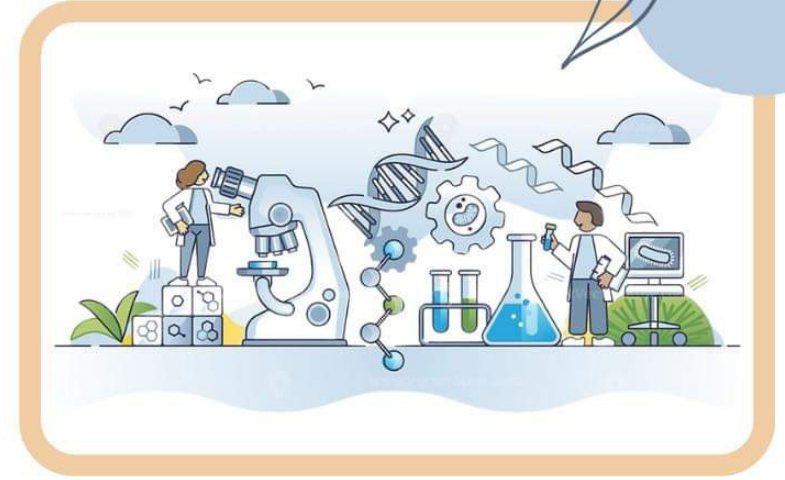


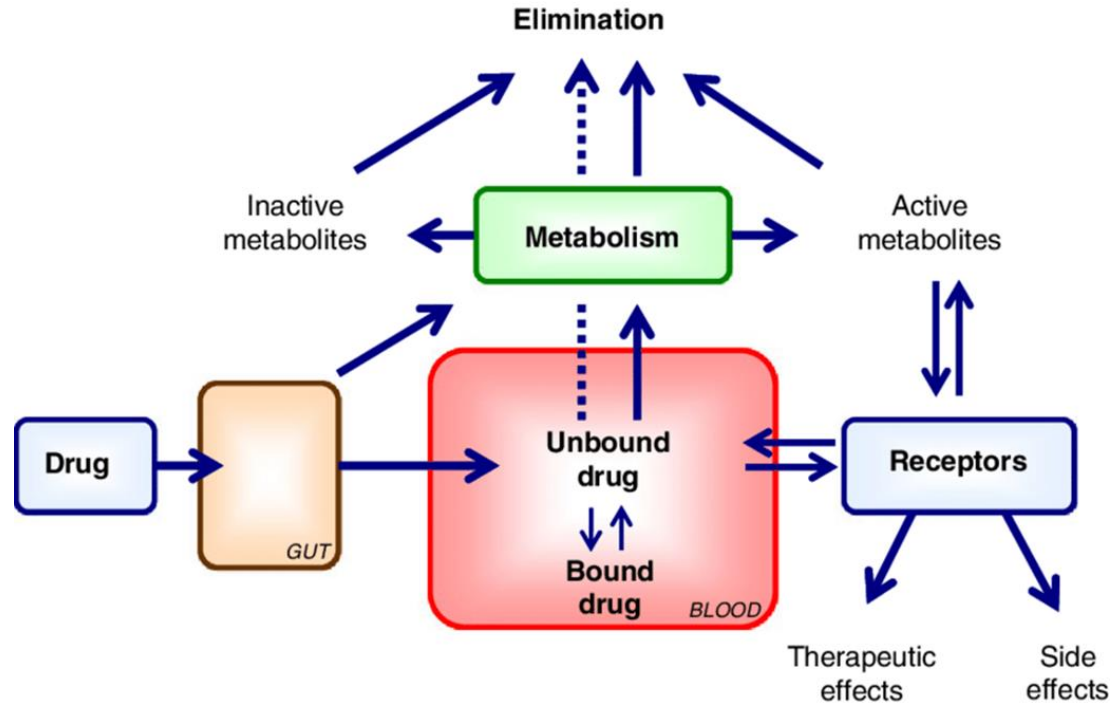
تفريغ بيوفارما

اسم الموضوع: Drug Distribution and Protein Binding

إعداد الصيدلاني / ة: ياسمين خليل



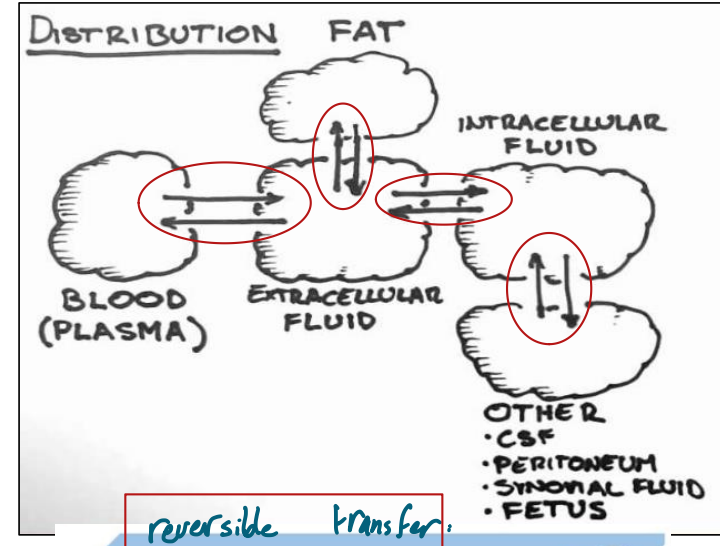
Drug Distribution and Protein Binding



Distribution

metabolism cause
→ irreversible biotransformation

- 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



→ الدواء يمكن ينقل من أنسجة إلى الدم والعكس
• كما يمكن تركيز الدواء بالدم أو أنسجة
الأنسجة، يرجع به قبل الدواء من الدم إلى الأنسجة (passive)
• وبه قدرة كما يمكن تركيز الدواء في الأنسجة مع مقاومة
مع الدم رج يصير يرجع الدم ويخرج للكبد ويصير له
إفراج

Distribution

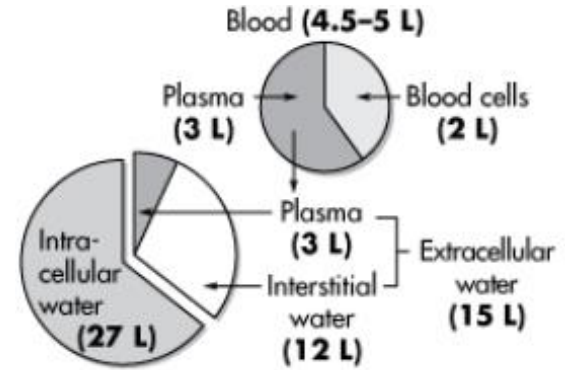
Drug distribution in the body depends on:

1. **Its lipophilicity** → *الدوية ذات الطبيعة الدهنية لها قدرة على اختراق الأغشية الخلوية بسهولة*
2. **Blood flow** → *في الأماكن التي يتدفق فيها الدم بكمية عالية، فإن توزيع الدواء يكون سريعاً*
3. **Protein/tissue binding** → *كل ما كان ارتباط الدواء ببروتين الدم عالياً، مع بقاء ٧٠% أو أكثر من الدواء مرتبطاً بالبروتين، فإن توزيعه يكون محدوداً. أما إذا كان ارتباطه ضعيفاً، فإن توزيعه يكون سريعاً. أيضاً، إذا كان الدواء يرتبط بنسبة عالية من بروتينات الدم، فإن توزيعه يكون محدوداً. أما إذا كان يرتبط بنسبة قليلة، فإن توزيعه يكون سريعاً.*

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

Summary :-

- ♥ High plasma binding
= low distribution
- ♥ High tissue binding
= high distribution



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

extra cellular fluids = 15 L

- plasma = 3 L
- Interstitial = 12 L
- Intra cellular = 27 L

The total = 42 L body

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

حجم الحجم تحسب الدواء وليس الجسم، يعني دواء $V_d = 42L$
يعرف حجم يصل في الدم، أما بـ 42L صكك وأصل الجسم ما فيه
أحيان 42L في بينهم إنه ربع 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

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

الدم والوائل المحيطة به

محور النصف الدواء (محور الدواء داخل الجسم وفيه تستهلك فعالية للنمو)
 صرمة نبات

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 distribute among the body [plasma + tissues]

Drug Distribution Patterns

أنماط

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

في الدم حيث يتحرك في blood circulation ولا يخرج

يقع بدم لأنه أمثل شغل في الدم (صديق)

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 V_d + stay in the blood

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 V_d = موزون

مع إسهال ذائب في الماء بس لأنه سهل إزالتها فليس بالثقل بقدر تغير عتاءه الخلاء

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.

