Doctor 021

PHARMACOLOGY

Sheet no. 3

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FIRST-PASS EFFECT

• Drugs absorbed from the GIT must pass through the gut wall and portal vein to the liver before reaching the systemic circulation.

- As a beginning To understand First pass effect concept:

➢ We must understand **first pass** meaning:
it is drug passage from the lumen of intestine to the systemic circulation by multiple stages.

• The drug may be metabolized in the gut wall, portal vein, and the liver prior to entry to the systemic circulation.

• Or, it may get excreted by the liver through bile (for some medications).

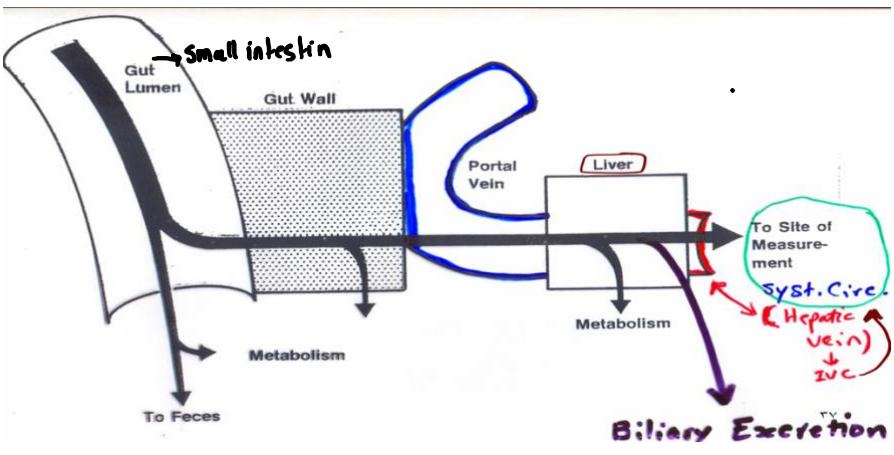
• This will lead to incomplete delivery of the dose given to the systemic circulation.

• This process is called "first-pass effect"

- **OR "first-pass metabolism"**(if there is no biliary excretion)
- **OR "pre-systemic elimination"**(because metabolism is a kind of elimination, pre-systemic→before reaching systemic circulation)

- First-Pass Effect happens In case of **orally given** drug.
- In case of intravenous given drug there is no first pass effect, because drug reaches the systemic circulation immediately.
- **Therapeutic blood concentration may still be reached by using larger dose.Therefore, the oral dose is usually higher than intravenous dose for such drugs,** to compensate the lost metabolized drug.
- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration.**

➢ Drug journey From intestine to systemic circulation:



- **Intestine→gut wall→portal vein→liver→hepatic vein→inferior vena cava(IVA) →systemic circulation**. then it will be disturbed to the body and reaches the site of action.

- First pass effect Metabolism could happen in :

1. **Gut wall** (significant amount)
2. **Endothelium of portal vein** (small amount because of its small size)
3. **Liver** (main location of metabolism)

**Side Note:drug metabolism occurs in all organs in our body, but in varying proportions, it even happens in the hair follicles.

- To sum up:

- Main site of Metabolism→liver
- Main site of Absorption→upper portion of small intestine(movement of the intestine would take the drug down),and the upper portion jejunum.

❖ In colon there is no absorption but certain drugs could be metabolized by the gut flora(microbes living there).

❖ If the drug left the site of absorption, absorption stops, so remain drug leaves with feces.

- There are 2 solution to first pass effect problem:

1. Changing the site of administration to another with no first-pass effect (intravenous)
2. increasing the douse

- Ex: If the required dose for therapeutic effect was 100 mg, and the first-pass effect was 50%. The patient must take 200 mg (100 will be lost and the rest will do the therapeutic effect.)

