◉ Sheet ○ Slides

number : 3

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"A hero is no braver than an ordinary man, but he is braver 5 minutes longer"

It's going to be long, but it's easy if you try to understand... Good luck!

In the last lecture we have talked about the mechanisms of drug permeation, and the last thing we mentioned was carrier mediated transport *(active transport and facilitated diffusion)*. We have hundreds of these carriers not only one, two or three. We'll continue with examples for active transport and facilitated diffusion:

Active transport:

- **A**TP **B**inding **C**assette (ABC) family, which needs binding to ATP and includes:
  (the word family means that we have different iso-forms of these transporters)

  a. **The P- glycoprotein(P-gp)** , that is found in the villi of the GI tract to prevent the absorption of toxins , also called **The MDR-1** (**M**ulti-**D**rug **R**esistant type 1) transporter, which is found in the brain, testes and other tissues and expels many drugs
  ** Resistant implies that the drugs do not reach the system`s circulation, therefore don't reach the site of action because they got expelled by these transporters which prevent their entry through the cell membrane.

  b. **MultiDrug Resistant-associated protein (MRP)**, which is similar to this ABC family and responsible for cancer cells' resistance.

- When we talk about drug transportation and the permeation methods, we are not only referring to absorption but to distribution and elimination as well "the passage through membrane in general".
- Remember you have protein transporters for the drug, some of them allow and facilitate the entrance of a drug to the cell (absorption) , others expel the drug outside the cell.
- In the kidney, the entrance of a drug to the cell means re-absorption of the drug, but when it get expelled it stays in the lumen of the duct, so they prevent the passage of this drug through the circulation, or they facilitate its

excretion in the kidney, and that will accelerate the elimination of the drug from the body in general.

- Remember when you accelerate elimination or reduce absorption you reduce the concentration of that drug at the site of action. And there are some transporters that increase the concentration of a drug at the site of action; in fact this is a huge subject in pharmacology and physiology because carriers are important for endogenous substances.

Facilitated diffusion

- **Solute Carrier Family of transporters (SLC):** They facilitate the passage of drugs by using the solute concentration "electrolytes- using the ion gradient"

** The differences between ABC and SLC**

	ABC	SLC
ATP	Needs energy "active transport"	Doesn't need energy, it needs a carrier
Driving force	ATP -energy	Solute concentration
Direction of movement	Against the concentration gradient –either in or out	According to the concentration gradient

- ❖ Other methods that are concerned in drug transport are **endocytosis and exocytosis** (exocytosis: for the release of neurotransmitters and hormones such as insulin. and the endocytosis is specific for certain drugs. These mechanisms will be explained later in this course but we will go through **two examples** of endocytosis as a way of transport)

1) **Vitamin B12:**

It has to bind to the intrinsic factor which is *(a protein that exists in the stomach*), it binds to it and moves with it all the way to the terminal ileum, where the whole

complex is absorbed by receptor mediated endocytosis. And then absorption of vitamin B12 happens by endocytosis

2) **Iron:**

It's absorbed mainly in the duodenum and maybe the upper jejunum by endocytosis

Those are the ways of permeation, some of them are general such as lipid diffusion and others are specific for certain molecules

Quick revision

Ways of permeation:
1- lipid diffusion
2- aqueous diffusion
3- carrier mediated transport
active transport and facilitated diffusion
4- Endocytosis and Exocytosis

- ✓ These processes determine how rapidly and for how long the drug the drug will appear in the target organ, the site of action and the amount of drug that is eliminated. *(If the drug, for example, is lipid soluble, the movement through the membrane is faster and it will reach the site of action easily and if it's water soluble it finds it hard to reach the site of action)*

Keep in mind the rate determining step

- ✓ Drugs in the body behave mainly according to the law of mass action; it is spread and distributed in all directions randomly once it's in the body. How? (the absorption, distribution and even elimination all happen at the same time but the rates are different)

Barriers against transport

What do we mean by a barrier against transport?