الادوية تختلف باختلاف قدرتها على المرور عبر الأغشية حسب طبيعتها lipophilic/hydrophilic

+ موزون حل كبير أو موزون + M.W ...

مثل أن BBB صعب بوصول الادوية بس kidneys + liver سهل بوصولهم، ودوار سواء حسب أدوية لاء

Drug Distribution Patterns

تتركز الدواء في site of action مع يعطي effect

اما تتركز في مكان آخر مع Side effect. Site of action مع يعطي effect.

has high volume of Distribution

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**.

تتركز في الغدة الكبد 1000 ضعف تركيزه في الدم

➤ 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.

الأضنان ولدائمة

8 يغطي للأضنان

أضنان لينة

➤ Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.

Such as: BBB

➤ Note that, the highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

Cause of their high

permeability even for big hydrophobic drugs + blood perfusion

Drug Distribution Patterns

Other examples

- Flutamide, antiandrogen drug, is highly concentrated in prostate (20 times that of plasma)
- ^{Polar} Digoxin is highly bound to the myocardial tissue leading to long distribution half life.
- The chlorinated hydrocarbon, DDT (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.

كثيرا ، إذا هذا الخط (1) إلى فيه يتفصل الادوية بالدم (hydrophobic)

- 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.

هون الادوية الذائبة في الماء قليلة تستوزع على الجسم كله عندنا في الماء

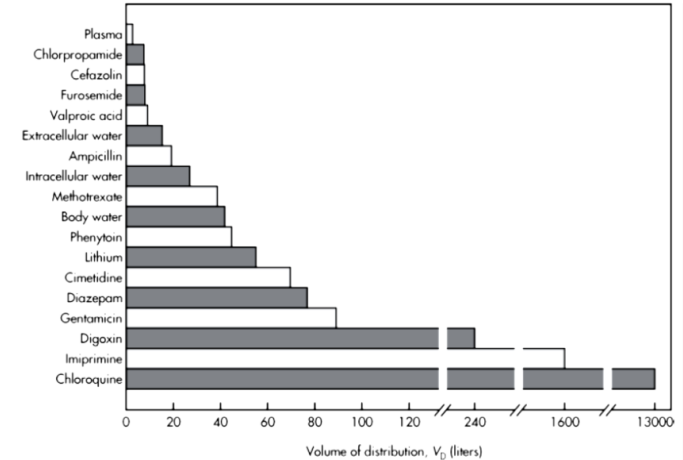
- **Pattern 2** would be expected to produce a V value of 30 to 50 liter, corresponding to total body water.

- Agents or drugs exhibiting **pattern 3** would exhibit very large values of V. Chloroquine has a V value of approximately 115 L/kg.

لو شخص وزنه 70kg في $V_d = 70 \times 115 = 8050$ جبه اعلى في بدنه للدائل

- Drugs following **pattern 4** may have a V value within a **wide** range of values.

صاعده في محدودية لأنه ممكن يتفصل على درجة ذوبان water/lipid وعلى قدرته على اختراق الأغشاء وتوزع ...



Volumes of body fluids	
Fluid substances	Volume (liter)
Extracellular Fluid	19 = 3 + 16
Plasma	3
Interstitial fluids	16
Intracellular fluids	23
Total body water	42 = 19 + 23

لشخص وزنه 70

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

Factors Affecting Distribution	
A- Rate of distribution	B- Extent of Distribution
سریع التوزع طردی 1. <u>Membrane permeability</u> 2. <u>Blood perfusion</u> طردی	درجه التوزع (صداة) الامتزاز والتألیف الدهون اربع يكون في بشكل اوسع (الاصان بعيدة عن الدم) 1. <u>Lipid Solubility</u> 2. <u>pH – pKa</u> 3. <u>Plasma protein binding</u> 4. <u>Tissue drug binding</u> طردی

عن طريقه انما تتحرك

lipid solubility

[unionized form - lipid soluble]

بالتالي ربح يوصل اصان بعيدة عن الدم

High plasma binding

= low distribution.

