

MID – Lecture 3

Pharmacokinetics

﴿ وَإِن تَتَوَلَّوْا يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ ﴾

اللهم استعملنا ولا تستبدلنا

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Before you start!

Please ensure you scan this QR code to assess your knowledge from the previous lecture.



[OR CLICK HERE](#)

Mechanisms of Permeation of Drug Molecules

- They are selective, saturable and inhibitable.
- Many cells contain less selective membrane carriers that are specialized in expelling foreign molecules including drugs:

A. ATP-binding cassette (ABC) family:

Efflux pump ; prevents entry of drugs and toxins into the body

- It includes **P-glycoprotein** or the multidrug- resistance type 1 (MDR1) transporter found in the brain, intestine, testes, neoplastic cells, and other tissues (even found in bacteria) .

Found in the cell membrane, P-glycoprotein actively transports drugs out of the cell, contributing to drug resistance, including in bacteria. This bacterial resistance arises from the development of P-glycoprotein, which reduces the effectiveness of certain drugs and causes resistance for the drug action

(p-glycoprotein kicks the drug outside the cell)

Mechanisms of Permeation of Drug Molecules

B. The multidrug-resistance associated protein (MRP) transporters (also from the ABC family):

Active transport ; requires energy

- **They play a role in excretion of drugs and their metabolites into urine and -mainly- bile.**
 - Some forms of excretion , particularly in bile, are active processes.
 - Bile excretion is primarily used for larger molecules , in contrast to urinary excretion
 - For example , when a drug is metabolised through conjunction with glucuronic acid, it forms a bulky glucoronide compound . Due to its large size it cannot pass through filtration ; active biliary excretion is used
- **They mediate the resistance of some tumors to chemotherapeutic agents.**
 - This prevents the drug from entering neoplastic & cancer cells. If a drug cannot reach its site of action, it will not be effective in the body. In our case, the drug won't be able to enter and destroy cancer cells nor inhibit the cells' growth (sites of action)

Mechanisms of Permeation of Drug Molecules

C. The solute carrier families (SLC): Facilitated diffusion ; requires transporters

- They **do not bind ATP** but **use ion gradients for transport energy.**
- They are important in the transport or the uptake of neurotransmitters across nerve ending membranes.

↓
Neurotransmitters can either enter the cell alongside sodium or enter while sodium is transported out.

↓
For ex. In the sympathetic nerve terminal, the action of catecholamines is terminated primarily through reuptake by the SLC

Mechanisms of Permeation of Drug Molecules

4. Endocytosis and exocytosis:

- Endocytosis is responsible for **transport of vitamin B₁₂ complexed with the intrinsic factor across the wall of the gut into the blood,**

Vitamin B12, when complexed with intrinsic factor in the stomach, travels to the terminal ileum, where it is absorbed through receptor-mediated endocytosis

- and **iron associated with transferrin into developing RBCs.**

Iron binds to transferrin, allowing it to enter developing RBCs, where it helps in forming hemoglobin

Note : Vitamin B12 deficiency leads to megaloblastic anemia, while iron deficiency results in iron-deficiency anemia

- Exocytosis is responsible for secretion of many substances from cells such as **neurotransmitters and some hormones.**

Exocrine secretions, some endocrine secretions, large hormones, & proteins are not released directly through the cell membrane but rather through exocytosis. Even small molecules, such as catecholamines and acetylcholine, are secreted via exocytosis

Mechanisms of Permeation of Drug Molecules

- *These principles of permeation of drug molecules apply to drug absorption, distribution and elimination (metabolism and excretion) “ADME”*



These principles/mechanisms apply to any passage through a membrane, whether passive or active; one or another of these mechanisms will always be involved

- *These processes determine how rapidly and for how long the drug will appear in the target organ, the site of action, and organs of elimination.*

Barriers Against Drug Permeation & Transport **part 1**

→ (blood-brain barrier, placental barrier, testicular barrier, and prostate barrier)

- Although they share similarities, they are not identical

1. Tight junctions between endothelial cells and absence of pores. No diffusion occurs across the membrane regardless of whether the drug is water-soluble or lipid-soluble.

