Medical Committee
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PHARMACOLOGY

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SHEET

SLIDES

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Pharmacokinetics

Salam everybody ; hope you're doing well ☺

Here we are going to complete our discussion in the two previous lectures about pharmacokinetics of drugs.

Don't worry; it will be an easy lecture inshallah. I promise ☺

* Enterohepatic cycling of drugs :

- The prefix " entero " means " gut " , therefore; the enteric system is the digestive system (الجهاز الهضميّ المعويّ) and is related to intestines.

- The prefix " hepat " refers to the liver .

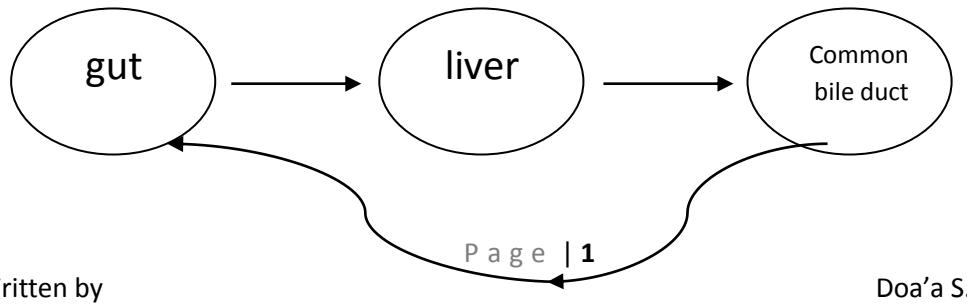
- Accordingly, the Enterohepatic cycle is related to both the digestive system and the liver. It is a cycle between the liver and the intestines.

- When a drug is taken orally " by **mouth** " , it goes to the gut , it is absorbed there (It doesn't matter whether the absorption is achieved by the duodenum or the intestines , the important point is that a drug is absorbed by a part of the gut whatever it is) . After the drug is absorbed by the **gut** , it goes through the **portal vein** to the **liver** then to the **systemic circulation .**

- The path that I have already mentioned (in bold above) is the **normal(ordinary)** track of an orally taken drug .

- Sometimes and for certain drugs, there is what we call " **biliary excretion** " . In this case, after the drug is absorbed in the gut and reabsorbed again by the portal vein to the liver , some of it goes to the hepatic vein (i.e. enters the systemic circulation) while another portion of the drug enters the common bile duct (i.e. excreted in bile) . The portion of the drug that was excreted in bile goes to the gut again.

- We can summarize the Enterohepatic cycle of a portion of a drug by the following chart: (Refer also to the picture that clarifies the path during this circulation in the slides)



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It is clear now that it is a circulation ☺

- Again, in enterohepatic cycle a portion of the drug dose circulates between the liver and the intestines without going to the systemic circulation. According to this, the Enterohepatic cycle reduces the amount of the drug entering the systemic circulation **(i.e. it reduces the bioavailability of the drug) .**
  Remember that in the previous lecture we have mentioned many factors that contribute in lowering bioavailability and the enterohepatic cycle was one of them. Now you've understood what is enterohepatic cycle and its role in lowering the bioavailability of a certain drug.

- Do you think that the enterohepatic cycle will affect the half-life of the drug?
  Yes, if a portion of the drug undergoes the enterohepatic cycle, **the half-life of that drug will be prolonged** because the portion that was excreted in bile goes again to the gut and therefore can be *reabsorbed* again, it again goes to the liver and part of it goes to the systemic circulation while another part goes to the common bile duct and the cycle continues. (The drug stays for more time in the body that's why we said that its half-life was prolonged due to the enterohepatic cycle) .

- Remember that we said that some drugs undergo enterohepatic cycle but not all of them. Only if a portion of the drug can be excreted in bile, the drug has the *characteristic* of enterohepatic cycling. Some drugs cannot be excreted in bile and therefore they do not undergo the enterohepatic cycle.