سريع التوزع تحت

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	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

سریوم آلبومین

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. hydrophilic الدواء سواد hydrophilic غير قابل للذوبان في الدهون BBB مادة متعادلة تكون too lipophilic مادة دهنية
- 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, ^{الحروق} burns will alter the permeability of skin and allow drugs and larger molecules to permeate inward or outward.
الحرق في الجلد يسمح بدخول الأدوية كبيرة الحجم
- In meningitis, which involves inflammation of the membranes of the spinal cord or brain, drug uptake into the brain will be enhanced. →
حيثما
ربما إنه صعب دخول الأدوية BBB
لأن السحايا تتصلب (عماقنا الله)
- 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.
علامة طردية بين تدفق الدم وتدفق الدواء
- 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.
ممكن أن الأدوية التي تخترق الصفيحة + الجبل النوع
بدون حواء + non-polar

Factors Affecting Drug Distribution

A. Rate of distribution

1. Membrane permeability:

جدران الأوعية الدموية منفذة للدار بين الدم والخللا

- 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.

هذه العملية تحدث فقط للمركبات الصغيرة فقط.
water soluble compounds only.

- 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.

Cause unionized drug has more lipid solubility sure
So it'll pass easily.

- On the other hand, brain capillaries seem to have impermeable walls restricting the transfer of molecules from blood to brain tissue.

it receive only high lipid soluble drugs + unbound + unionized

- Lipid soluble compounds can be readily transferred but the transfer of polar substances is severely restricted.

صعبة لأنها ذائبة في الماء

hydrophilic

- This is the basis of the "blood-brain" barrier.

BBB

lipid soluble drugs has high rate of distribution
Cause they can pass the membrane easily.

but as we said that water soluble drugs can pass the membrane only if their M.W is too low + small size

مثلا هبة: المواد الذائبة في الدم هبة سود حبة كبيرة أو صغيرة عادي عند المعقدة على عبور الخلايا من الدم
أما الذائبة في الماء فبها للعجم تأثير كبير، الكبيرة صارج تفسر أيضا الصغيرة مع تفسر عادي Simple diffusion

Distribution to the tissues

كانه طرح الدم عليه كبير ديمية، الدم الواسع للعضو كبيرة.

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

• العضو الذي له blood perfusion عالي رح يكثر فيه rate of distribution كماي كان

- The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions.

→ drug conc on the blood = drug conc on the tissues and cells

- Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.

أدوية تتحرك بسرعة في
Skin, bone, adipose
tissues.

- 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 the highest
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

1) the lowest
blood flow

عشان يسهل تعبنا لهجه مخزن للأدوية
كانه صا عند صا ته صفة دم زي البامتي

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.
- روح يضاهيهم وقت طويل لا يذهب
صرت يهلن مع اللانج دايجي ثبات الحكونة من الدهون، في يأخذ وقت لحوط يطلع الدم ويذهب من الجسم.

2. Effects of pH:

- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.
 - Changes in pH occurring in disease may also affect drug distribution. For example, blood becomes more acidic if respiration is inadequate.
- تأثير على الدواء إذا ionized (أو لا)
مثالي لو شخص اختنق ومهاجمة نقص O₂ بالتالي هيا اسمها Acidosis وترفع نسبة H⁺
عنده دموعه الدم يتغير عاليه بالتالي شو؟ روح تتأثر درجة تأين الدواء وروح بالتالي تعذب الأدوية
غير كما في

Factors Affecting Drug Distribution

3. Plasma protein binding: *high plasma binding = low drug distribution* عندما يرتبط الدواء مع بروتينات الدم، فإنه لن يتوزع في الأنسجة بسهولة

➤ 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. ($\uparrow$ protein binding = $\downarrow$ 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 α 1-acid glycoproteins and lipoproteins. *acidic drugs $\rightarrow$ Albumin*
basic " $\rightarrow$ α -1 acid glycoprotein

➤ The functional groups on the protein molecules that are responsible for electrostatic interactions with drugs include: *سُكُونِ الروابط إلى جزيئات الدواء مع البروتين؟*

- ⁽¹⁾ NH₃⁺ of lysine, ⁽²⁾ N-terminal amino acids, ⁽³⁾ NH₂⁺ of histidine, ⁽⁴⁾ S- of cysteine, and ⁽⁵⁾ 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.

*لغني (أولاً) دواء من خلال الروابط بين الجزيئات والدواء والبروتين
بعد ذلك بتعزيزه من الخسائر القوية بينهم*

Factors Affecting Drug Distribution

• What is the effect of protein binding on drug action?

الدواء المرتبط مع البروتين خارج الجسم لا
absorb و distribute
free action إكس إكس جسم بهما
eliminate و إكس

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.