1) The junctions between endothelial cells are tight, which will reduce the movement of substances in between cells, making the membrane impermeable for drugs. And when those junctions are not tight (for ex. in Capillary dilation "broken capillaries" substances can move through the spaces between the cells not only through the cell.
   Remember that a capillary is made out of only one cell layer

2) The absence of pores in the cellular membrane , which exist to allow the movement of water soluble substances, so their absence reduces the entrance of water soluble substances into the cell

3) The presence of thick basement membrane on which the endothelial cells lay, this would decrease the passage of drug molecules through the membrane
4) The presence of connective tissue (CT) cells around the endothelial cells, sometimes this exists in the blood brain barrier (glial cells) ,these cells will make the membrane thick so the passage will be low

5) Drug export pumps (such as p-gly, MDR and other transporters –mentioned earlier) they expel the drug and prevent its entry to the cell.

6) The presence of Intracellular and Extracellular enzymes that metabolize drugs (metabolism of drugs will be discussed later) which means faster elimination of the drug, the drug in this case will not enter the cell because it is destroyed (partial absorption), the amount that will reach the blood circulation will be less.

Main barriers against transport in the body:

a- **Blood brain barrier (BBB)**

we are concerned about this barrier because many substances cannot cross it, therefore cannot reach the brain. And in order to cure a brain disease (CNS disease) you should give the patient a drug that can cross BBB to be effective.

b- Placental barrier

and this is important too because we give the mother a drug we do not want the drugs to reach the fetus at a critical time, because that can cause congenital defects. OR few times a fetus get sick and we want a drug to cross the placental barrier, so it is very important to know the Blood-Placenta barrier

**fetal circulation & mother circulation are separated, so some drugs cross the barrier while the child and the maternal blood are not mixed **

- **An example of that**: if the fetus were born before 40 weeks *especially before 36 weeks*, the surfactant would not be well developed, so the fetus will suffer from a respiratory stress and may die, why? Because the fetal alveoli don`t open properly, as a result from a shortage of a phospholipid named surfactant that would prevent the closer of an alveoli by preventing the walls from sticking. So to solve this problem, before the anticipated delivery we give the mother a drug (a steroid) that can cross the placenta and reach the fetus and produces a developed surfactant therefore breath normally.
  Usually in this method we give the needed drug in a specific amount that won't hurt the mother.

The First Pass Effect:

If I gave the patient an oral medication, it goes through the walls of intestine to the portal circulation then to the portal blood vessels and it goes to the liver and finally

the hepatic vein to reach the systemic circulation. But if you give the drug intravenous, sublingual, intramuscular or subcutaneous it will go to the systemic circulation directly.

What happens in the first pass effect? The drug can be metabolized in the intestine, endothelial of portal vein and liver, it also can be excreted in bile before reaching the systemic circulation – so it reduces the amount of the intact drug in the systemic circulation.

Drugs that undergoes first pass effect there is a difference in its doses for oral and IV administration because in oral administration not the complete dose will reach the circulation.

(In the liver two things can happen to the drug; metabolism and excretion with the bile)

- Some of the drug is not being absorbed (didn't pass at all) this is not FIRST PASS EFFECT. This happens for different reasons such is being metabolized by the bacteria in the gut, destruction by gastric acid.

- **First pass metabolism:** sometimes this term is used interchangeably with First Pass Effect but actually they are different because first pass metabolism happens in the gut, portal vein and liver. It does not include renal elimination (excretion).

- Pre systemic elimination: is the best term that can describe the First Pass Effect.

- Drug metabolism usually terminates the action of the drug , because it changes the drug so it doesn`t function anymore

- The concentration of the drug metabolites after the oral administration it will be higher than IV because the whole dose had passed through the liver (great amount of metabolism). But in IV the amount that

reached the liver is equal to the amount that reached any other part of the body; to kidney, heart, muscle…

- If part of the drug was eliminated pre-systematically, what is the **solution**?
  We increase the dose!
- What is the ratio of the dose you are giving to your patient if the dose is 50% eliminated during the first passage?
  You should double the dose

✓ **Liver cirrhosis**: a disease in which the architecture of the liver is changed, so the liver is not functioning well and therefore will not metabolize the drugs normally, so you should consider this situation in giving a drug that undergoes first pass effect (you DON'T have to increase the dose in order not to have a drug toxicity). And we have shunting between the portal vein and the systemic circulation so the drug goes directly to the circulation without going through the liver.

