Lecture 5
Pharmacology

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Second Year
Passion Batch
Distribution:

- Drug distribution: is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells.
- After the drug is absorbed and entered to the plasma, it should be distributed to the organs.
- We can’t decide which organs that the drug should go to, so it will distributed everywhere.

- Plasma
- Interstitial fluid
- Intracellular fluid

- Distribution factors:
  1. Blood flow (the major factor)
  2. Capillary permeability
  3. The degree of binding of the drug to plasma and tissue proteins (Albumin binding sites)
  4. Volume of distribution (Vd)

These factors influence the distribution and concentration of drugs.
Now we will talk about factors one by one:

- **Blood flow**:
  - The more blood flow the more distribution.
    - Blood flow to the brain, liver, and kidney (respectively) is greater than that to the skeletal muscles and adipose tissue.
    - The high blood flow permits drugs to rapidly move into the central nervous system (CNS).

- **Capillary permeability**
  Just Capillaries have the permeability for exchanging drug, and this depends on:
  a. Capillary structure:
    - Capillary structure may have slit junctions between endothelial cells e.g., in the liver and spleen or continuous structure (no slit junctions) such as in the brain (BBB).

     (BBB) is a highly selective barrier separate blood circulation from brain extracellular fluid. so not all drugs can enter the brain, in other words, not all drugs can be distributed to the brain. 

    - so we have 3 major factors (rules) that determine if the drug can cross the BBB:
      1. Hydrophobic (lipophilic) (uncharged).
Lipid-soluble drugs can penetrate into the CNS because they can dissolve in the membrane of the endothelial cells

2. Small molecular size (drug structure).
3. Carrier (for active transport) such as levodopa. *the drug in this case is aqueous solution.

b. Drug structure:
   - Hydrophobic drugs which have no net charge readily move across cell membranes.
   - Hydrophilic drugs, which have positive or negative charge, do not readily penetrate cell membranes.

➢ The degree of binding of the drug to plasma and tissue proteins:
   - Plasma albumin is the major drug-binding protein and may act as a drug reservoir. (90%)
   - Another plasma protein is globulin or (beta globulin). (10%)

The rule of drug-protein binding:
As the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein.

Competition for binding between drugs and drug displacement:
• The drugs with high affinity for albumin can be divided into two classes:
Class I drugs: If the dose of drug is less than the binding capacity of albumin. The binding sites are in excess of the available drug, and the bound-drug fraction is high.

Class II drugs: These drugs are given in doses that greatly exceed the number of albumin binding sites. And a relatively high proportion of the drug exists in the Free State, not bound to albumin.

- A Class I drug, such as warfarin, is given a Class II drug, such as a sulfonamide antibiotic.
- Warfarin is highly bound to albumin

Warfarin is a drug used to prevent angina and MI and it has a narrow therapeutic index that is mean any small increase in the dose we will reach toxic dose easily!

- Gums
- Trauma under the skin
- Blood in the urine

1. Distribution
Competition for binding between drugs and drug displacement:

have a high affinity when taking two drugs together, one has a lower affinity to plasma proteins (warfarin) and the other has a higher affinity (sulfonamides). When taking warfarin, it has a high affinity for plasma proteins, occupying 30% of the plasma volume. This can increase the plasma concentration of warfarin and lead to a toxic dose.

Drugs are divided into two types:

Type I → with lower affinity to plasma proteins e.g. warfarin

Type II → with higher affinity e.g. sulfonamides (a drug which is given for diabetes patients)

In the case of a patient with heart disease and diabetes, what is the recommended approach?

1. we can make warfarin dose lower than usual
   - by reducing the dose of warfarin, we can stay below the toxic dose.

2. we can change the other drug
   - by changing the other drug, we can reduce the affinity of warfarin from the plasma proteins.

Volume of distribution (Vd)

- Drug distribute into any one of three functionally distinct compartments of body water:
  - Volume of distribution (Vd)
  - Drug distribute into any one of three functionally distinct compartments of body water.
1. Plasma compartment: If a drug has a very large molecular weight or binds extensively to plasma proteins.

2. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid.

3. Total body water: If a drug has a low molecular weight, hydrophobic and doesn’t bind to plasma proteins.
   - In general about 42 liter in a 79-kg individual are water.
     a) 4-5 liters are plasma
     b) 10 liters are interstitial fluid (between the cells)
     c) 28 liters intracellular fluid

Notes:
- A+B are called extracellular volume and C is called intracellular volume
- The volume in plasma is not constant for example in pregnancy the volume increase (that is the reason why pregnant women has anemia approximately at the 4th month (this anemia is diluted anemia).
- Most of the drugs that enter the cells are steroids e.g. cortisone because it has a high lipophilicity.
VD is a useful pharmacokinetic parameter for calculating the loading dose of a drug.