This was in a normal liver, **but If the patient is having liver cirrhosis and there is shunting of blood by-passing the portal circulation ,so giving a larger dose orally will lead to substantial increases in concentration of the drug and drug toxicity.**

- **liver cirrhosis**: a severe fibrosis of the liver**,** that causes changes in the architecture of the liver leading to changes in blood flow, protein

binding, and drug metabolizing enzymes so, Drug metabolizing enzymes are primarily decreased due to loss of liver tissue**)**

❖ so, as a doctor, if a patient came to you with liver cirrhosis, you must decrease his drug doses to protect him from drug toxicity.

➢ Conclusion:if 50% of a drug was metabolized and 50% reached the circulation then,

- The first 50% is called→first pass effect.
- The second 50% is called→bioavailability.

Which takes us to the next concept:

BIOAVAILABILITY (التوافر الحيوي)

➢ The amount of dose, which reaches the systemic circulation.

- **It is the fraction of the <u>unchanged</u>**(not metabolized)**, <u>active</u> drug reaching the systemic circulation, following drug administration; irrespective of the route.(orally, intravenous, intramuscular)**
- **Bioavailability is equal to "1"or 100% following intravenous drug administration.** (no first-pass effect→ no drug loss → all the dose will reach the systemic circulation)
- **After oral administration, bioavailability may be less than 1, because of:**

1.First-pass effect.

2.Incomplete absorption. for example a very lipid soluble drugs cannot reach the membrane easily, it must be lipid soluble to pass the membrane and some water soluble to reach it.

3.Incomplete disintegration and dissolution.

- Exeplination: solid form drug must be disintegrated, dissolved in order to get absorbed.
- Sometimes due to manufacturing faults, incomplete disintegration or dissolution happens.

4.Destruction of drug within GIT lumen by bacteria, gastric acid

- **Gastric acid** destroys some drugs(like penicillin) so penicillin is given intravenous not orally)**, ..etc.**

5. Faulty manufacturing of the dosage form.

6. Enter-hepatic cycling. {discussed later}

➢ How to measure bioavailability?

- **The area under the blood concentration versus time curve (AUC) is a common measure of the extent of bioavailability.**

  How do we get the (concentration-time)curve?
  by Giving patient a drug, then Taking serial blood sample's with time, then we measure concentrations of the drug in the blood sample with respect of time.

➢ There are 2 measurements related to bioavailability:

- Rate of bioavailability
- Extent of bioavailability

  ❖ Any defect in either of them results in **low bioavailability.**

• reduction causes, of the <u>extent</u> of bioavailability(absorption):

1. The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.

- **Too hydrophilic drugs can NOT cross lipid membranes easily.**
- **Too lipophilic drugs are NOT water soluble enough to reach the membrane (to cross the water layer adjacent to the cell).**

➢ **Drugs may NOT be absorbed because of the presence of a reverse transporter (P- glycoprotein), that pumps the drug out of the gut wall cells back into the gut lumen.**