- <u>A clinical application for the enterohepatic cycle :</u>
  This cycle is important in cases of drug overdose. Let's see how and why.
  In cases of drug overdose (put in mind that we're talking here about drugs that undergo enterohepatic cycle), we usually put something that catches the drug after it is excreted in bile through the common bile duct and before it gets again to the gut, this way the enterohepatic cycle was interrupted and we've *prevented the reabsorption* of the drug by the gut again .
  (Reabsorption must be reduced to prevent the toxic effect of more and more drug since we have overdosage) .
  Logically speaking, when reabsorption of a drug is prevented, *elimination of it increases*. A substance is used to trap the drug before it reaches the gut again in order to prevent its reabsorption, this substance after attaching to the drug continues its journey till it is

expelled outside the body via feces. Now the excess drug is out of the body and the problem of overdosage was solved ☺

Let's return to the substance that was used to trap the drug. This substance usually is " activated charcoal " .

" Activated " means that this charcoal " فحم مُعَدّل " is treated in a special way . It is cleaned first in order to remove the debris and thus increasing the surface area. When the surface area of this material increases, the amount of it that can **adsorb** the drug increases too. (Charcoal cannot bind to the drug , it has the ability to adsorb it) .

(المقصود أن هذه المادة تلتصق بالدواء سطحياً و لكن لا ترتبط به)

Once charcoal adsorbs the drug, it is excreted out of the body. In other words, charcoal accelerates drug elimination from the body and reduces its half-life of elimination.

- **Question :**

Enterohepatic cycle occurs when a drug is taken orally, will it occur if a drug is given intravenously?

Answer: The **only** determinant of the enterohepatic circulation is excretion through the common bile duct regardless the way the drug entered the body by. If an intravenously given drug goes from the blood to the common bile duct to be excreted there, the enterohepatic cycle occurs. It is not a must for this cycle to occur that the drug must be taken orally. It occurs whenever a drug is excreted in the common bile duct. <u>BUT</u> there are two main things that differ when the way of drug administration differs:

1- When the drug is taken orally, the whole dose will go to the liver, while when it is taken intravenously, only a small portion of it will go to the liver because the liver here is treated as any other organ in the body. In IV administration, the blood (containing he drug) is distributed to all body organs including the liver which takes a limited amount of it .

2- When the gut absorbs the drug after biliary excretion, if the drug was taken orally then this is a *REABSORPTION* process because the drug was absorbed before by the gut while when biliary excretion occurs after taking a drug intravenously then this is an *ABSORPTION* process (from the blood to the bile) because the drug was not absorbed before by the gut.

- The doctor asked **a question** :

Suppose that a drug is present in high concentration in the blood (overdose) but it doesn't go into bile, can we accelerate the elimination of the drug by putting activated charcoal **in the blood**?

Answer: Gastric (intestinal) secretions are fluids that come from the blood. When blood transfuses into the lumen of the gut carrying drug molecules with it, these drug molecules may diffuse from the blood to the gastric secretions due to their high concentration in the plasma (they do not go to the bile). When the drug diffuses, charcoal can be used to trap it and eliminate it from the body.

(This happens only when the drug is presenting in high concentration in the blood (overdosed), so that significant amounts of the drug will transfuse to GI secretions).

- Notice that **we put charcoal in the gut not in the blood** in order to trap the drug.

- To sum up this topic , you should be familiar with three major points regarding the enterohepatic circulation :

1- It reduces drug bioavailability.

2- It prolongs the drug's half-life of elimination .

3- **Gastrointestinal dialysis:** Interruption of this cycle by activated charcoal aids in accelerating the elimination of related drugs.

*Volume of distribution (VD) :

- If we have a **beaker** filled with a solvent and a known amount of solute (drug) is dissolved in it, drug molecules distribute through the solvent molecules in a homogenous way. As a result, if we take a sample of that solution and measure the *concentration* of the drug in that sample which equals the concentration in the beaker, then we can know the *volume* of the fluid in the beaker.