2. The presence of thick basement membrane at which endothelial cells lie. Recall fick's law of diffusion !
Thickness hinders passage of drugs

$$(C_1 - C_2) \times \frac{(Area \times Permeability Coefficient)}{Thickness}$$

3. The presence of connective tissue cells around endothelial cells (such as astrocytes in the brain). Tight junctions, membrane thickness, and astrocytes are all crucial factors in maintaining the integrity of the blood-brain barrier (BBB)

Barriers Against Drug Permeation & Transport **part 2**

4. The presence of drug export pumps.

These pumps are present in the brain's choroid plexus, the intestine, and other organs. When a drug enters the cell, the cell expels it through efflux mechanisms

5. The presence of intracellular and extracellular enzymes that metabolize drugs. placental barrier metabolizes drugs and prevents their passage to the fetus

First-Pass Effect تأثير العبور الأول

The drug passes through three stages: first, **the metabolically active intestinal mucosa** (which is metabolically active); then the **portal vein to the liver**; and finally, it reaches **systemic circulation**

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

First-Pass Effect

- 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**”

When referring to first pass **metabolism** we are excluding excretion since this drug is not excreted through bile it is only metabolized in the intestine and/ or the liver.

or “**pre-systemic elimination**”.

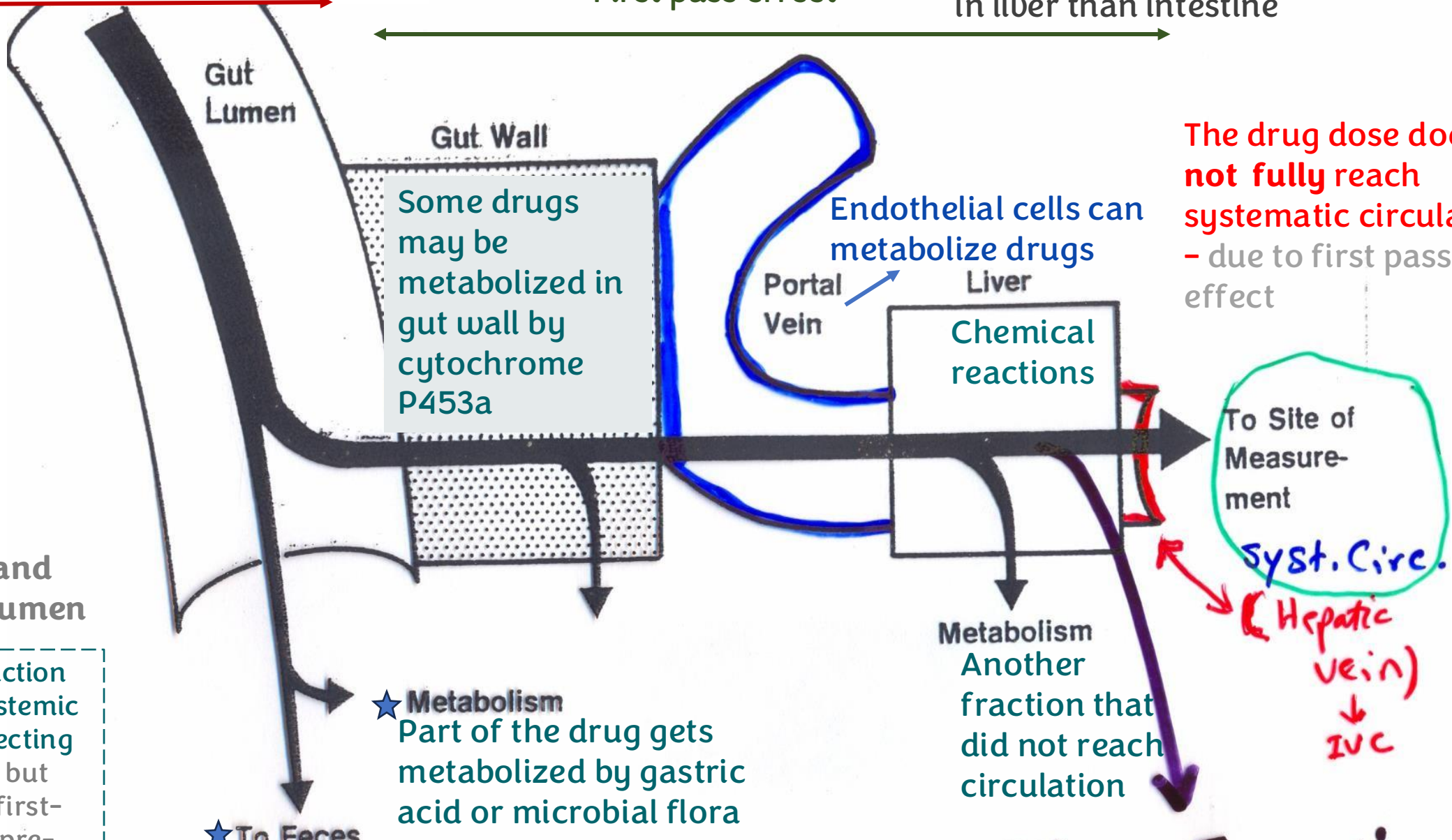
↳ General term that refers to the elimination of the drug before reaching systemic circulation including biliary excretion. However not including metabolism by microbial flora.