✓ Human beings are not equal in the content of the drug metabolizing enzymes in the liver, we have different amounts so different metabolism effect. So drugs that undergo first pass metabolism will have tremendous amount of variations in the amount of the drug that reaches the systemic circulation and that means **Interindividual variation** in the drug response.

How can we know the amount that reaches the circulation? By what we call bioavailability.

Bioavailability: توافر حيوي

Is how much of the drug reaches the circulation active and intact "not altered or changed even by adding only one element"? All of it? Half? 30%? The fraction not the amount

And it could be known by knowing how much the liver and all the other organs extracted "**Extraction Ratio".**

Suppose that during the first passage 40% of the dose was extracted by the liver, how much is left to reach the circulation? 60%. So bioavailability is 60% or 0.6.

Bioavailability = 100% (or 1) – Extraction ratio

Excretion ratio: is different according to the interindividual variation, we'll know how to calculate it in later lectures

- Remember that metabolism happens mainly in the liver (not only there), and the intestines come in the second place and then the portal vein.
- Not all drugs go through renal excretion.
- Not all drugs are metabolized, not all drugs are excreted in bile.
- Metabolism and excretion is a capitalistic of the drug not the individual, for example:

  Drug A is eliminated by metabolism & renal excretion
  Drug B is eliminated by renal excretion only
  Drug C is eliminated by metabolism and excretion of metabolites…

Look at the **Morphine,** a pain killer which is completely absorbed but its extraction ratio is 0.76 so the bioavailability is 0.33. And when we give the same dose of Morphine to many people, some will have their pain relieved, other not and the rest are in-between.

The reasons that make the bioavailability less than 1 in case of oral administration:

1) First pass effect (this is <u>one</u> of the reasons)

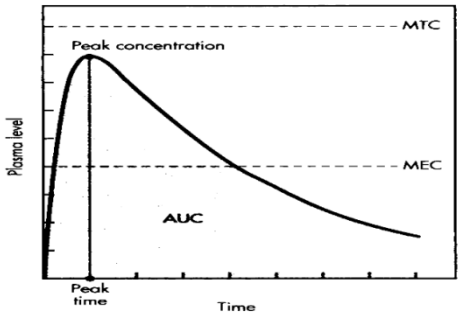
2) Incomplete absorption: if the drug is very Polar or very Lipid soluble it cannot be fully absorbed; very polar doesn`t pass through membranes, very lipid soluble doesn`t have enough water solubility to reach the membrane.

3) Incomplete disintegration and dissolution
   The tablet you take orally is not only composed of the drug , only a portion of it represents the drug and the rest of it are binders and many other substances that makes the tablet suitable to be taken by mouth and sometimes it contains additives like starch that gives the tablet its shape. So the tablet should first disintegrate into fragments so the drug would come out

and then dissolute with the flow.

4) Destruction of the drug within the GI lumen by gastric acid and Bacteria, *(this is not a first pass effect)*
    - Penicillin is a very important antibiotic still being used these days. It would be useless if you take it orally because it is destroyed by the gastric acid in the stomach.
    - Some bacteria that exist in the intestines "such as microbial flora" can also destroy drugs or metabolize them for ex. Degoxin is a drug used in case of a heart failure. 10% of the population have bacteria in their intestines that metabolize it. This affects the dose that should be given.
    - The usage of degoxin should be associated with measurement to its plasma concentration , which means you are not allowed to use degoxin unless you have a facility to measure the plasma concentration of the drug, because it should be monitored , what is really bad about this drug that the adverse effect happens to the heart itself.
    - BUT be aware when you give antibiotics to treat infection, you may kill these bacteria, and that means the elimination they used to do for drugs is no longer there! So the dose should stay the same to avoid drug toxicity.
5) Manufacturing fault
6) Enterhepatic cycling of a drug *(will be discussed next time)*

****** The area under the blood concentration vs. time (AUC) is a common measure of the extent of Bioavailability.



And there is something called **rate** of the bioavailability maybe the same drug from different factories have the same extent but different rate.