- The volume equals; the amount of the added drug (in milligram for example) divided by the concentration (in mg per volume). So you have three variables. If you know any two of them, you can find the third one.

*But the body is not a beaker...

- In the **body**, we have different tissues with different affinities to the same drug. So don't expect that the drug will distribute homogeneously through different tissues. Therefore, there will be differences in the concentration of the drug in different tissues due to various affinities which depend on the *Physiochemical properties* of both; the drug and the tissue.

- Mostly, drugs' concentrations are measured in blood (plasma or serum) because blood is the most accessible tissue. So how do we benefit from the concentration of the drug in the blood for a drug that concentrates mainly in muscles for example?

There's a relationship between the concentration of the drug in the blood and its concentration in other tissues (muscles, fat, bone, ..., etc). (Meaning that the concentration of a drug in muscles is not equal to its (drug's) concentration in blood (or plasma) but proportional to it, concentration in fat is not equal to that in blood but proportional to it differently from that in muscles, concentration in bone is not equal to that in blood but proportional to it differently from both muscles and fat, and so on.

- If we measure the concentration of a drug in the blood and the given dose is also known, we can calculate the " volume of distribution " by dividing the dose amount over the concentration in the blood, but we cannot know where the drug goes (its destination).
- Now let's compare the real volume of different materials in the body and the VD of some drugs :

<u>In a normal 70 kg man the volume of :</u>

Plasma = 2.8 L
Blood = 5.6 L
ECF = 14 L
TBW (total body water) = 42 L
Fat = 14-25 L

The volume of distribution for:

Aspirin = 11 L
Ampicillin = 20 L
Phenobarbital = 40 L
Digoxin = 640 L
Imipramine = 1600 L
Chloroquine = 13000 L

Regarding the volumes of distribution, we notice large numbers (volumes) of some drugs (like Chloroquine and Imipramine) that exceed the sum of the whole available volumes in the body! So from where did these large numbers come?

The amounts of some drugs are very high in certain tissue(s), that means that their concentrations in blood are very low, when we divide the amount of the drug in the body over the blood concentration of it, an extremely large volume is yielded, so these volumes are not real ones. In pharmacokinetics, volumes of distribution are called "apparent" volumes because they are not real.

(أحجام ظاهرية من أجل **التعبير** عن مستوى تركيز الدواء في الدم و ليست أحجاماً حقيقية يتوزع الدواء فيها)

Volumes of distribution just reflect the **apparent** space available for the drug in the tissues to distribute through.

- **The larger the volume of distribution, the more drug distributed in tissue(s) outside the blood compartment .**

(The drug is present in tissues rather than the blood).

- A key to understand what we are talking about is to know that drug concentration is measured in the blood, so when the Volume increases, concentration decreases.

(العلاقة عكسية بين الحجم و التركيز ، فعندما تكون قيمة الحجم صغيرة يكون تركيز الدواء عالياً في الدم و قليلاً في الأنسجة الأخرى ، و عندما تكون قيمة الحجم كبيرة ، يكون تركيز الدواء قليلاً في الدم و عالياً في الأنسجة الأخرى)

- The smaller the volume of distribution, the more drug present in the blood rather than in tissues, why is the VD value very small for some drugs?

  1- Because the drug is very polar or ionized so that it cannot cross the membranes of body tissues and it stays in the blood giving us a high drug concentration. (Remember that a drug's concentration is measured in blood).

  2- Because the drug is extensively bound to plasma proteins resulting in large molecules that cannot cross plasma membranes of tissues, therefore the drug stays in the blood rather than other tissues.

- Comparing between the numbers above, for example VD for Aspirin is close to the volume of ECM, so we can say that Aspirin (VD= 11 L) is best distributed in ECF (14 L). Phenobarbital (VD=40L) is best distributed in TBW (42 L) and so on. For drugs with high volumes of distribution that exceed the total available body volume, we can tell that they are highly distributed in other tissues. But we can't tell which tissues from these values above, other methods are applied to determine the best places (tissues) for an optimum drug distribution. The values of VD in such cases are only reflections of the drug concentrations in the blood but they are not real.

