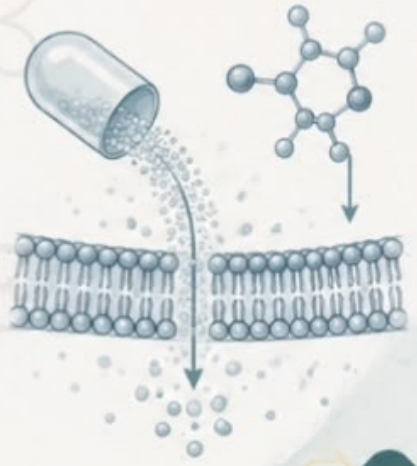
لجان الدفعات

BIOPHARMACEUTICS

MORPHINE ACADEMY



by Hadeel Alzoubi

Drug distribution

Distribution

Drug distribution: means the reversible transfer of drug from one location to another within the body.

- The distribution of drugs in the body depends on:

1- their lipophilicity

2- protein binding.

Low plasma binding or high tissue binding or high lipophilicity usually means an extensive tissue distribution.

انتشار واسع في الأنسجة

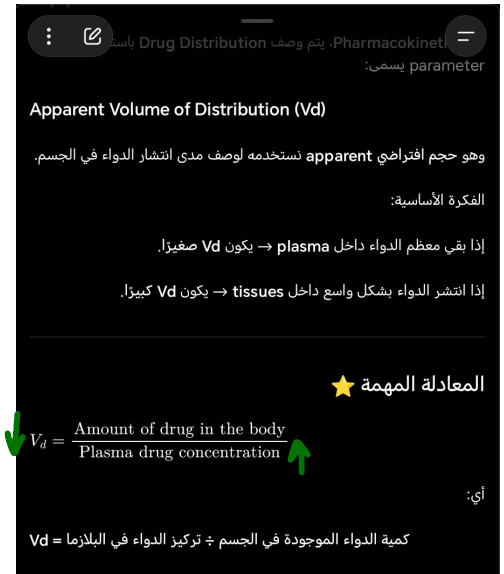
الدواء يفضل البيئات الدهنية.
→ يعبر membranes بسهولة
→ يتوزع في tissues وخصوصًا fat
→ غالبًا يزيد Vd

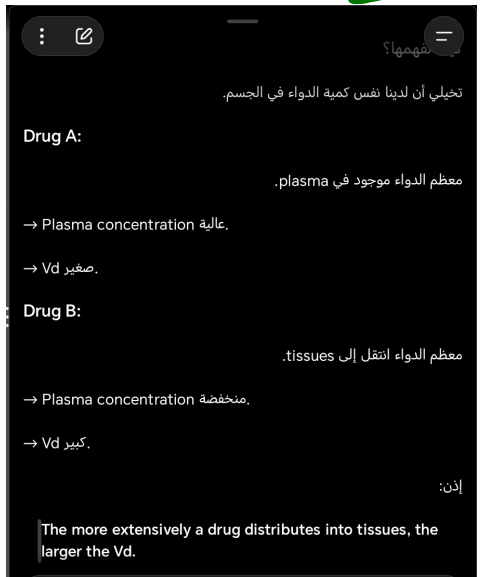
Distribution

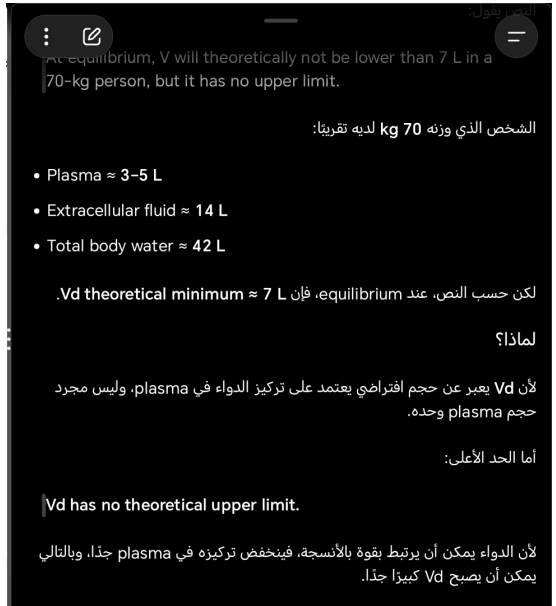
- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution.

