Lecture 5

Pharmacology

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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.

  عند أخذ أي دواء رح يروح هي الأماكن :

  - 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

ذكرت الدكتورة مثال على ذلك للتوضيح ال (warfarin) :

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 !

وبيظهر على شكل نزيف في :

- Gums

- Trauma under the skin

- Blood in the urine

الآن لو اعتبرنا البروتينات الي في البلازما كراسي...وكان في 300 كرسي و أضفنا 100 جزيء وارفارين... 30 منهم جلسوا ع الكراسي (ارتبطوا بالبروتينات الي في البلازما) بيضل 70 ما ارتبطوا ببروتينات وضلوا حرين الحركة بداخل البلازما ...

هلأ هدول ال 70 ممكن يحدثلهم 3 عمليات :

1. Distribution

2. Make action
3. elimination

هلا نيجي نحكي عن ال:

Competition for binding between drugs and drug displacement:

عند أخذ دوائين معاً أحدهما ال (warfarin) والدواء الآخر يحب الارتباط بالبروتينات أكتر من الوارفارين (have a high affinity) رح يرتبط بالبروتينات في البلازما وياخد مكان ال 30% الخاصة بالوارفارين فبيزيد تركيز الوارفارين الحر بالبلازما وممكن يصل لل ((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)

فبديهياً رح نستنتج انه (II) يأخذ مكان (I)

طيب لو حدا معه مرض بالقلب وبنفس الوقت مريض سكري كيف ممكن أتعامل مع هالحالة ؟؟!

بهي الحالة يجب مراعاة تأثيرهم ع بعض ببسبب ال (drug displacement) الي رح يصير لانه اذا صار رح يسبب الوفاة بسبب ال bleeding الي رح يصير بسبب ال warfarin لما يوصل لل toxic dose الحل كالتالي :

1. we can make warfarin dose lower than usual
   بحيث حتى لو زاد تركيزه ما نوصل لل (toxic dose)
2. we can change the other drug

بحيث انه يكون اله (affinity) أقل من الوارفارين

- **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 4^{th} 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 .

يعني هي المعادلة رح تكون خاطئة لو حسبنا التركيز بعد أخذ الدواء عن طريق الفم لانه هناك عوامل أخرى مثل ال (F) تكون في حال الأخذ عن طريق الفم وتقلل من ال (dose) التي تم امتصاصها

Relationship of <u>drug displacement from proteins</u> to <u>VD</u> :

- 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

توضيح:

- The protein binding will not affect the drug with the large volume of distribution

ما حدا يبعت للدكتورة ايميل الموضوع بسيط جداً ☺

*اذا كان ال (VD) عالي ... اذاً ال (drug) مش رح يكون موجود بالبلازما ...

كل الدواء راح على ال (interstitial fluid and intracellular fluid)

اذاً الدواء المتبقي في البلازما حتى لو صارله (displacement) من دواء ثاني

ما رح يأثر كثير يعني رح يكون التأثير قليل جداً...

*من ناحية تانية اذا كان ال (VD) منخفض للدواء هذا يعني انه الدواء كله بالبلازما لذا :

Any small change will change the concentration

*مثال على ذلك :

Panadol : it has a wide therapeutic index → the toxic dose for it is 10 grams

يعني اذا قررت تنتحر البنادول ما رح ينفع لانه بتحتاج 20 حبة لتوصل لل toxic dose و بعديها رح يصير hepatotoxicityفقط ☺

That is mean paracetamol doesn't effected by protein displacement

هلا شو أنواع الأدوية الي ببتأثر بالبروتين 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 → وبالتالي بنعرف انه ممنوع نعطيهم مع بعض

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

توضيح :

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

هذا يعني اذا كان الدواء (highly distributed) رح ينتشر بكل ال (fluids) الموجودة بالجسم

واذا بدنا نتخلص من الدواء لازم يروح للكبد

مشان هيك رح يحتاج لوقت أطول حتى يخرج من الخلايا وبصير عنده (long half life)

أما اذا كان (high molecular weight) ما رح يدخل للخلايا ورح يضل بالبلازما

ف رح يكون ذهابه للوقت أسرع وبكون (short half life)

ملاحظة مهمة : على جميع الحالات الدواء لازم يروح للكبد مشان يصيرله (detoxification)

والدواء حتى لو كان اله(long half life) رح يطلع من الخلايا عن طريق ال(concentration gradient)

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) يعني بدل 3 مرات باليوم مرة واحدة بتكفي

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

هلأ السؤال .. انه 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 (urinary infection) بحيث انه بكون (active)

مثال آخر ذكرته الدكتورة الي هو ال rifampin or rifampicin

هو دواء يعطى لمرضى السل (TB) لمدة 6 أشهر لسنتين ..

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 → that drugs is called prodrugs\
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➢ **Clearance** :

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

المرأة الحامل بصير معها clearance by breastfeeding

يعني الأدوية تصل للحليب أيضاً بالتالي لازم تنظم عملية الرضاعة و أخذ الدواء يعني تترك فترة ما بين الرضاعة والدواء .

****ارجع للمعادلة بالسلايدات (سلايد رقم 4) المعادلة مهمة من حيث فهم العلاقة بين أطراف المعادلة

كل ما كان ال VD أكبر كان ال t1/2 أكبر وبالتالي لما يكبر المقام رح يقل الناتج ...

الخلاصة :اذا اذا زاد ال VD ==> رح يزيد ال half-life ==> ويقل ال CL

اذا قل ال VD==> رح يقل half-life ==> ويزيد ال CL