NOT a part of first pass effect

First pass effect

Note ; there is much more metabolism in liver than intestine

*since the drug didn't pass yet



The drug dose does not fully reach systematic circulation - due to first pass effect

★ Metabolism and feces in gut lumen

Reduces the fraction that reaches systemic circulation (affecting bioavailability), but we don't call it first-pass effect nor pre-systemic elimination.

★ Metabolism Part of the drug gets metabolized by gastric acid or microbial flora

★ To Feces Part of the drug may not be completely absorbed (not all of the dose is delivered to the circulation)

Biliary Excretion
Some drugs may be exerted in bile

First-Pass Effect

- **Therapeutic blood concentration may still be reached by using larger dose.**
- **Therefore, the oral dose is usually higher than intravenous dose for such drugs.**

There is a difference between the oral dose and the **parenteral dose** (refers to drugs administered via a route other than oral administration ,e.g. injections). For example: propranolol (beta-blocker) the oral dose is 40mg however the intravenous dose is only 2mg .

If a fraction of the dose is lost due to first pass effect, how can we compensate for this loss?

1. Increasing the oral dose. For example: if I have a drug with dosage form 500mg and I want all of it to reach the systemic circulation however only 350mg reach the circulation -> I will increase the dose so that an additional 150mg will reach the systemic circulation.
2. Sometimes there is extensive pre-systemic elimination (drug is 70% or 90% metabolized) -> we change the route of administration and give the drug through IV.

First-Pass Effect

- **Also the concentration of drug metabolites after oral administration will be higher than after intravenous administration (why?).**

Different perfusion after oral and IV administration

The nature and concentration of the metabolites is different when the drug is administered orally or through IV.

- ❑ When the drug is given orally, it goes directly to the metabolizing organ. In contrast, when administered through IV not all of the blood supply reaches the liver, which affects the concentration of the metabolites.
- ❑ Through oral administration the drug reaches the intestine, and it will be metabolized via different enzymes producing different metabolites than when given intravenously, where it goes directly to the liver and is acted upon by different enzymes.

First-Pass Effect

- **If the patient is having liver cirrhosis and there is shunting of blood by-passing the portal circulation, giving a larger dose orally will lead to substantial increases in concentration of the drug and drug toxicity.**
- In cases of liver cirrhosis (the most severe and extensive pattern of liver fibrosis), there is shunting of blood from the portal to the systemic circulation =by-passing the portal circulation -> reducing the amount of blood that passes through the liver. As a result, giving the drug without awareness of a patient's liver cirrhosis allows the entire large dose to go to the systemic circulation (so there is substantial increase of the concentration of the drug in the blood)-> causing adverse effects and toxicity (if extreme dose is given).

Bioavailability التوافر الحيوي

or percentage

- It is the **fraction of the unchanged active drug** reaching the systemic circulation, following drug administration; irrespective of the route.

A fraction of the drug can be lost through intramuscular administration as some of the drug precipitates between muscle fibers or orally in metabolism and biliary excretion that occurs in the intestines and liver.