هو حجم افتراضي

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







Drug distribution patterns

بشكل عام:
Extensive tissue distribution
→ ↑ Vd
→ كمية أكبر من الدواء موجودة خارج plasma
→ قد يحتاج الدواء وقتًا أطول ليعود من tissues إلى plasma ثم يتم التخلص منه
→ Half-life ↑ غالبًا
وهذا مهم جدًا في الأدوية التي تتراكم في tissues.

إذا كان الدواء يتوزع بشكل واسع في الجسم، فإن tissues قد تعمل كنوع من reservoir للدواء.
يعني:
بعد إعطاء الدواء → يدخل tissues
عند انخفاض plasma concentration → قد يعود الدواء من tissues إلى plasma
لذلك قد يؤثر حجم التوزيع على شكل وتركيز الدواء في plasma وعلى fluctuation في steady state.

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

يؤثر مدى انتشار الدواء على نصف عمر الدواء
وعلى التباين في تركيزه في حالة التوازن.

Distribution can be thought of as following one of four types of patterns:

1- The drug may remain largely within the vascular system. (blood/plasma) 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.

Pattern 1 → Plasma → Vd ≈ 3–5 L

ال Man وال dex بضلو في ال plasma يحموها

Drug distribution patterns

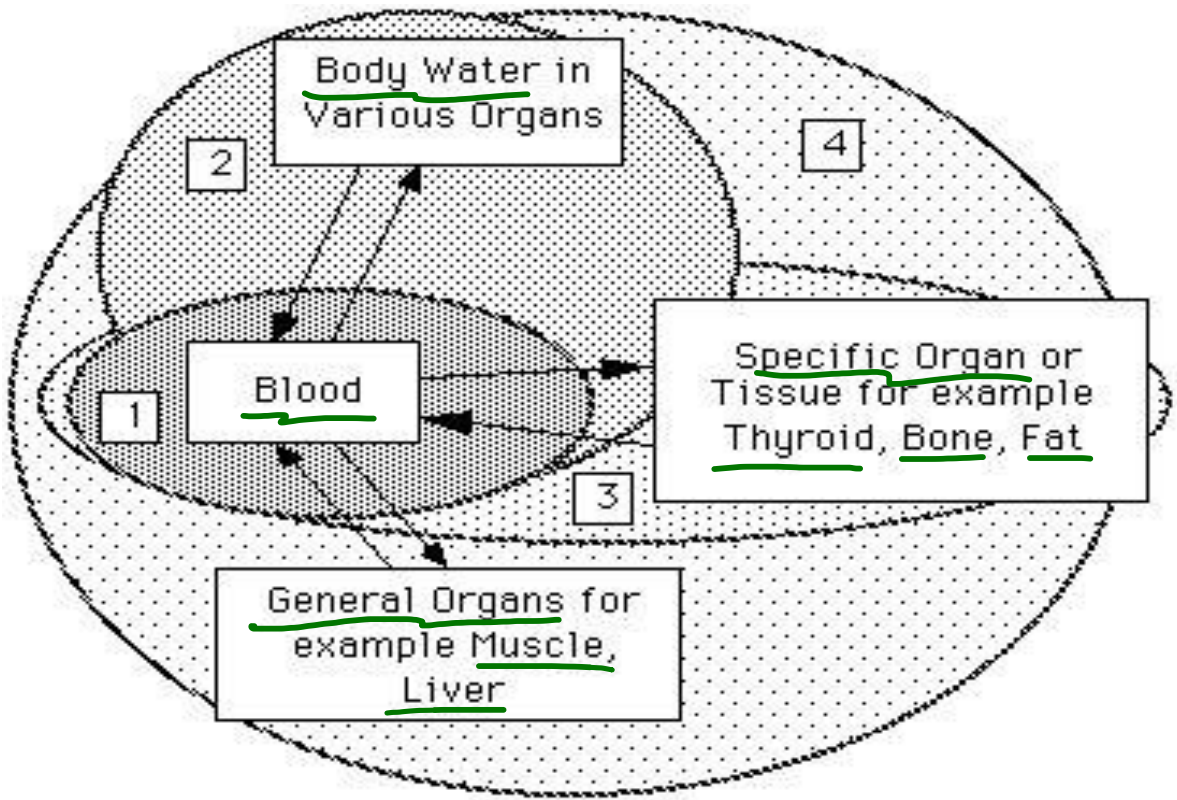


Diagram Representing Various Volumes Distribution Patterns

Drug distribution patterns

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

⭐ الكحول والـ Sulfar بحبو المي

Pattern 2 → Total body water → Vd ≈ 30–50 L

Drug distribution patterns

3- A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action. → كيس معه

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.

Vd extremely large=115 L/ kg

اللي آخرها ine هي بتتركز في أماكن معينة

Drug distribution patterns

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.

التبقع

