Pharmacology

Subject :

Lec no :   4

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وَقُل رَّبِّ زِدْنِي عِلْمَا

للوصول الى guidance الفارما و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

شرح دكتور شريف و دكتور طارق للمادة

شرح فودة لمادة الميد

شرح فودة لمادة الفاينل

تفاريغ دفعة اثر جدااا قوية ، خاصة مادة الفاينل لانها بتحتاج تفاريغ كثير ، و برضه تفاريغ جهينة بدفعة وريد قوية

جداول رح تساعدكم كثييييير بحفظ الأدوية بمادة الفاينل

كويزات الدكاترة

الدراسة صعبة وَ رُبَّما مُملة!! ولكنها ستوصلك إلى حلمك هذا الحُلم لن يتحقق وأنت نائم وأنت خائف وأنـت خائف لن يتحقق وأنـت تشتكي لن يتحقق و أنـت لا تذاكر هذا الحُلم سيتحقق فقط بالدراسة والإجتهاد بالتنقل بين الكتب والمراجع بالليالي الطويلةِ من المذاكرة وبالتعب فبالتأكيد ، حُلمك يستحق التعب! فلا تتخلى عن هدفك استمر حتى وإن لم تجري الأُمور كما خططت لها ولا تسمح لإحدٍ بإن يوقفك أبِهرهم بنتائجك! لديك حُلمٌ كبير وأنـت تستحق أن تُحققه .

DISTRIBUTION OF DRUGS

❖ <u>It is</u> the passage of drug through body compartments which are separated by capillary walls and cell membranes.

❖ Body fluid compartments:

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** of normal body
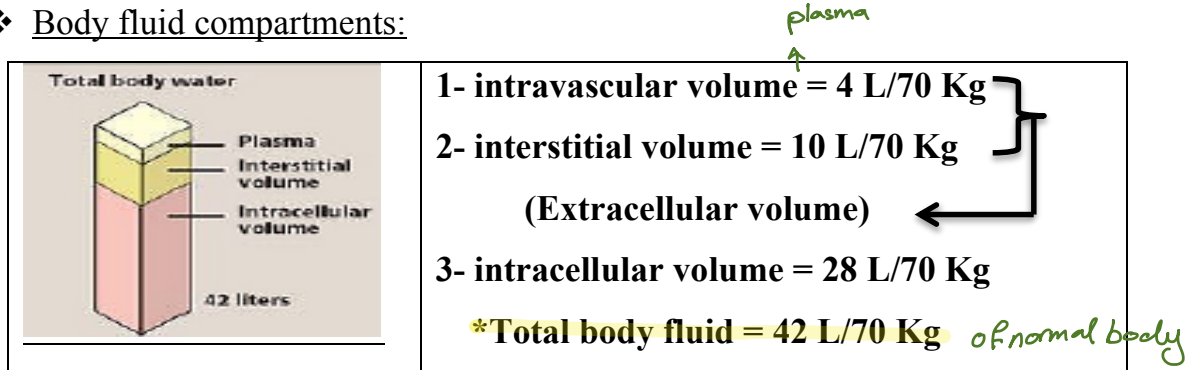
✳ **Pattern of distribution:**

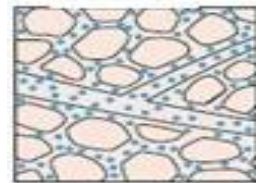**1. Plasma compartment (one compartmental model):**

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

- 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.
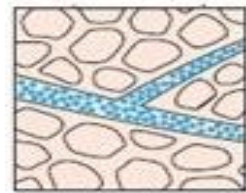
- e.g. Heparin , Dextran.

2. Extracellular fluid (two compartmental models):

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

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

- If a drug has a **low molecular weight** and is **lipophilic**
- 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.

- 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)

4. Tissue reservoir: Drugs concentrated in certain tissues

يكون وجود في
مكان معين mainly

- **Iodine** in thyroid & salivary glands
- **Calcium & tetracyclines** in bone & teeth
- **Chloroquine** in liver
- **Thiopental** in fat (Redistribution ??)

جاي عليها
سؤال في الامتحان + مطلوب نمتحن
شويني
عنها

❖ Volume of Distribution (V$_d$)

- 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).