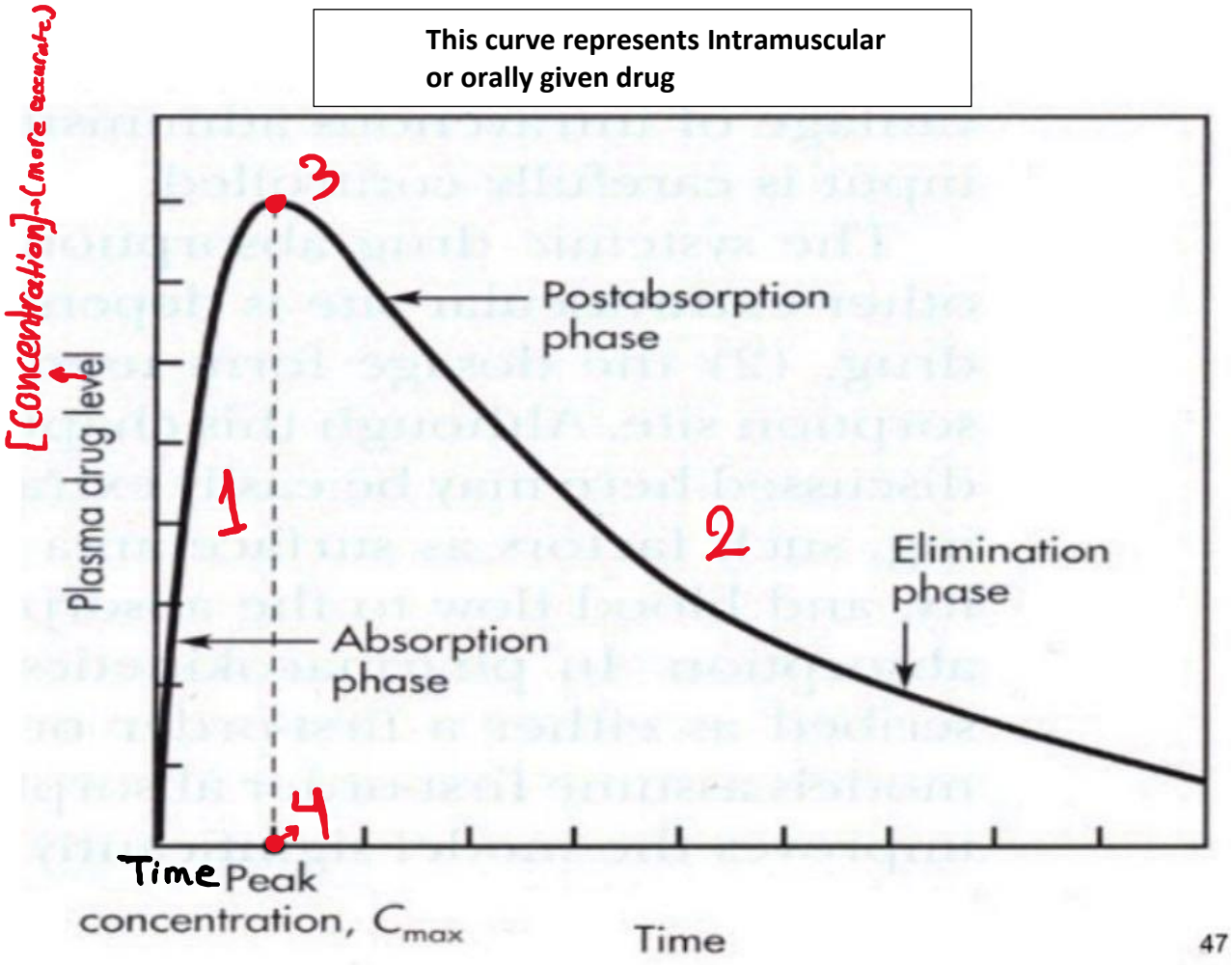
- Remember: P- glycoprotein is an efflux protein that prevents the absorption of the drug.
- this protein is inhibitable protein and it may be inhibited by:

  <u>some drugs</u> **and** ***<u>grapefruit juice</u>*****, which will result in increasing bioavailability rate, and allows toxin's and some other drugs to reach the circulation.**

Side note:doctor mentioned that some people drink grapefruit to loose weight but sadly it doesn't help in losing weight ☹ , it will only removes (p-glycoprotein) for 36 hours from your body, after drinking only 1 cup of it!

• **Grapefruit juice also inhibits pre-systemic elimination of some drugs thus, increases their bioavailability.**

now, lets talk about curves(☺)



1→**Absorption phase**(absorption rate is higher than elimination rate).

2→**Elimination phase**(elimination rate is higher than absorption rate)

