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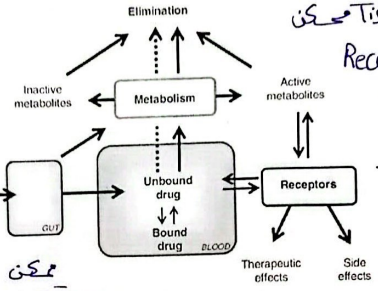
Drug Distribution and Protein Binding



Lecture 7

Drug ال Absorption وهناك بحدث GIT بال Gut عند أخذ الدوا بسير إلى ثم يعبر ال Blood ومن خلال Circulation بوع بتوزع ال Tissues وبترك الدم (Distribution)

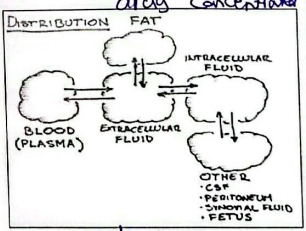
↳ Transport from Place to another

②

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
↳ Blood conc. of drug decrease drug concentrated in tissue



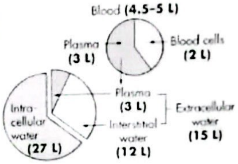
- Kidney
- Liver
- Skin
- brain
- muscles
- colon

↳ may drug bind to Protein in blood such as: Albumin

Distribution

Drug distribution in the body depends on:

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



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

- Low plasma binding, high tissue binding, high blood flow or high lipophilicity usually means an extensive tissue distribution.
- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution.
- At equilibrium, V will theoretically not be lower than 7 L in a 70-kg person, but it has no upper limit.
- The extent to which a drug distributes affects the half-life of the drug and the fluctuation of the concentration at steady state.

Drug Distribution Patterns

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.

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

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.

(5)

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. → يكون قليل جدا
- **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. Lipid Soluble اذا كان ال Drug هو
- Note that, the highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted. Distribution يصير Fatty tiss فيروح عند

↑ Blood flow for these areas; ↑ Drug installing; ↑ Distribution

(5)

Drug Distribution Patterns

Other examples

- Flutamide, antiandrogen drug, is highly concentrated in prostate (20 times that of plasma)
- Digoxin 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.

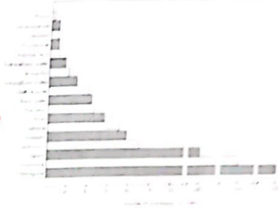
ex: DNA, that cause destruction to cells

قل V فلازم يزيد ال D

(7) ↓V : ↑ Drug in blood : ↑ Distribution

Drug Distribution Patterns

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



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

(8)

Factors Affecting Drug Distribution

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

Fick's Law:

$$\text{Diffus} = \frac{D.A(C_s - C_b)}{X}$$

- 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

Conjestive HF

Blood Perfusion

Distribution

regarding to hydrostatic Pressure

Drug

vein

tissue

Pressure

Scanned with CamScanner

(9) ↑ Particle Size : ↓ Diffusion / ↑ MW : ↑ Particle Size : ↓ Diffusion

Permeability through capillaries

Table 10.1 Permeability of Molecules of Various Sizes to Capillaries

	MW Molecular Weight	Particle Size Radius of Equivalent Sphere A (0.1 mm)	Diffusion Coefficient In Water (cm^2/sec) × 10^5	Diffusion Coefficient Across Capillary (cm^2/sec × 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

(10)

Factors affecting drug distribution

A. Rate of distribution

* there is high Permeability for Liver

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. → Gaps between cells
- 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).

Barrier هي ← تمنع دخول الـ Soluble molecules الى Brain و Spinal Cord

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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.

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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.

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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 (fatal)	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

High Blood flow

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Factors Affecting Drug Distribution

B. Extent of Distribution → اهم الكفية اللي بتعمل لها Distribution ال

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.

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.

Ph< pKa for base → so it basic drug → ionization

* RBC's bind to drug so ↓ Distribution

* Glycoprotein or albumin or Glycoα acidic when bind to drug it will be unavailable to distribution

(15)

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. → Lipid + Protein (Low density lipoprotein) LDL/VLDL/HDL (very low) — Acid Protein bind to basic drug
- The functional groups on the protein molecules that are responsible for electrostatic interactions with drugs include:
  - NH3+ of lysine, N- terminal amino acids, NH2+ of histidine, S- of cysteine, and COO- of aspartic and glutamic acid residues.