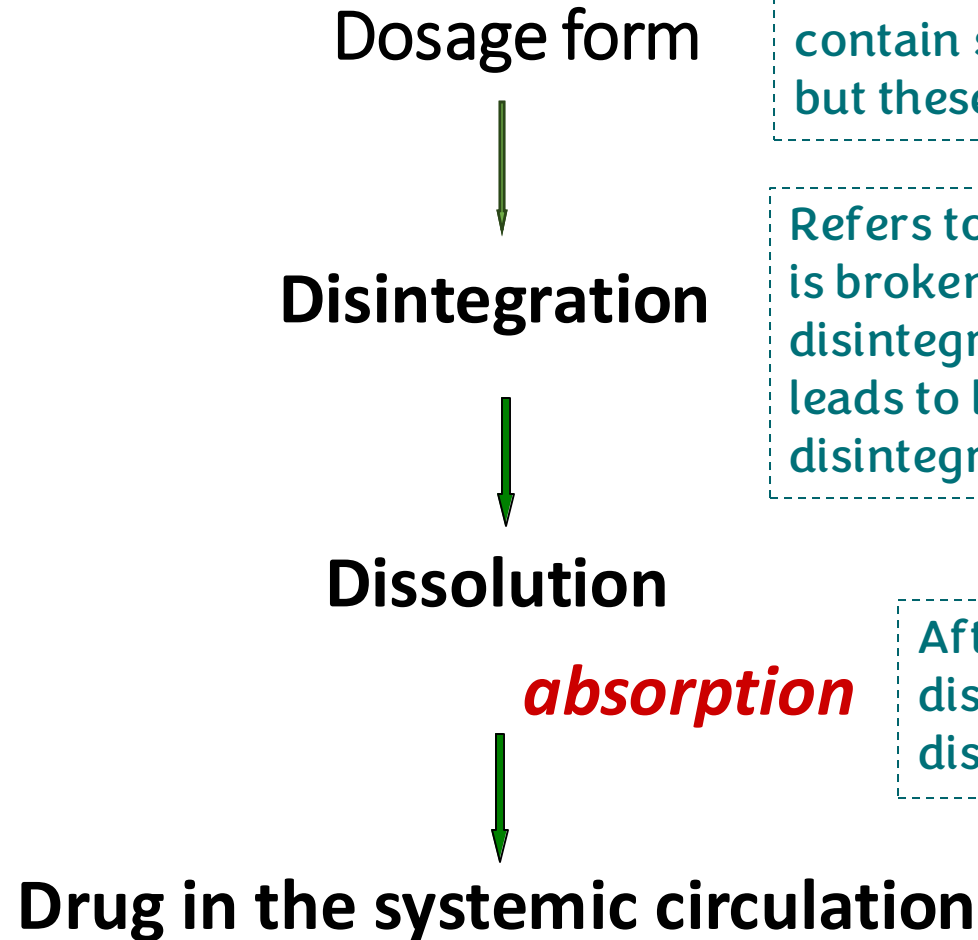
- It is equal to “1” or 100% following intravenous drug administration. (the whole administered dose reach the systemic circulation)

Bioavailability

- **After oral administration, bioavailability may be less than 1, because of:**
 1. First-pass effect.
 2. Incomplete absorption. → Excretion in the intestines.
 3. Incomplete disintegration and dissolution. Discussed in the next slide
 4. Destruction of drug within GIT lumen by gastric acid, bacteria, ..etc. → Again, this is not a part of the first-pass effect.
 5. Faulty manufacturing of the dosage form. Which leads to failure/ low disintegration and dissolution.
 6. Enterhepatic cycling.

The drug or part of it cycles between the intestines and the liver without reaching the systemic circulation. It will be discussed later in detail but briefly it is when the drug absorbed in the liver and excreted in bile then it is reabsorbed in the intestines then excreted in bile and the cycle continues.

Further explanation of the Incomplete disintegration and dissolution.



Solid form such as tablets or capsule. Solid dosage forms contain substances other than the drug for several reasons, but these substances should be inert.

Refers to the process by which the solid dosage form of a drug is broken down into smaller particles in the intestine. Failure in disintegration could occur due to faulty manufacturing → this leads to low bioavailability (as the dosage form that doesn't get disintegrated will not enter the systemic circulation).

After the solid dosage is disintegrated it needs to be dissolved in solution to be absorbed this is called dissolution.

Note: In oral administration we have solutions (as either suspension or syrup formulation) these don't need neither disintegration nor dissolution because they are already ready for absorption.

Bioavailability

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

The Rate of bioavailability differs from the Extent of bioavailability

Rate is affected by disintegration

Where Two drugs can have the same AUC (extent) but differ in how quickly they reach the systemic circulation (Rate).

We can also compare the Bioavailability of two dosage forms using the AUC

Bioavailability

Causes of reduction of the extent of 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).**

= it doesn't reach the systemic circulation

Bioavailability

2. 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.

- If the drug that we use is a substrate of the P-glycoprotein (efflux transporter) in the intestines, absorption will be reduced since everything enters eventually returns.

Bioavailability

- **Inhibition of the reverse transporter by the use of some drugs and **grapefruit juice**, may be associated with substantial increase in drug absorption and thus **bioavailability**.** = Causing adverse effects
- **Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.**

= it contains substances that inhibit the metabolism of the drug.

Many drugs are a substrate for both : **efflux transporter** and the **metabolizing enzyme**.

Thus, the inhibition of both by grapefruit juice will deliver a huge amount of the drug to the systemic circulation.

Therefore, elderly people should avoid taking medications with juice and instead take them only with plain water

Grapefruit juice is considered as a drug itself -> taking 6 drugs + grapefruit juice = taking 7 drugs
as it has a pharmacological action on the delivery of the drug to the circulation.