نعتبر من انو فنجان القهوة هو (C)
وكمية السكر الي بداخلها (A)

Vd = 35L
of drug

حماي كلها طوت
كتابة تعبرن Vd

او

Vd = 35L

او عيان وزنه (70) فيقسم
$= \frac{35}{70}$

0.5L/kg

له لو اعطاني اياها
في حماي الصورة انا
بكون محتاجة اجنور وزن
الجسم لانلاقي جو حتي
جو (Vd)

لو قال اذا انت
(70kg normal adult)
اعرف انو

70 × 0.5

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

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

او في

Q = A

حنوري/خاصري

- 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**.

- **Importance of V$_d$**

مدتر للبول

Furosemide 20mg
Tablets

DIGOX
(digoxin tablets, USP)
250 mcg (0.25 mg)

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.
- Large V$_d$ (e.g. digoxin) indicates extensive tissue distribution.

(420L) → هدا حش عدد حقيقي $= \frac{\text{عدد كبير}}{\text{عدد صغير}} = $ عدد كبير

جنب ليه جميل طلع ؟ لومثلا هدا الدوا في ال Liver ، رح يكون كتير condense عدالستسكا الخ
وال protien داخله الكتر في ال plasma ، بصيرال C تاع الplasma قليل وال drug جنب ما اشوف (U2g)
فمنا هدا لو احتجت fluid حتى ارجع ال C بين ال plasma و ال Tissue بري (420L)

V = 3/M → plasma
V = 10/11/12 → interstitial + plasma
V = 40/35 → " + plasm + tissue
V = 400 → Multi compartment
متركز بالTissue جدًا +

+ الليدوماي نجسم فيه (420h) ← بس هو معنه الانواع لا معنا وتترك ال mesm بكمية قليلة

2. In cases of drug toxicity:

غسيل كلى
- Dialysis is **not useful** for (**high**) V_d drugs (most of drug is in the tissues).

- Dialysis is **useful** for **low** V_d drugs (most of drug is in the blood).

بدي أعطي جرعة ← **3.** V_d can be used to calculate the **loading dose (LD):** (أعطي إياها)
كبيرة للعلاج حتى اوصل
ل ـء بسرعة بعدها
بخفف الجرعات

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

4. V_d can be used to calculate the **total amount of drug** in the body: ←
في حالة أخذ عدد كبير من
الأدوية و بدنا نعرف بالزبط
(إلي ماخذها)
كم اخذ (مثل حالات الانتحار)

$$[A = V_d \text{ x } C_p]$$

❖ **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. → والعكس صحيح

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):

رح يفوت الـ Tissue ولا لأ؟
- Most of drugs when introduced into the body are bound to plasma proteins (pp) e.g.

الدوا أول ما يفوت الدم ما بكون free ←
جزء بكون free وجـزء رابط مع plasma

- **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
شـ رح يجيب

وهيك يضل حتى كل الـ
free بيشتغل و يكمل
(ADME)

Free fraction	Bound fraction
• Active	• **In**active
• Diffusible	• **Non**diffusible
• Can be Metabolized	• Can**not** be metabolized
• Can be Excreted	• Can**not** be excreted
	• Act as a reservoir for drug

(handwritten margin notes in Arabic/English: "action بتدريجل", "un able to do action", "مابروح لعضعا TISSUE ظل جوال plasma", "store of drug", "فايدته", "كل مايقل الا عضعا بيعطي")

- **Significance of Binding to Plasma Proteins**

1. The binding of drug to plasma proteins **limits its tissue penetration & decreases its V_d.**

   (green handwriting: لو كان الدوا مرتبط مع الplasma بشكل قوي او بكمية كبيرة يبقى اكيد الكمية الي رح تروح لل tissue قليلة بالتالي رح يقل ال vd)

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

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

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

- Aspirin, sulphonamide displace warfarin → bleeding.
- Sulphonamide displaces bilirubin → kernicterus in premature neonates.