من كاد جسم
free drug
مع جسم فيه
العمليات
بشكل بطيء

• ارتباطه من البلازما عالي
بالمستوى تأثيره مع دهن لوقت طويل

الدواء المرتبط مع البروتين خارج تنقل عبر الغشاء إلى
إذا صاروا بحالة free

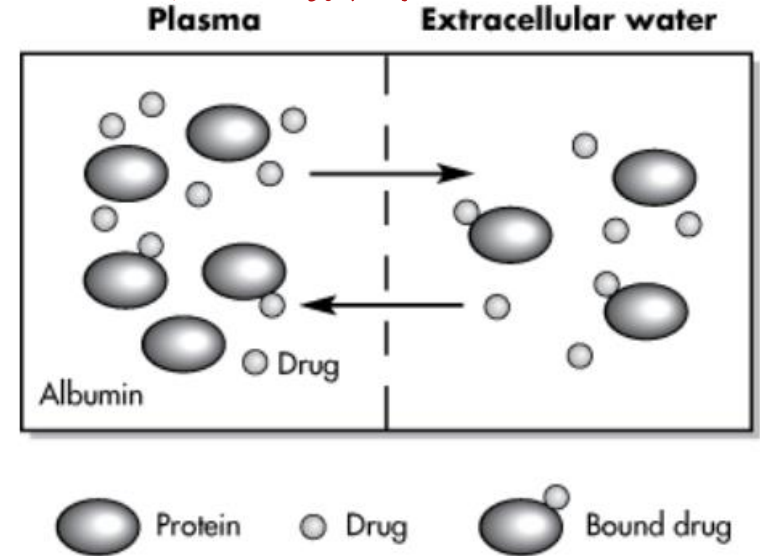


Diagram showing that bound drugs will not diffuse across membrane but free drug will diffuse freely between the plasma and extracellular water.

Factors Affecting Drug Distribution

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

- 90% of proteins are produced in liver
- 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.
- في كلتا الحالتين، يكون هناك انخفاض في تركيز البروتينات في الدم، مما يؤدي إلى انخفاض نسبة الدواء المرتبطة بالبروتينات، وبالتالي زيادة نسبة الدواء الحرة في البلازما. هذا يؤدي إلى تأثير علاجي أكبر، مما يتطلب جرعات أقل من الدواء.

D. There may be competition between drugs.

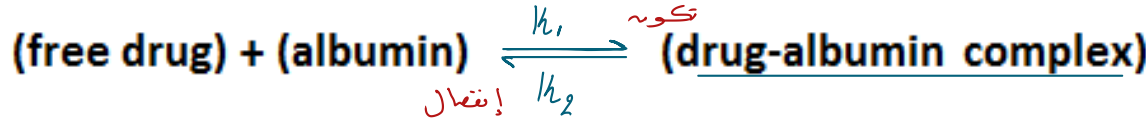
- In which agents that are bound very tightly, such as coumarin anticoagulants, are able to displace less tightly bound compounds from their binding sites.
- إذا كان هناك دواء مرتبط بقوة مع البروتينات، مثل مضادات التخثر الكومارين، فإنه يمكنه إزاحة المركبات التي ترتبط بشكل أقل قوة من مواقع ارتباطها.

Factors Affecting Drug Distribution

بالتالي ربح يزيدوا من توافر الدواء في الأجزاء
مرتبط مع البروتين قبلهم في بدنها ثم تنقله من
البروتين معصاهم بالأفنية لتعاضد الأدوية يا إخوانه
(بريد كية free drug)

from protein binds with drug
to free protein and free drug

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



rate constants,

القانون هاديمي إنه يكون عندي
صاين يكون إهم ثابت تكون
وثابت إنتقال

k_1 : association constants ثابتة كوة
 k_2 : dissociation constants ثابتة إنتقال

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

علاقة k_1 مع ثابتة k_2 عكسية يعني؟ يعني إذا كانت k_1 عالية هاد صغاه إنه كثير إرتباط بين الدواء + البروتين (complex) والعكس صحيح أصاين $k_2 \propto 1/k_1$ عادية

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

➤ The lower the K_D → the higher the affinity high k_1 = ارتباط

➤ The higher the K_D → the lower the affinity low k_1

- As the concentration of drug increases in plasma, the percent that is bound will decrease.

كل صاين أدوية الجوع ربح يزيد تركيز الدواء في الدم وهاد ربح يقلل نسبة و ليس كمية الدواء المرتبطة مع Albumin [إنه كية ثابتة] صاين دواء

Factors Affecting Drug Distribution

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

High tissues binding = $\uparrow V_d$ = high distribution.