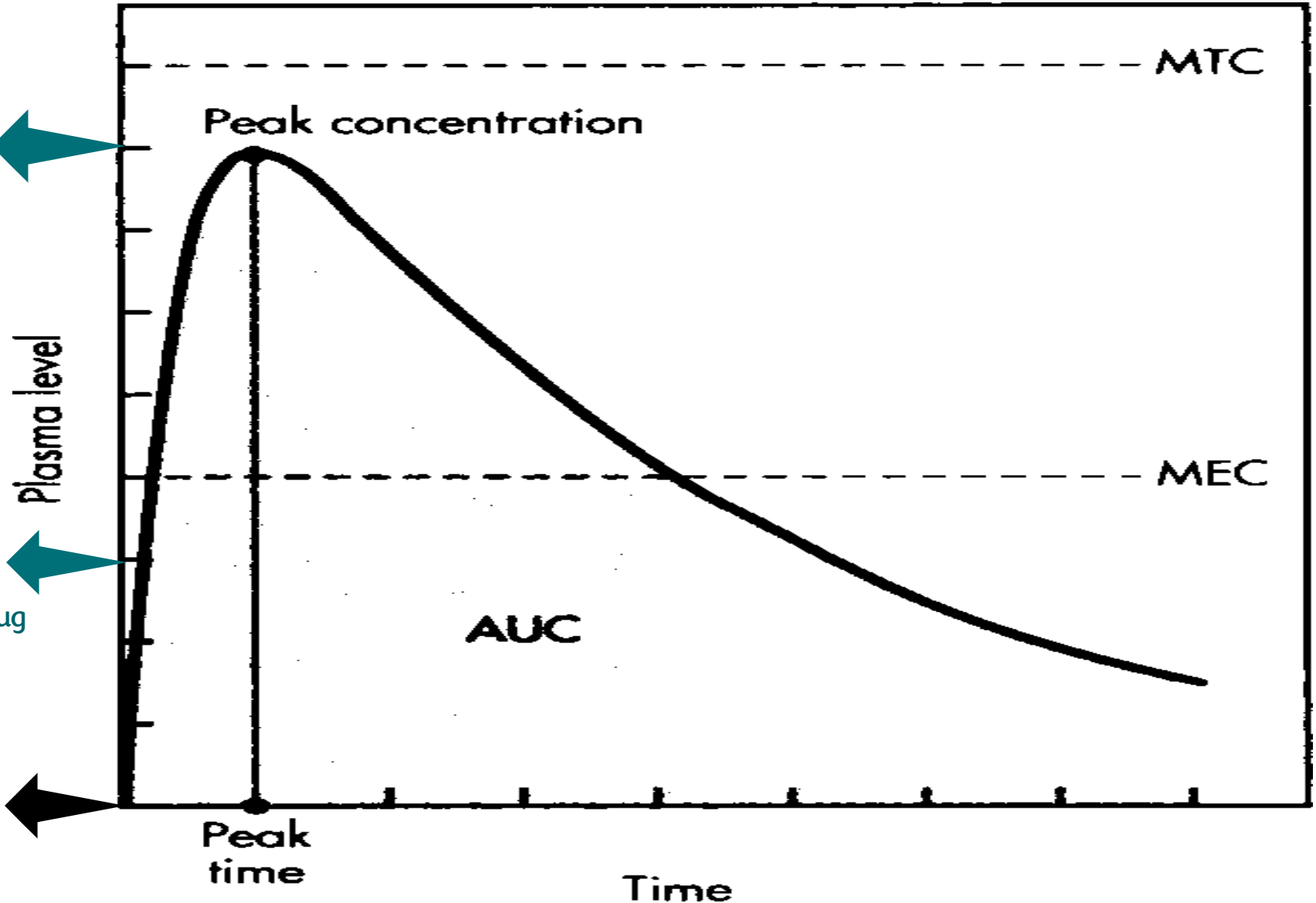
Initial concentration if it was given :