- To summarize:
  VD is the size of body fluid that would be required if the drug molecules were to be homogenously distributed through all parts of the body.
  Notice that a homogenous distribution of a drug in the body is only an *assumption* - as we explained before - due to differences in physiochemical properties in tissues and drugs.

- VD reflects the apparent space available for the drug in the tissues for distribution and it doesn't represent a real volume.

- You have to memorize the following equation that relates the ***bioavailable (intact and active)***** amount of the drug (Ab), with drug plasma concentration (Cp):

$$VD = Ab/Cp$$

***Ab doesn't necessarily represent the given amount of the dose; you must take the bioavailability of the drug (that reach the body intact and active) into consideration; for example if the drug is 70% bioavailable, then you should multiply the amount of the given dose with 0.7 (because 30% of the dose will not reach the systemic circulation). When the bioavailability is one (or 100%), then Ab represents the amount of the dose.*

*Drug binding in plasma:

- The most important drug binding protein is albumin. It is an abundant plasma protein. It is synthesized in the liver. Albumin level in the blood is affected (decreased) when there is a liver disease or when it is lost through the kidney due to renal problems. Otherwise, very little factors affect the concentration of albumin.

  Albumin can bind a large variety of drugs (basic and acidic), and it is difficult to be saturated. In very few cases we can say that binding of a drug to albumin is saturable but most of the time it is not saturable.

- Another plasma protein that binds drugs is alpha1-acid- glycoprotein. It only binds basic drugs. It is an acute phase reactant which means that its concentration increases due to inflammation and other chronic cases. As the protein concentration increases, binding to the drug also increases (more **bound** drug molecules are there, bound drug molecules are not active and are not eliminated, that's why this plasma protein is important).

- This point will be clarified later in this sheet inshallah ☺

When the disease/inflammation that led to the increased concentration of alpha1-acid-glycoprotein is cured, the concentration drops again and binding becomes less (less bound drug molecules and more free drug molecules). Too much free drug molecules may lead to toxicity. When the drug is bound to a plasma protein it is neither active nor eliminated.

Only FREE drug molecules act for curative purposes (pharmacological action) and only FREE drug molecules are eliminated.

- It is important to be familiar with acute phase proteins because the concentrations of drugs change according to the severity and the activity of diseases by affecting these proteins' concentrations first.
  The body normally has nearly constant concentration of albumin (Albumin is not an acute phase protein). On the other hand, the concentration of alpha1-acid-glycoprotein (acute phase) is changeable in the body which makes it an important drug binding plasma protein especially in cases of inflammation as we explained previously.

- Important note:
  Bioavailability means how much drug is present in the systemic circulation in an active form. **(it includes both bound and free drug portions)**
  Even if the drug is in the active form, it does NOT mean necessarily that it'll produce the curative action because this action depends on many other factors. For example, for a certain drug, there should be specific receptors to produce the action, if these receptors were absent due to a genetic abnormality, then there'll be no action of the drug even it is present in high amounts. Here, there is no action of the drug although bioavailability is high. Bioavailability does not always reflect the activity of the drug. *It can lead to it under normal conditions.*

- Binding to plasma proteins is *reversible* and follows the law of mass action .

** The law of mass action :

*If the taken drug after entering the circulation collides with a protein, it'll bind to it.

*If it collides with a receptor, it'll act.

*If it collides with an organ of elimination, it is eliminated.

** Reversibility :

The reaction between the drug and the protein is reversible :

Drug (D) + Protein (P) ⟷ Drug-Protein complex (DP)

- Protein–bound drugs do not achieve the *action* of the drug because only free drug molecules can do so, but they're both included in the term of bioavailability which refers to the drug available in the system whether it's bound or not.