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

Drug distribution patterns

4- 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.*

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

🔥 الخلاصة الذهبية للحفظ

احفظي هذه السلسلة:

Pattern 1

Vascular → Plasma → 3–5 L → Mannitol/Dextran

Pattern 2

Body water → 30–50 L → Ethanol

Pattern 3

Specific tissues → Very large Vd → Chloroquine / Iodine / Tetracycline

Pattern 4

Non-uniform → Wide range of Vd → Most drugs

أين نجد أعلى concentrations غالبًا؟

حسب النص:

- Kidney
- Liver
- Intestine

لماذا؟

غالبًا بسبب دور هذه الأعضاء في:

- Drug elimination
- Drug metabolism
- Drug excretion

خصوصًا:

Kidney → Excretion

Liver → Metabolism

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. وهذا يتوافق تقريبًا مع: Plasma volume
- Pattern two would be expected to produce a V value of 30 to 50 liter, corresponding to total body water. لأنه قريب من 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.

Drug distribution patterns

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

Factors affecting drug distribution

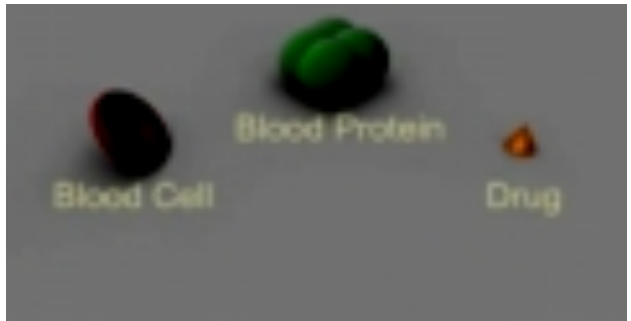
How fast does the drug reach different tissues?

How much / How far?

How extensively does the drug distribute throughout the body?

Factors Affecting Distribution	
A- Rate of distribution	**B- Extent of Distribution**
1. Membrane permeability 2. Blood perfusion	1. Lipid Solubility 2. pH – pKa 3. Plasma protein binding 4. Tissue drug binding

Blood perfusion is the flow of blood through the tiny blood vessels in the body's tissues to deliver oxygen and nutrients and remove waste



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.