1. Intravenous (IV)
(high)

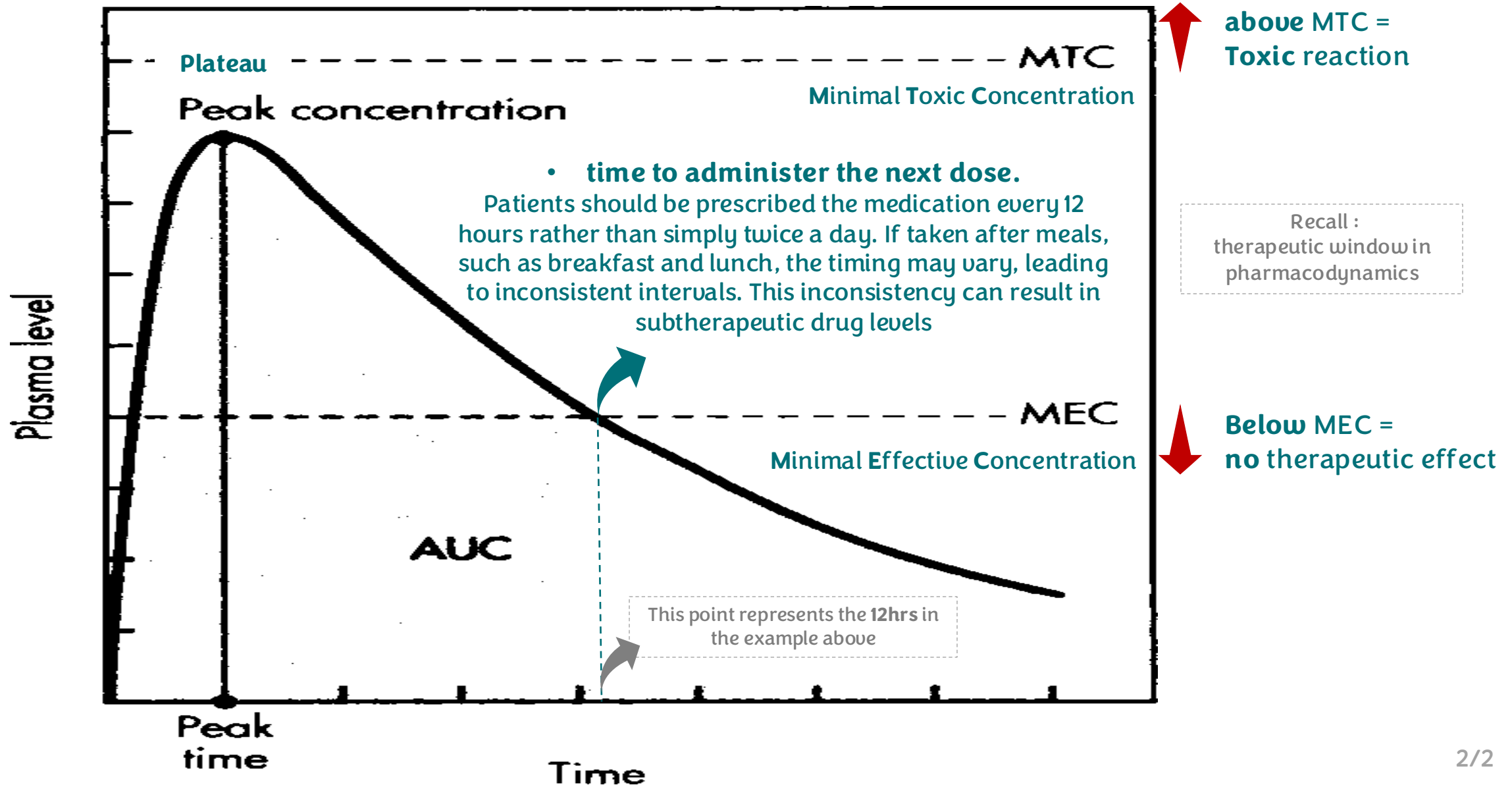
2. Intramuscular (IM)

It contains BVs -> some of the drug enters immediately

(in this figure)
The drug has been given orally as the concentrations starts from ZERO