Some of the causes for extent reduction are that the drug is either too hydrophobic or too hydrophilic and some drugs may not be absorbed as a result of reverse transporters such as P-glycoprotein. *"you will have a closer look at the curve soon!"*

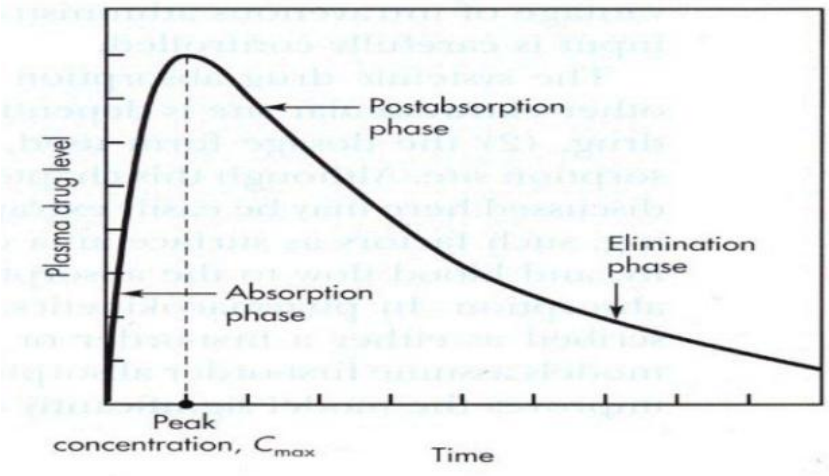
- How can I measure the extent of bioavailability?

Give a dose and measure a drug in serial blood sample "in consequent periods of time depending on the half life of the drug. If its half life is 2 hours, we take blood samples over 8 hours then you measure the area under the curve.

P-glycoprotein can be inhibited thus increase the extent of bioavailability by **grapefruit juice. (It can also inhibit the gut wall metabolism and some of the hepatic metabolism).

Remember that you should always take the drug with water not Juice to avoid **food-drug interaction**.

Example: **Cyclosporine** is an immunosuppressant that is used in organs transplantation, the discovery of this drug led to a revolution in organs transplantation. This drug is very lipid soluble, low absorption, also it's metabolized in the intestines & in the liver. So the amount that reaches the systemic circulation is very low almost 15% only. This drug is given to the patient with grapefruit juice, so it would inhibit the p-glycoprotein, the metabolism and increase the bioavailability from 15% to 30%.



- This scale represents a drug level vs. time after oral administration
  - Absorption phase : absorption faster than elimination because the dose is in the intestine
  - Elimination phase : elimination faster than absorption
  - The platue –peak concentration- Cmax: absorption and elimination are almost equal
  - The drug follows the law of mass action, it is spread to all parts of the body (just like throwing a stone in water , or throwing sand in air it`ll spread all over the place and in all directions; this is the mass action), when the drug also reaches the circulation, the heart pumps it to the whole body, the molecules that reach the kidney will face renal excretion, the molecules that reach the liver will be eliminated by metabolism , the molecules that reach the receptors will give me an action. All at the same time but at different rates.
  - Tmax : the time to reach Cmax
  - The area under the curve represents the extent of absorption / extend of bioavailability
  - Rate of bioavailability :can be calculated by three factors; AUC " the extent of bioavailability", Cmax & Tmax "rate"
  - If Tmax was shifted to the right (increased), the Cmax will be lower and the rate of bioavailability will decrease.
  - Rate & Cmax : direct correlation
  - Rate & Tmax : inverse correlation

Bioequivalence: التكافؤالحيوي

When a drug is first manufactured, the manufacturing company takes a patency. And that prevents any other company from producing this drug for 15 years or more, after that period, if a company wants to produce this drug and sell it, the first company product is considered a standard drug, and this new product should approach the result given by the first drug. The 2nd drug should be tested and compared with the standard drug; therefore the 2nd drug should prove that it

is **equivalent** to the standard drug. If the drug proved its equivalence to the standard, it is given the right to be manufactured and sold.