الأدوية Water soluble تعبر بشكل أبطأ.
ويعتمد معدل عبورها بشكل أكبر على:
Molecular size

Low molecular weight
يمكن أن تعبر بواسطة:
Simple diffusion
لكن عندما يصبح:
Molecular diameter > 100 Å
يصبح انتقال المركب بطيئًا

السبب:
Unionized drug :
عادةً:
→ أكثر Lipid soluble
→ يعبر membranes بسهولة أكبر.
Ionized drug :
عادةً:
→ أكثر Water soluble
→ يعبر lipid membranes بصعوبة أكبر.
إذن:
Higher fraction of unionized drug → faster membrane transfer

Tricky نقطة ⚠️
لا تقولي:
"Ionized drugs cannot cross membranes."
هذا خطأ.
الأصح:
Ionized drugs cross lipid membranes less readily than unionized drugs.
وقد تعبر عن طريق آليات أخرى أو عبر pores حسب نوع membrane.

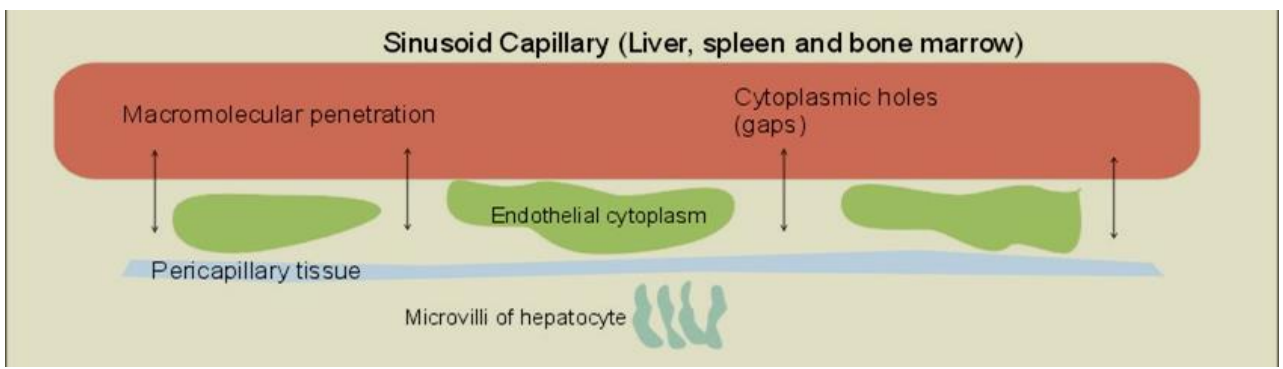
Factors affecting drug distribution

استثناءان:

- There are two deviations to the typical capillary structure which result in variation from normal drug tissue permeability.

i) Permeability is greatly increased in the renal capillaries by pores in the membrane of the endothelial cells, and in specialized hepatic capillaries, known as sinusoids which may lack a complete lining. This results in more extension distribution of many drugs out of the capillary bed.

