$

- Where K_D is the equilibrium dissociation constant. It is a measure of the affinity of the drug for albumin:

➢ The lower the KD ⟶ the higher the affinity
➢ The higher the KD ⟶ the lower the affinity
➢ As the concentration of drug increases in plasma, the percent that is bound will decrease.

Factors Affecting Drug Distribution

4. Tissue drug binding (tissue localization of drugs):

High tissues binding = ↑ Vd = high distribution.

- In addition to plasma protein binding, drugs may bind to intracellular molecules. صفات بس يرتبط الدواء مع بروتين
- The affinity of a tissue for a drug may be due to: binding to tissue proteins or to nucleic acids, or in the case of adipose tissue, dissolution in the lipid material.

هو يعني ارتباط الدواء بكل ما هو أنسجة أخرى غير البروتينات.

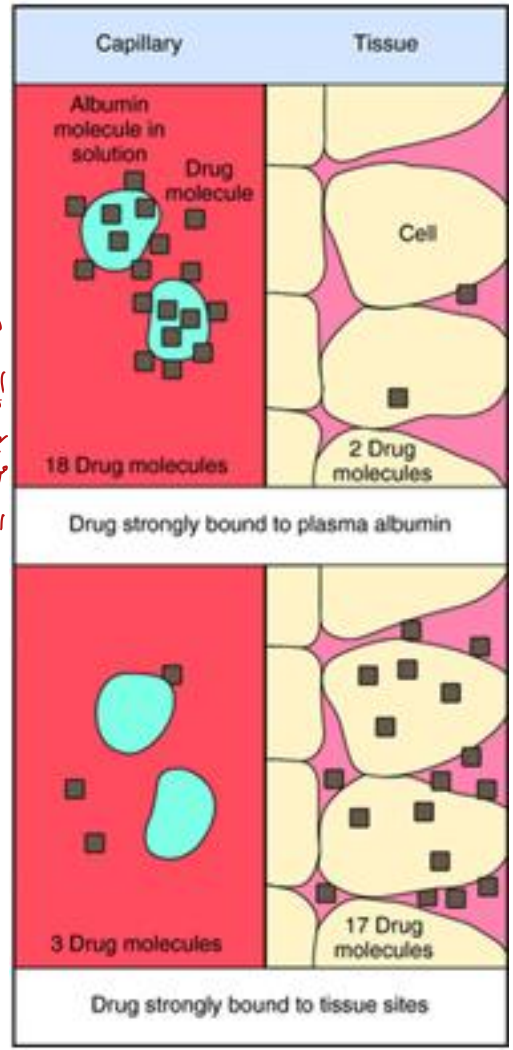
e.g. The concentration of **chloroquine** in the liver is due to the binding of the drug to DNA.

CNS drug

e.g. **Barbiturates** distribute extensively into adipose tissue, primarily because of their high lipid solubility.

يرتبط على الحديد و Ca

e.g. **Tetracyclines** bind to bone thus should be avoided in young children or discoloration of permanent teeth may occur.



Factors Affecting Drug Distribution

Other distribution considerations

- **Weight considerations:**

A. Body composition of the very young and the very old may be quite different from 'normal', that is the average subject in whom the parameter values may have been originally determined.

B. Another group of patients in which body composition may be greatly altered from `normal' is the obese. These patients have a higher proportion of adipose tissue and lower percentage of water.

➢ Thus for drugs which are relatively polar, volume of distribution values may be lower than normal.

➢ For example the apparent volume of distribution of antipyrine is 0.62 l/kg in normal weight subjects but 0.46 l/kg in obese patients.

➢ Other drugs such as digoxin and gentamicin are also quite polar and tend to distribute into water rather than adipose tissue.

🔻قال رسول الله ﷺ : سَبْعَةٌ يُظِلُّهُمُ اللهُ يومَ القِيَامَةِ في ظِلِّهِ، يومَ لا ظِلَّ إلاَّ ظِلُّهُ: إمَامٌ عَادِلٌ، وَشَابٌّ نَشَأَ في عِبَادَةِ اللهِ، وَرَجُلٌ ذَكَرَ اللهَ في خَلاَءٍ فَفَاضَتْ عَيْنَاهُ، وَرَجُلٌ قَلْبُهُ مُعَلَّقٌ في المَسْجِدِ، وَرَجُلاَنِ تَحَابَّا في اللهِ، وَرَجُلٌ دَعَتْهُ امْرَأَةٌ ذَاتُ مَنْصِبٍ وَجَمَالٍ إلى نَفْسِهَا، قالَ: إنِّي أَخَافُ اللهَ، وَرَجُلٌ تَصَدَّقَ بِصَدَقَةٍ فأخْفَاهَا حتَّى لا تَعْلَمَ شِمَالُهُ ما صَنَعَتْ يَمِينُهُ.

🔻 اللهم إني أستغفرك ممّا تبت إليكَ منه ،ثم عُدت فيه ، وأستغفرك ممّا جعلته لكَ على نفسي ، ثم لم أفِ لكَ به ،وأستغفرك ممّا زعمت أني أردتُ به لوجهِكَ الكريم ، فخالَط قلبي فيه ما قد علمت.

🔻 اللهم أغفر لي ولوالدي وللمسلمين والمسلمات والمؤمنين والمؤمنات الأحياء والأموات

اللهم انصر الإسلام والمسلمين ،واكتب النصر لإخواننا المستغفين في غزة ولينان والسودان واليمن وكل مكان

اللهم أرحم زميلنا أيهم واجعله في عليين يتنعم في نعيم جنات الخلود واجمعه وأهله في الفردوس

اللهم إنّا نسألك الاخلاص في القول والعمل ،ونسألك توبة قبل الموت وشهادة عند الموت ومغفرة بعد الموت وعفوًا عند الحساب وامانًا من العذاب ونصيبًا من الحنة آمين