(margin notes: "العكس صحيح لو الا drug اكبر free", "نقص بسبب نقص في تقذية أو الا بمعنا ما يصنع اوال زيادتا فيها مشاكل فـ بتنزلو مع urine", "يعير و بعمل Jaundice", "الاطفال الصغار", "للقراءة فقط")
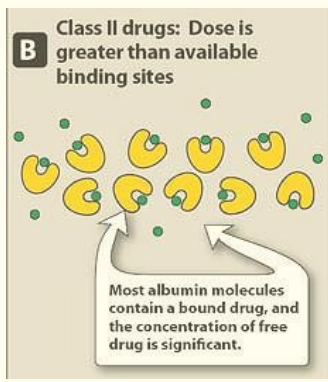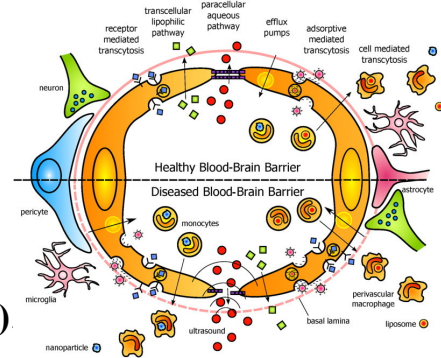
{When two drugs with high affinity for albumin are given, they compete for the available binding sites. The drugs with **high affinity** for albumin can be divided into two classes:

1. **Class I drugs:** If the dose of drug is less than the binding capacity of albumin i.e. **low dose/capacity ratio** → high bound fraction and **small free fraction**

2. **Class II drugs:** If the doses greatly exceed the number of albumin binding sites i.e. **high dose/capacity ratio** → **high free fraction**.

* When a patient taking a Class I drug, such as warfarin, is given a Class II drug, such as a sulfonamide antibiotic. Sulfonamide displaces warfarin from albumin, leading to a rapid increase in the concentration of free warfarin in plasma → ↑ therapeutic effects, as well as ↑ toxic effects → bleeding}
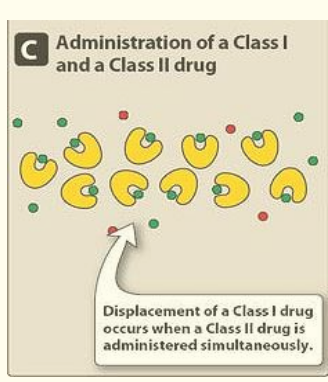
Jaundice — Yellowing of eyes — Yellowing of skin — Excess bilirubin in blood

Kernicterus — Bilirubin moves from bloodstream into brain tissue

B Class II drugs: Dose is greater than available binding sites — Most albumin molecules contain a bound drug, and the concentration of free drug is significant.

C Administration of a Class I and a Class II drug — Displacement of a Class I drug occurs when a Class II drug is administered simultaneously.

✱A.D.A.M.

4) Binding to cell and tissue constituents:

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

❖ Passage across barriers:

Passage of Drugs to CNS

1. **Lipid-soluble** drugs pass freely through BBB, e.g. general anesthetics and other CNS depressants.

2. **3ry amines** can pass while 4^{ry} NH_4^+ compounds (ionized) cannot.

3. **Some hydrophilic** antibiotics e.g. penicillin can pass **inflamed BBB** only

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Passage of Drugs to the Fetus   جنين

- 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** of pregnancy → **teratogenicity** e.g. thalidomide → phocomelia   تشوهات في الأجنة

  ➤ Oral anticoagulants → fatal hemorrhage in the newborn.

  ➤ Oral hypoglycemics (sulfonylureas) → prolonged neonatal hypoglycemia.

  ➤ Aminoglycosides → 8th cranial nerve damage.

  ➤ During labor, Morphine → respiratory depression (asphyxia neonatorum).
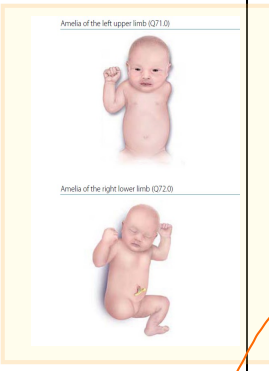
Passage of drugs to breast milk

➤ 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.

➤ Oral penicillins and purgatives → diarrhea in baby.

➤ Anticancer drugs → decrease growth of baby.

➤ Bromocriptine & sex hormones → suppress lactation.

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