Kidney → Pores
Liver → Sinusoids
Both → High permeability

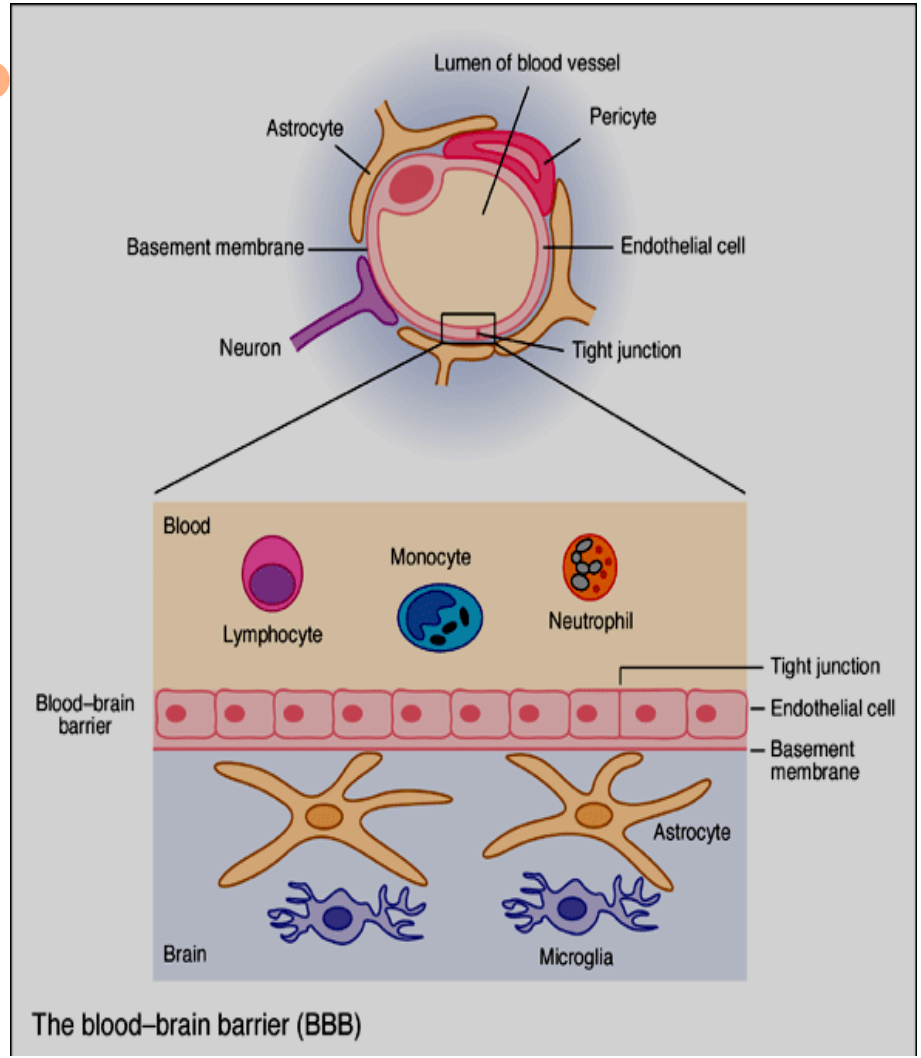


عكس الكلية والكبد تمامًا.

II) On the other hand, brain capillaries seem تجد 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. (BBB)



The blood–brain barrier (BBB)

Factors affecting drug distribution

حتى لو كان الدواء قادرًا على عبور membrane، يجب أن يصل أصلًا إلى organ.
وهذا يعتمد على:
Blood flow / Blood perfusion
كل organ يحصل على كمية مختلفة من blood flow.

② Blood perfusion rate:

- The rate at which blood perfuses to different organs varies widely:

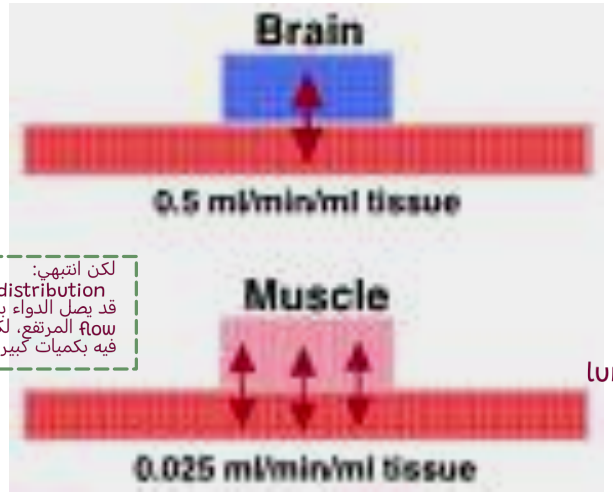
Blood Perfusion Rate		
Organ	**Perfusion Rate (mL/min/mL of tissue)**	**Percent of cardiac output (CO)**
Bone	0.02	5
Brain	0.5 - 0.55	14 - 15
Fat	0.01 - 0.03	2 - 4
Heart	0.6 - 0.7	4
Kidneys	4.0 - 4.5	22 - 24
Liver	0.8 - 0.95	25 - 27
Muscle	0.025 - 0.030	15
Skin	0.04 - 0.05	5 - 6