VD = Dose / plasma con.

VD is not constant, there are factors effect on it these factors are:

1. The drug (the changes are related mostly to the drug)
2. The patient
   - Why the changes are related mostly to the drug?

Because it depends if the drug: hydrophobic or hydrophilic, has a small or big particle size, affinity to protein binding sites in plasma.

The equation above expresses the ideal conditions, which appear in IV injection not orally.

Relationship of drug displacement from proteins to VD:

- If VD is large: Change in free-drug concentration in the plasma is not significant.
- If Vd is small: Change in free-drug concentration in the plasma is significant
- If Therapeutic index is small: any increase in drug concentration may have significant clinical consequences
The protein binding will not affect the drug with the large volume of distribution

Any small change will change the concentration

Panadol: it has a wide therapeutic index \( \rightarrow \) the toxic dose for it is 10 grams

That is mean paracetamol doesn’t effected by protein displacement

1. Drugs have a narrow therapeutic index (عددها قليل)
2. Have a low volume of distribution (يعني رح يكون تركيزها بالبلازما كبير)
3. Have a high affinity to proteins

Now, if those rules found in drug , that means there are protein binding significant \( \rightarrow \)

Note: VD for each drug is constant
Relationship of drug half-life (t1/2) to VD

- Half-life (t1/2): time it takes to reduce the plasma drug conc by half
- If a drug has a large VD, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases VD can increase the half-life and extend the duration of action of the drug.
- Any factor that increases the volume of distribution can lead to an increase in the half-life and extend the duration of action of the drug.
- Vd increase → t1/2 increase → duration of action increase

Highly distributed drug means that the half-life is long.

So the relationship: if VD is high → the half-life is long → the duration of drug is long → we have to give the patient less times of drug (frequency)

Chapter one part 1 is done ....
Chapter one part 2:

- **Drug clearance:**

  Drugs clearance by:
  
  1. Hepatic metabolism
  2. Excretion (elimination) into the urine or into the bile

  These elimination process cause plasma conc of drugs to decrease exponentially

  نَعْلَا السؤال .. اهنا ليش اعتبرنا آخر خطوتين مع بعض ؟ لانه مو كل الأدوية بصيرلهم (metabolism)

  **Note:** Not all drugs are exerted in the urine they metabolized and then go to bile.

  * 85-90% of drugs are metabolized.
  * 10-15% of drugs aren’t metabolized (exerted in urine by active as it). e.g. penicillin → so that we use it to treat urinary infection.

  السؤال إذا ا الدواء ما صارله (metabolism) كيف رح نستفيد منه ؟!!

  رح نستفيد من خلال معالجة ال (active) بحيث انه يكون (urinary infection)

  مثال آخر ذكرته الدكتورة الي هو ال rifampin or rifampicin هو دواء يعطي لمرضى السل (TB) لمدة 6 أشهر لستنين ..

  This drug results in red colure in:

  Tears, urine, saliva and sweat

  لكن هذا اللون هو لون الدواء نفسه مو ناتج عن الدم ..
- **Metabolism:**

Metabolism: is the process of transforming lipophilic drugs into more polar readily excretable products.

- The liver is the major site for drug metabolism, and other tissues, such as the kidney and the intestines.
- Some agents are initially administered as inactive compounds (prodrugs) and must be metabolized to their active forms.

**Notes:**

- The liver is a factory for synthesis and waste products elimination.
- Not all metabolism processes are bad, sometimes when the drug is inactive it’s become active in the liver \( \rightarrow \) that drugs is called prodrugs.

- **Clearance:**

  - Clearance is the amount of drug eliminated from the body per unit time.
  - Total clearance = clearance by liver + kidney + saliva + sweat...etc.

  *clearance by breastfeeding* 

المرأة الحامل بصير معها

يعني الأدوية تصل لللحبوب أيضاً بالتالي لازم تنظيم عملية الرضاعة وأخذ الدواء يعني تترك فترة ما بين الرضاعة والدواء.

****راجع للمعادلة بالسلاليدات (سلايد رقم 4) المعادلة مهمة من حيث فهم العلاقة بين أطراف المعادلة.
كل ما كان الVD أكبر بالتالي لما يكبر المقام رح يقل الناتج ...
CL الخلاصة: إذا زاد الVD رح يزيد الhalf-life =\( \rightarrow \) ويقل الCL، إذا أقل الVD رح يزيد الhalf-life =\( \rightarrow \) ويقل الCL.