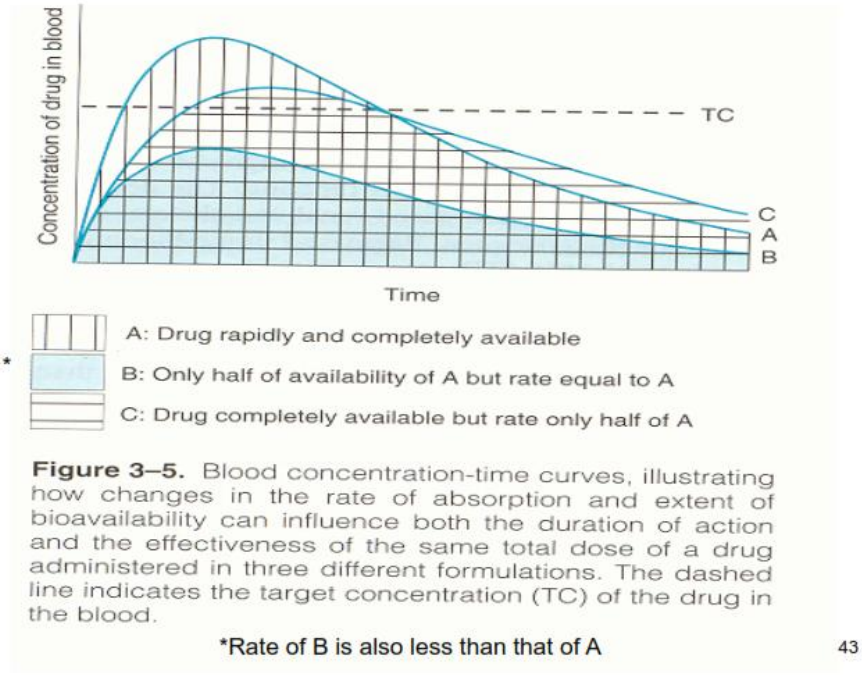


Figure 3–5. Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

- This slope represents the same drug different manufacturers
- Drug A is the standard drug
- The area under the curve is not the same for these 3 drugs
- The dashed line represent the therapeutic concentration (TC): the drug concentration should be more than the TC to have an effect in the body.
- The drug before it reaches the TC has no effect in the body
- The second dose is given just before the slope crosses the dashed line (TC) for the second time so that we`ll always have a therapeutic concentration
- Drug B : never reached TC, the area under the curve is much less than drug A. Drug B should not be marketed because it's not equivalent to A
- Drug C: the area under the curve isn`t significantly different from A; the extent of bioavailability is almost the same. But the rate is different, so this drug should be stopped, but also it can be accepted as an alternative for drug A, in case the time isn`t a critical situation for the patient, in other words the rate isn`t important and the drug isn`t used in emergency situation, and this should be mentioned in the label of the drug. They should mention that *in*

comparison with the standard drug, drug C was equivalent in the extent but not the rate, or the company will be legally suited.

- The usage of drug C isn`t preferred , because the time that the drug stays above TC is lower than it is for drug A , in order to keep the effect of drug C (keep it above TC) you should give the drug more frequently, and this is not allowed. The same drug should be given to patients in the same frequencies even though it has different manufacturers.
- Drug C : the peak is low, which means lower effect of the drug

(The only case to accept a drug and allow it to be marketed is if the drug slope is shifted to left or right (same slope, only shifted))

Always Earned, Never Given!