هذه الأعضاء:
→ يصلها الدواء بسرعة
→ يحدث rapid equilibration

High blood flow organs

High perfusion → Fast distribution

Low perfusion → Slow distribution



لكن انتبهي:
Fast distribution ≠ Extensive distribution
قد يصل الدواء بسرعة إلى organ بسبب blood flow المرتفع، لكن هذا لا يعني بالضرورة أنه سيتراكم فيه بكميات كبيرة.

lungs

Factors affecting drug distribution

- 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.

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.

وهذا قد يؤدي إلى:
- Prolonged drug storage
- Slow release
- Prolonged half-life

Factors affecting drug distribution

العلاقة الأساسية

Unionized form
→ More lipid soluble
→ Crosses membranes more readily

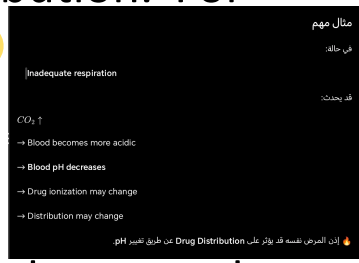
#Ionized form
→ More polar
→ Crosses lipid membranes less readily

لذلك تغير pH في الجسم قد يغير:
Drug distribution

معدل خروج الدواء من circulation يعتمد على:
Degree of ionization
وهذا يتأثر بـ:
pKa of drug
pH of environment

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.



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)

إذا ارتبط الدواء بقوة مع plasma proteins:
→ يبقى في central blood compartment
→ يقل انتقاله إلى tissues
→ يقل Vd

Factors affecting drug distribution

Plasma protein ↑

- 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.

⚠ Tricky Point
ليس كل acidic drug يرتبط فقط بـ Albumin،
وليس كل basic drug يرتبط فقط بـ α1-acid glycoprotein.

- ***Forces involved:***

- Groups on the protein molecules that are responsible for **electrostatic interactions** with drugs include:

N
S
C

  - NH3+ of lysine
  - N- terminal amino acids
  - NH2+ of histidine
  - S- of cysteine
  - COO- of aspartic and glutamic acid residues.

Initial electrostatic attraction
↓
Van der Waals + Hydrogen bonding
↓
Stable drug-protein complex

Factors affecting drug distribution

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

يتم تعزيز الارتباط بواسطة

لكن انتبهي: هذا لا يعني بالضرورة أن total absorbed dose انخفضت فعليًا؛
بل إن free concentration تكون أقل.

عندما يكون جزء كبير من الدواء مرتبطًا بالبروتين:

→ يقل free drug
→ يقل الجزء المتاح للوصول إلى tissues/receptors
→ قد يقل pharmacologic effect initially

What is the effect of protein binding on drug action?

الأفضل التفكير في:

Protein binding reduces the free fraction available for distribution and action.

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

2. 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.

High protein binding → low free fraction → slower elimination → prolonged drug effect

من الدكتوره

Factors affecting drug distribution

Digoxin
warfarin
Sulfon amide
protein bind ال drugs هذول ال
لهم عاليه

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

إذا انخفضت كمية plasma proteins:

protein binding يقل →
free drug يزيد →
pharmacologic effect يزيد →
→ قد نحتاج إلى:
Dose reduction

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.*

↳ بسبب ممكن أخسر كمية كبيرة من الalbumin

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.

Factors affecting drug distribution

🔥 سؤال Tricky جدًا

إذا كان شخص لديه **hypoalbuminemia**، ماذا يحدث لدواء highly albumin-bound؟

الجواب:

Free fraction increases

وليس:

Total drug concentration necessarily increases.