- When protein concentration drops, free drug molecules increase, they'll do more action of the drug since they are free. Also, drug elimination will be faster. When faster elimination occurs, *the complex (DP) dissociates more to give more free drug* (i.e. the rxn above shifts to the left). Here in the case of low plasma protein concentration, if we measure the **total drug concentration**, it'll be lower than expected due to the increased elimination of free drugs **BUT** surprisingly, the **free drug concentration** may not be affected (it may be also higher than expected!) because the DP complex is compensating the eliminated drug by dissociation to give free drug again.

This is the most important point we want to reach to.

If you measured the drug level (you measure total drug concentration) and it is low, you shouldn't decide immediately to increase the dose because this low total drug concentration could be due to low protein concentration as we explained above and actually free drug portion is not affected in this case, so if you give the patient more dose, this may lead to toxicity! What you should do is to measure plasma proteins' levels first (mainly albumin).

Now, you've noticed that the clinical importance of plasma protein binding is to help interpretation of measured plasma drug concentration.

- Plasma protein binding is also a site for drug-drug interactions, or we can call it **displacement**. That means, if two drugs bind to the same site, they will start competing with each other, resulting in increased levels of the free drug concentration.
- Again, displacement of protein binding sites and low levels of drug binding plasma proteins lead to decreased total concentration of the drug but free drug level may not be affected.
- *The drug is considered extensively bound to plasma proteins when 90% or above of it is bound and 10% or below is free*. To ensure this, in slide #57, we have two drugs; A & B:

  ** Drug A: 95% bound, 5% free

  ** Drug B: 50% bound, 50% free

  Drug A: is considered extensively bound to plasma proteins. Therefore, if the amount of free drug increases by 5% due to a certain reason, the effect of plasma proteins as we explained previously will work and thus free drug percentage will be doubled from 5% to 10% resulting in an increased action of the drug or this might lead to toxicity.

  Drug B: not extensively bound to plasma proteins, so if the amount of free drug increases by 5% due to a certain reason, the free drug percentage will increase only from 50% to 55% which isn't an effective biological difference, therefore, the action of the drug won't increase noticeably.

  **As a result, the percentage of free drug increases significantly for drugs that bind with proteins extensively.*

*Drug clearance (CL) :

- Drug clearance is the *volume* of blood or plasma (not the body) that is completely cleared of drug *per unit time*.
- Drug clearance does not tell us how cleaning of blood occurs (Could be by elimination out of the body or by distribution to body tissues), so clearance is a measure of both elimination and distribution. There are renal clearance, hepatic clearance and many other types.
- How is it calculated?
  It is equal to rate if elimination of the drug divided by its plasma concentration:

Clearance (CL)= rate of elimination/Cp

You may ask yourself that clearance measures cleaned blood by both elimination and distribution, so why I cannot see an indicator of distribution in the equation?

Actually, plasma concentration is affected by both elimination and distribution, so distribution is considered in the equation by considering Cp.

- We are going to discuss two types of clearance :

1- Renal clearance (CLR) :

It is the volume of blood that is completely cleared by the kidney per unit time (by elimination for sure).

*Calculation:

CLR = Cu.V/Cp

Where:

Cu: concentration of drug in urine.

V: urine flow rate (volume of urine gotten per time)

Cp: plasma concentration of the drug.

2- Hepatic clearance (CLH) :

It is the volume of the blood that is completely cleared by the liver per unit time (by metabolism and biliary excretion).

*Calculation:

CLH = (blood flow.Ci – blood flow.Co) / Ci

CLH = blood flow (Ci – Co) / Ci

Blood flow = Q , (Ci – Co) / Ci = ER (the extraction ratio of the drug) , so :

CLH = Q.ER

Where:

Ci: drug conc. in blood going to the liver

Co: drug conc. in blood leaving the liver

Q: blood flow (constant in and out)

ER: the extraction ratio of the drug

** Note:

ER is an indicator of first pass effect. When it is high (above 0.7), then three is a considered (high) first pass effect, when it is low (below 0.3) then there is no considered (low) first pass effect.

Done ☺

Don't forget me from your Dua'a.

Regards ...

Your colleague: Doa'a S. Dahboor