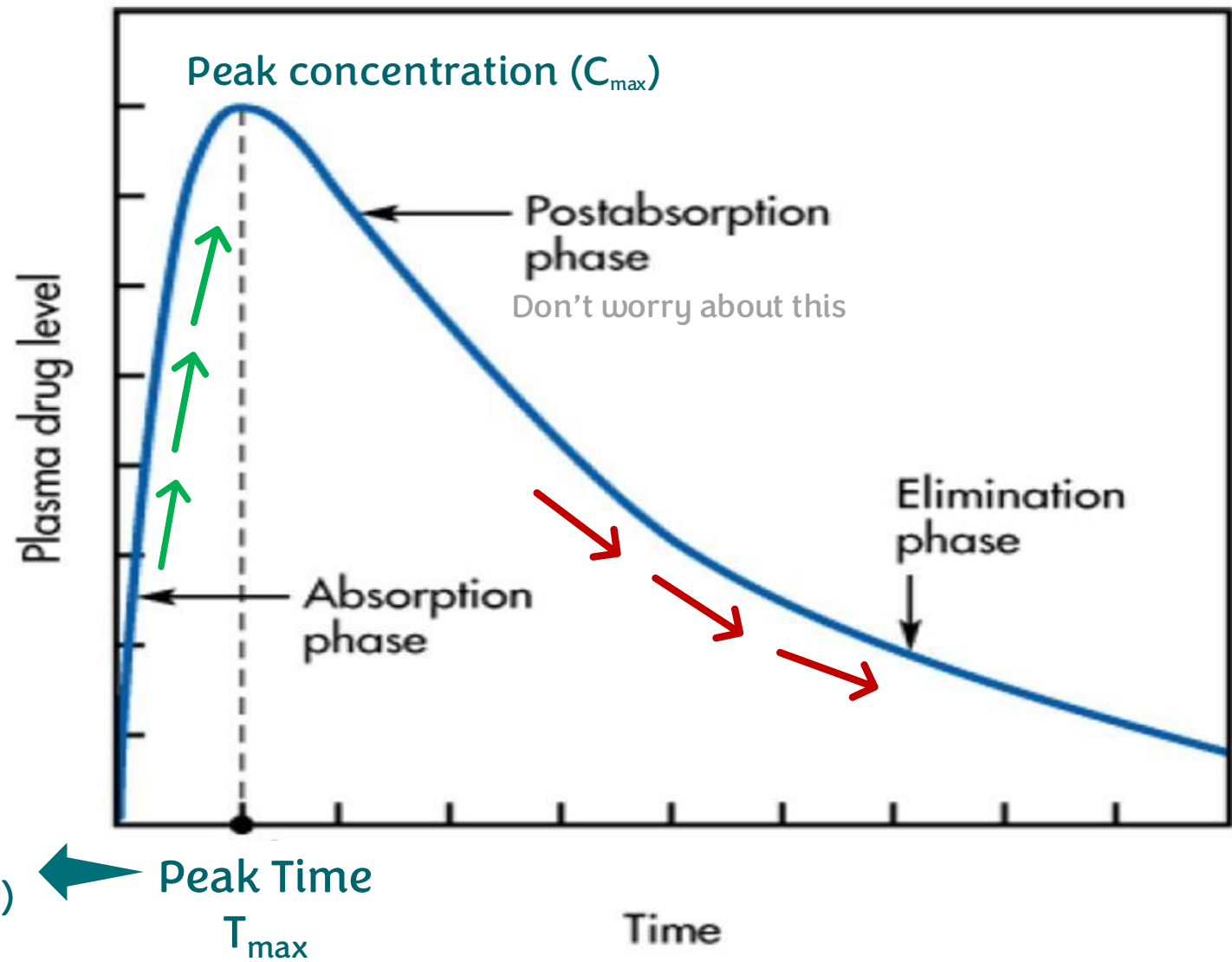
- The peak concentration of the dose should be between MTC & MEC therapeutic effect with minimal adverse reactions



- Peak concentration is when Absorption rate = Elimination rate

Absorption phase

absorption rate is faster than elimination rate.



Elimination phase

Elimination rate is faster than absorption rate

Time to reach peak concentration (C_{max})