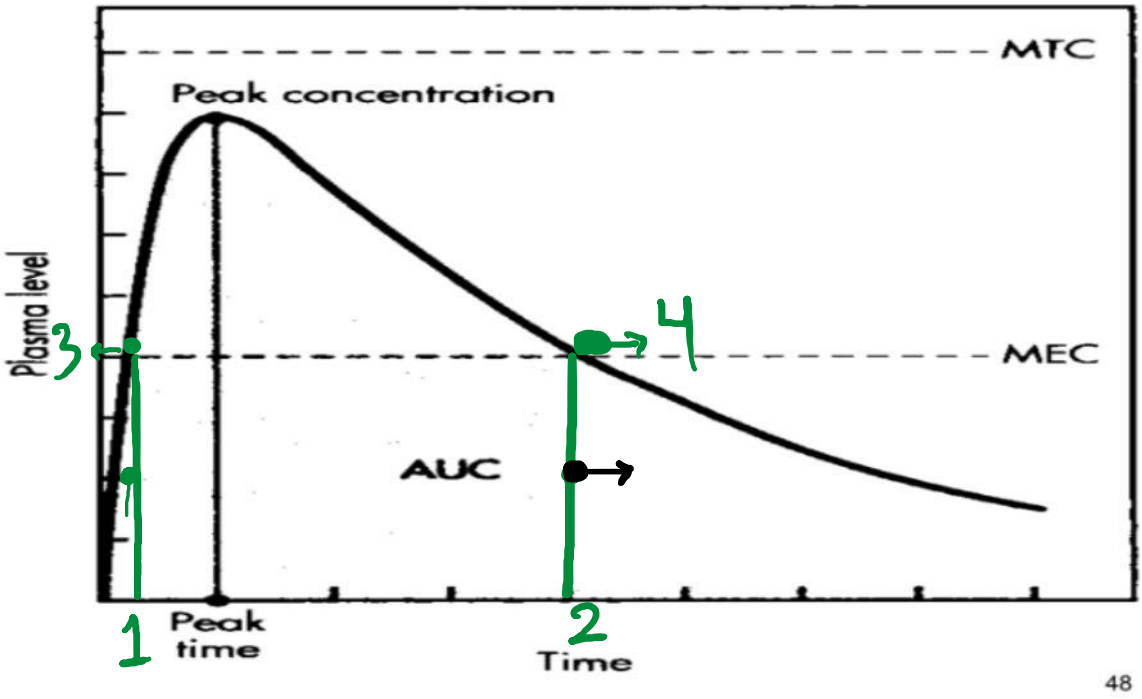
3→**peak concentration of the drug** {absorption rate = Elimination rate}

4→**time to peak concentration** (the time needed to reach peak concentration)

- peak concentration is relatable to maximum action, because the action of the drug is proportional to the concentration.
- Important:the peak concentration is the highest concentration thus it indicates the **highest intensity** of action

➢ To remember :Absorption continues to the last molecule of the drug if it's completely absorbed.

Q:dose elimination happens in the absorption phase?
Yes, there's elimination, but the absorption is faster, that's why its called absorption phase. And vices versa to the elimination phase.



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- **MEC→ minimal effective concentration.**
- **MTC→ minimal toxic concentration.**
- **AUC→ is the area under the curve(of plasma concentration versus time)** and it's an indicator to the **extent of bioavailability**
- 1→ onset action time (lag time).
- 2→ termination of action time (the concentration below it is not effective)
- 3→ onset of action
- 4→ termination of action

➢ Note: drug concentration must be in the therapeutic range between MTC and MEC to get the therapeutic effect without adverse effects.

❖ This curve represents one dose, so for example if a-drug is prescribed as 2 pills every 8 hours that means the first dose (pill), will reach the termination time after 8 hours, thus another pill is taken just before the termination time to keep the concentration above between MEC and MTC all the time.

➢ To sum up

- To calculate:
  - **<u>Extent</u> of bioavailability→AUC**
  - **<u>Rate</u> of bioavailability→ peak concentration,peak time**

****doctor said** slide(48/49) will be discussed later(with clearance concept)

BIOEQUIVALENCE (التكافؤ الحيوي)

- It is the concept that represents the same drugs, with the same active substance, but from different factories.