- In addition to plasma protein binding, drugs may bind to intracellular molecules.
- 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
بجزيئات
أخرى غير
البروتينات.

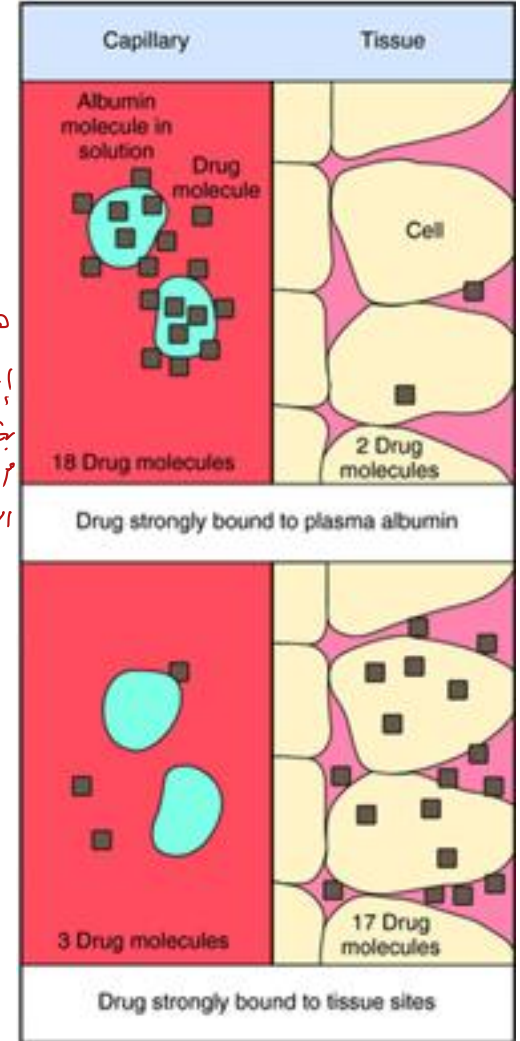
e.g. The concentration of **chloroquine** in the liver is due to the binding of the drug to **DNA**.

CNS drug

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

يرتبط على الصوديوم 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.

المرضى منهم سنية نسبة الدواء عندهم أكثر من العاد

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.

عشائر صلبة تحتوي الأدوية لذاتية من العاد يكون أقل من الطبيعي

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

antibiotic

➤ 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.

توزع في الشخص الطبيعى (أكثر من السمين)

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

عكس ذلك الأدوية لذاتية من الدواء ، فإنها راح يكون

توزعها بدلاً من عند السمينين

▼ قال رسول الله ﷺ : سَبْعَةٌ يُظِلُّهُمُ اللَّهُ يَوْمَ الْقِيَامَةِ فِي ظِلِّهِ، يَوْمَ لَا ظِلَّ إِلَّا ظِلُّهُ: إِمَامٌ عَادِلٌ، وَشَابٌّ نَشَأَ فِي عِبَادَةِ اللَّهِ، وَرَجُلٌ ذَكَرَ اللَّهَ

فِي خَلَاءٍ فَقَاضَتْ عَيْنَاهُ، وَرَجُلٌ قَلْبُهُ مُعَلَّقٌ فِي الْمَسْجِدِ، وَرَجُلَانِ تَحَابَّا فِي اللَّهِ، وَرَجُلٌ دَعَتْهُ امْرَأَةٌ ذَاتُ مَنْصِبٍ وَجَمَالٍ إِلَى نَفْسِهَا، قَالَ:

إِنِّي أَخَافُ اللَّهَ، وَرَجُلٌ تَصَدَّقَ بِصَدَقَةٍ فَأَخْفَاهَا حَتَّى لَا تَعْلَمَ شِمَالُهُ مَا صَنَعَتْ يَمِينُهُ.

▼ اللهم إني أستغفرك ممّا تبت إليك منه ،ثم عُدت فيه ، وأستغفرك ممّا جعلته لك على نفسي ، ثم لم أفِ لك به ،وأستغفرك ممّا زعمت أني أردتُ به لوجهك الكريم ، فخالط 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 ولبنان والسودان واليمن وكل مكان

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

اللهم إنّنا نسألك الاخلاص في القول والعمل ،ونسألك توبة قبل الموت وشهادة عند الموت ومغفرة بعد الموت وعفوًا

عند الحساب وامانًا من العذاب ونصيبيًا من الحنة آمين