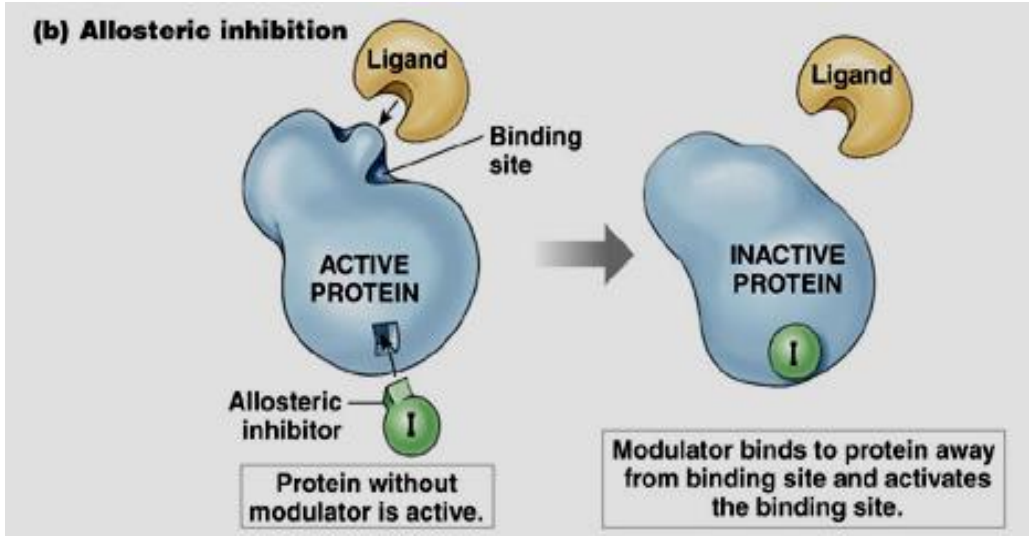
لأن:

Total drug = Free drug + Bound drug

وعند انخفاض Albumin:

Bound fraction ↓

Free fraction ↑



4. 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.

وهذا قد يؤدي إلى:
Increased pharmacological effect

وقد يزيد خطر:
Toxicity

Factors affecting drug distribution

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

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

where k1 and k2 are the association and dissociation rate constants, respectively.

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

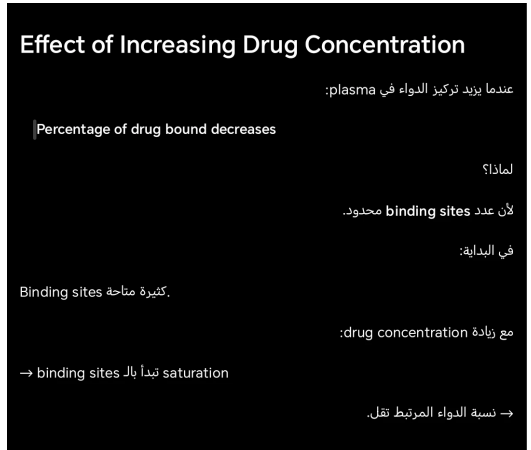
واذا قليل — هذا قليل — وهذا عالي

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

Factors affecting drug distribution

- 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):

- 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.

pattern 3 اللي كان في

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

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

pattern 3 برضو كان في

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

تكوين الجسم يختلف حسب:
Age
Obesity

1.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.

قد يختلف:
Body composition
عن الشخص البالغ المتوسط الذي تم بناء بعض pharmacokinetic parameters عليه.

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.

adipose tissue عندهم أعلى
water أقل

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

Vd

obesity ↑ ⟶ Vd of polar drug ↓

Lipophilic drug
→ يميل إلى adipose tissue
→ قد يكون Vd أعلى في obesity.

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.

🔥 مقارنة مهمة جدًا

Drug	Main Tissue Distribution
Chloroquine	Liver → DNA binding
Barbiturates	Adipose tissue → Lipid solubility
Tetracyclines	Bone + developing teeth