- **This term is used to compare the <u>rate</u> and <u>extent</u> of absorption(bioavailability) of different formulations of the same active drug.**
- **Two drugs are said to be equivalent, when the Extant and the rate of bioavailability are the same.**

- **This figure shows three formulations of the same drug (A, B, C)**

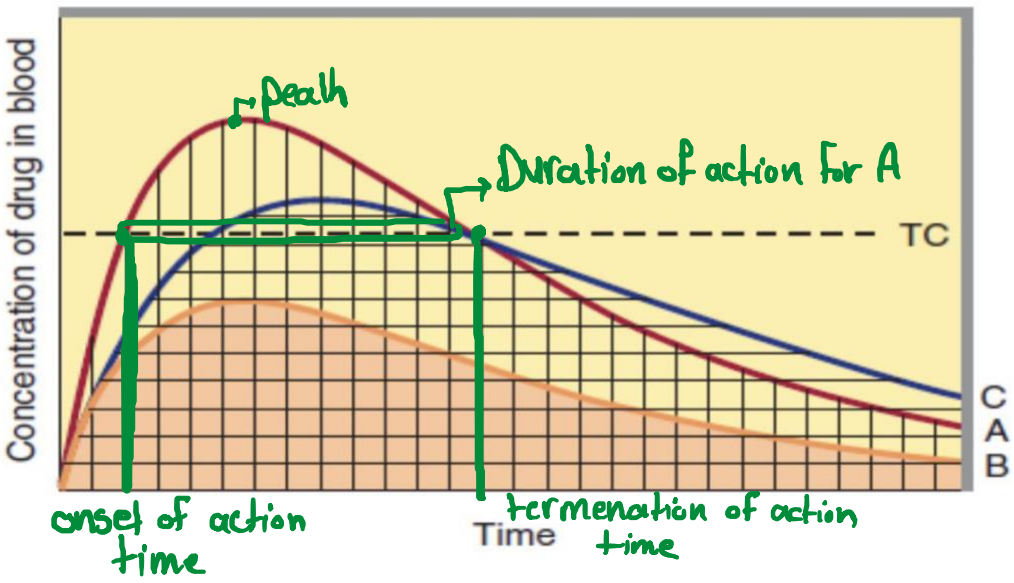


FIGURE 3-4 Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

- **TC→**therapeutic concentration or target concentration.

- **In comparing to A:**
- **C→**
  - **rate:**lower peak(intensity of action)than A →lower rate.

- **Extent:**if you calculated it you will find its equal to A, but regardless the same extent, since the rate is different then [NO BIOEQUIVALENC.]
- **NO bioequivelance**.

➢ **B→**

- lower **extent** than A
- **NO bioequivelance**.

❖ the first manufactured drug is the reference, any other drug must be bioequivalent to it to be approved.

➢ Note

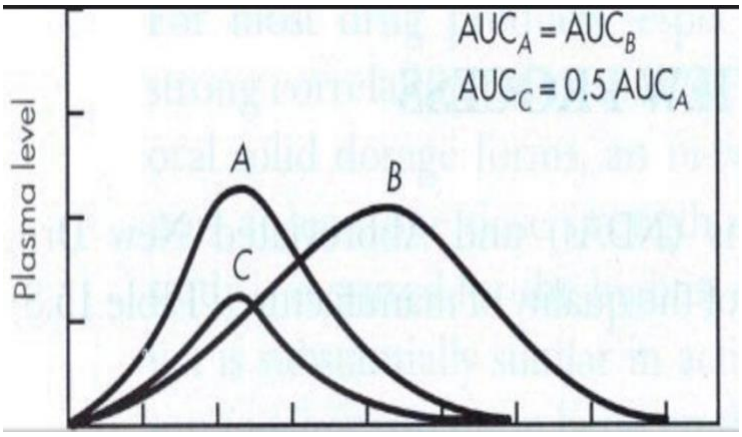
When the peak concentration shifts to the right→ this result in **decreasing** the **intensity** of action and **rate of absorption** of the drug , Since peak concentration indicates the intensity and the rate of absorption- as mentioned before.-

❖ The same case applies here

➢ A&B have the same extent but with different rates

➢ A&C have different extents

✓ So neither B nor C is bioequivalent for A.



✓ Conclusion:difference in only **one** factor is enough to say that 2 drugs are **<u>bio inequivalent</u> .**