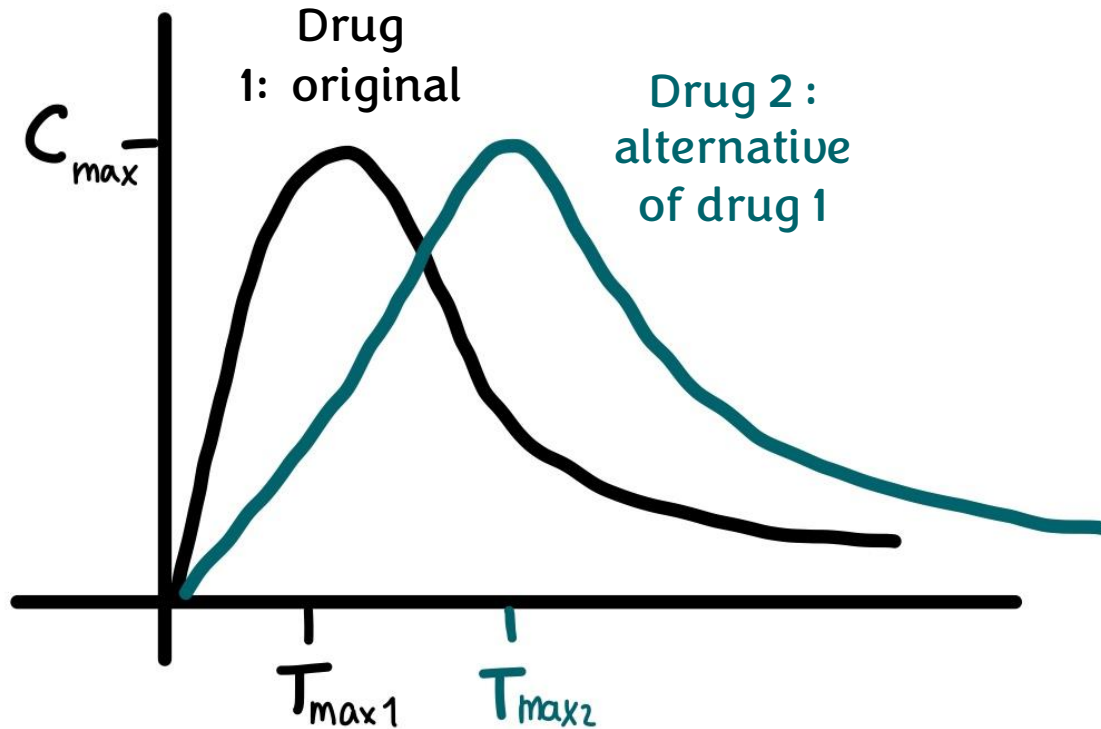
Peak Time

T_{max}

Importance of Time to Peak :

Suppose we have 2 drugs :

الدوا مقطوع بس عندي بديل
: البديل



Alternative drugs should
always be similar to the
original
(Will be discussed later)

Drug 2 reaches the same peak but at delayed time
= Delayed therapy

$$T_{max1} < T_{max2}$$

Effect of First-Pass Effect on bioavailability

- The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction ratio (ER):
- Bioavailability (F) = 1-ER. → Complete absorption
- If absorption is not complete, bioavailability (F) can be predicted from the extent of absorption (f) and ER.

$$F = (f) \cdot (1 - ER)$$

↓
Fraction absorbed

If 90% is absorbed : F = 0.9 (1-ER)

Due to first pass effect

Drug is Not completely bioavailable -> a fraction didn't reach the systematic circulation =

1- Extracted ratio by the intestinal wall, portal vein and liver OR biliary excretion

ER = first pass effect

2- Incomplete absorption : metabolism by the gut and gastric acid +not absorbed (to Feces)

Effect of First-Pass Effect on bioavailability

- **A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%.**

$F = 1 - ER$ (since its completely absorbed so $f=1$)
 $F = 1 - 0.67 = 0.33 = 33\%$

Morphine: analgesic given to patients with cancer or Myocardial infarction to relieve pain
(highly extracted)

- **Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.**

Bioavailability isn't constant due to differences among individuals in :

Hepatic drug flow : Adequate blood flow is required to deliver the drug to the liver.

Hepatic drug metabolism : differences in drug metabolizing enzymes.

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Extra References for the Reader to Use:

1. [Summery of Drug absorption \(4min\)](#)

اللَّهُمَّ كُنْ لِأَهْلِ غَزَّةِ عَوْنًا وَنَصِيرًا يَا رَبَّ الْعَالَمِينَ اللَّهُمَّ نَسْتُوذِعُكَ أَهْلِي غَزَّةَ وَفِلَسْطِينَ فَانصُرْهُمْ وَاحْفَظْهُمْ بِعَيْنِكَ الَّتِي لَا تَنَامُ، وَارْبِطْ عَلَى قُلُوبِهِمْ وَأَمْدِهِمْ بِجُنْدِكَ وَأَنْزِلْ عَلَيْهِمْ سَكِينَتَكَ وَسَخِّرْ لَهُمُ الْأَرْضَ وَمَنْ عَلَيْهَا

يقولُ اللهُ تَعَالَى: أَنَا عِنْدَ ظَنِّ عَبْدِي بِي، وَأَنَا مَعَهُ إِذَا ذَكَرَنِي، فَإِنْ ذَكَرَنِي فِي نَفْسِهِ ذَكَرْتُهُ فِي نَفْسِي، وَإِنْ ذَكَرَنِي فِي مَالٍ ذَكَرْتُهُ فِي مَالٍ خَيْرٍ مِنْهُمْ، وَإِنْ تَقَرَّبَ إِلَيَّ بِشِبْرٍ تَقَرَّبْتُ إِلَيْهِ ذِرَاعًا، وَإِنْ تَقَرَّبَ إِلَيَّ ذِرَاعًا تَقَرَّبْتُ إِلَيْهِ بَاعًا، وَإِنْ أَتَانِي يَمْشِي أَتَيْتُهُ هَرْوَلَةً.
الراوي : أبو هريرة | المحدث : البخاري | المصدر : صحيح البخاري

Quick reminder :
3 weeks left for mid exams :)