  (هدول بجاوا — Force interaction with drug)
- **Forces involved:**

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

Liver ممكن تشتغل Lipoprotein — Transporter to drug — تتوجه لل Liver — فحالة ال Distribution لل Drug — Liver

(16)

Factors Affecting Drug Distribution

Drug is not available for distribution in blood — معناها extracellular ECM سواء مع Plasma او — ارتباط مع Drug Albumin — لكن مابضل ال Drug مربوط وبصير redistribution وبطلع ال Drug وبصير Delay — زي digoxin

- **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.

long half life because bind to albumin

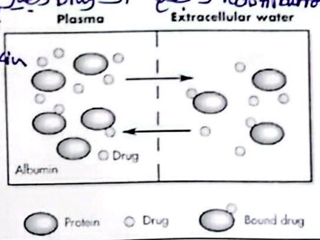

Diagram showing that bound drugs will not diffuse across membrane but free drug will diffuse freely between the plasma and extracellular water.

* Any alteration of albumin will affect on binding activity

فـ Aspirin بتأثر على lysine فبطل يرتبط مع ال Drug

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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.

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Factors Affecting Drug Distribution

- In general, plasma protein binding is reversible and obeys the law of mass action, where k_1 and k_2 are rate constants, respectively.

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

- 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.

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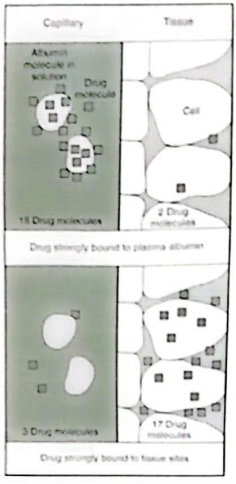
Factors Affecting Drug Distribution

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.

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.

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

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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.

water ↓ so Db

➢ 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.

Drug distribution notes

Slide 3 :

The concentration of drug in the plasma or tissues depends on the amount of drug systemically absorbed and the volume in which the drug is distributed. The apparent volume of distribution, V D in a model, is used to estimate the extent of drug distribution in the body (see and). Although the apparent volume of distribution does not represent a true anatomical, or physical volume, the V D represents the result of dynamic drug distribution between the plasma and the tissues and accounts for the mass balance of the drug in the body.

Slide 4:

Volume of distribution (Vd) is the apparent volume into which a drug disperses in order to produce the observed plasma concentration.

Mannitol is also used to help your body produce more urine. This medicine is used in people with kidney failure, to remove excess water and toxins from the body.

Vd = dose / plasma concentration

Generally, drugs with very large V D values have very low drug concentrations in plasma.

If the drug is distributed widely into the tissues or concentrates unevenly into the tissues, the V D for a drug may exceed the physical volume of the body (about 70 L of total volume or 42 L of body water for a 70-kg subject).

Slide 8:

Hydrostatic pressure represents the pressure gradient between the arterial end of the capillaries entering the

tissue and the venous capillaries leaving the tissue. Hydrostatic pressure is responsible for penetration of

water-soluble drugs into spaces between endothelial cells and possibly into lymph. In the kidneys, high

arterial pressure creates a filtration pressure that allows small drug molecules to be filtered in the glomerulus

of the renal nephron (s

At the arterial end, as the blood newly enters the capillary (), however, the pressure of the capillary blood is

slightly higher (about 8 mm Hg) than that of the tissue, causing fluid to leave the capillary and enter the

tissues. This pressure is called hydrostatic or filtration pressure. This filtered fluid (filtrate) is later returned to

the venous capillary () due to a lower venous pressure of about the same magnitude. The lower pressure of

the venous blood compared with the tissue fluid is termed absorptive pressure. A small amount of fluid

returns to the circulation through the lymphatic system.

Slide 10:

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

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.

Slide 12:

Angstrom is a unit of length equal to 10−10 m; that is, one ten-billionth of a metre, 0.1 nanometre, or 100 picometres. Its symbol is Å,

Slide 15:

A person with congestive heart failure has decreased cardiac output,

resulting in impaired blood flow, which may reduce renal clearance through reduced filtration pressure and

blood flow.

COO- carboxylic acid. NH2 azanide S sulfate

Acid glycoprotein (orosomucoid) is a globulin with a molecular weight of about 44,000 Da. The plasma concentration of 1-acid glycoprotein is low (0.4â 1%) and binds primarily basic (cationic) drugs such as propranolol, imipramine, and lidocaine. Globulins (-, -, -globulins) may be responsible for the plasma transport of certain endogenous substances such as corticosteroids. These globulins have a low capacity but high affinity for the binding of these endogenous substances.

Lipoproteins are macromolecular complexes of lipids and proteins and are classified according to their density and separation in the ultracentrifuge. The terms VLDL, LDL, and HDL are abbreviations for very-low-density, low-density, and high-density lipoproteins, respectively. Lipoproteins are responsible for the transport of plasma lipids to the liver and may be responsible for the binding of drugs if the albumin sites become saturated.

Erythrocytes, or red blood cells (RBCs), may bind both endogenous and exogenous compounds. RBCs consist of about 45% of the volume of the blood. Phenytoin, pentobarbital, and amobarbital are known to have a RBC/plasma water ratio of 4 to 2, indicating preferential binding of drug to the erythrocytes over plasma water. Penetration into RBC is dependent on the free concentration of the drug. In the case of phenytoin, RBC drug level increases linearly with an increase in the plasma-free drug concentration (). Increased drug binding to plasma albumin reduces RBC drug concentration. With most drugs, however, binding of drug to RBC generally does not significantly affect the volume of distribution, because the drug is often bound to albumin in the plasma water. Even though phenytoin has a great affinity for RBC, only about 25% of the blood drug concentration is present in the blood cells, and 75% is present in the plasma because the drug is also strongly bound to albumin. For drugs with strong erythrocyte binding, the hematocrit will influence the total amount of

drug in the blood. For these drugs, the total whole-blood drug concentration should be measured.

Slide 16:

Drugs may bind to various macromolecular components in the blood, including albumin, 1-acid glycoprotein, lipoproteins, immunoglobulins (IgG), and erythrocytes (RBC).

Albumin is a protein with a molecular weight of 65,000â 69,000 Da that is synthesized in the liver and is the major component of plasma proteins responsible for reversible drug binding (). In the body, albumin is distributed in the plasma and in the extracellular fluids of skin, muscle, and various other tissues. Interstitial fluid albumin concentration is about 60% of that in the plasma. The elimination half-life of albumin is 17 to 18 days.

Slide 17:

Albumin is responsible for maintaining the osmotic pressure of the blood and for the transport of endogenous and exogenous substances.

Alteration of the protein by a substance that modifies the affinity of the drug for the protein; for example, aspirin acetylates lysine residues of albumin

Slide 18:

Albumin has two known binding sites that share the binding of many drugs (). Binding site I is shared by phenylbutazone, sulfonamides, phenytoin, and valproic acid. Binding site II is shared by the semisynthetic penicillins, probenecid, medium-chain fatty acids, and the benzodiazepines. Some drugs bind to both sites. Displacement occurs when a second drug is taken that competes for the same binding site in the protein as the initial drug.

Many weak acidic (anionic) drugs bind to albumin by electrostatic and hydrophobic bonds. Weak acidic drugs such as salicylates, phenylbutazone, and penicillins are highly bound to albumin. However, the strength of the drug binding is different for each drug.

When a highly protein-bound drug is displaced from binding by a second drug or agent, a sharp increase in the free drug concentration in the plasma may occur, leading to toxicity. For example, an increase in free warfarin level was responsible for an increase in bleeding when warfarin was co-administered with

phenylbutazone, which competes for the same protein-binding site (; ;). Recently, studies and reviews have shown that the clinical significance of warfarin protein binding and its impact on bleeding are less prominent, adding other factors and explanations.

n chemistry, the law of mass action is the proposition that the rate of a chemical reaction is directly proportional to the product of
the activities or concentrations of the reactants.[

Moreover, any alteration of the protein structure may also change the capacity of the protein to bind drugs. For example, aspirin acetylates the lysine residue of albumin, which changes the binding capacity of this protein for certain other anti-inflammatory drugs, such as phenylbutazone.

Slide 20:

allosteric nature of protein binding. This means that the binding of a drug modifies the conformation of protein in such a way that the drug binding influences the nature of binding of further molecules of the drug. The binding of oxygen to hemoglobin is a well studied biochemical example in which the initial binding of other oxygen to the iron in the heme portion influences the binding of other oxygen molecules.