PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 3

Pharmacokinetics

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

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

Recall in the previous lecture, we've been talking about the special carriers (carrier-mediated transport)

- **They are selective, saturable and inhibitable.** ← Last information we've learned about them

- **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 (some but not all) 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 (acquired bacterial resistance)
(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 (molecules with high molecular weight), 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 inhabit 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 B_{12} 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 via endocytosis, 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.**
Thickness hinders passage of drugs

Recall fick's law of diffusion !

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

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 <u>incomplete</u> 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".

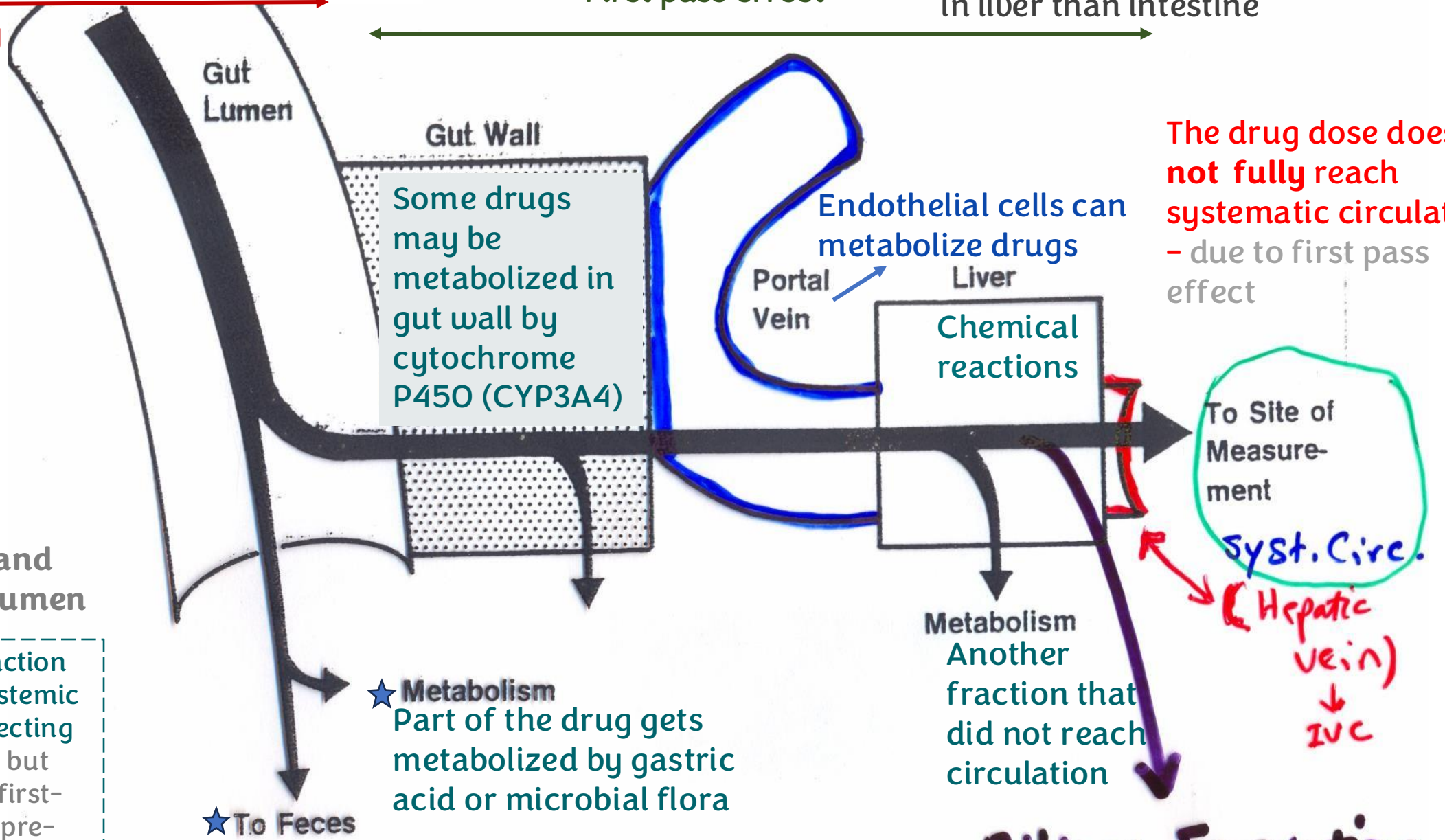
General term that refers to the elimination (metabolism and excretion) of the drug before reaching systemic circulation including biliary excretion. However not including metabolism by microbial flora.

NOT a part of first pass effect

*since the drug didn't pass yet

First pass effect

Note ; there is much more metabolism in liver than intestine



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.

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 administrated 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.

(You need additional 214.286 mg of the drug to compensate the lost 150 mg and ensure that 500mg reach the systemic circulation- total oral drug dosage = 714.286mg)

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 administrated orally or through IV.

- ❑ When the drug is given orally, it goes directly to the metabolizing organ. In contrast, when administrated 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

- **It is the fraction of the unchanged active drug** or percentage **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.**

Dosage form

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.

↓

Disintegration

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).

↓

Dissolution

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

absorption

↓

Drug in the systemic circulation

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.**

Can you predict the drug's function from its name?
Hint: it ends with lol

- **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).**

(because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells)

= 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 contain substances that inhibits 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)

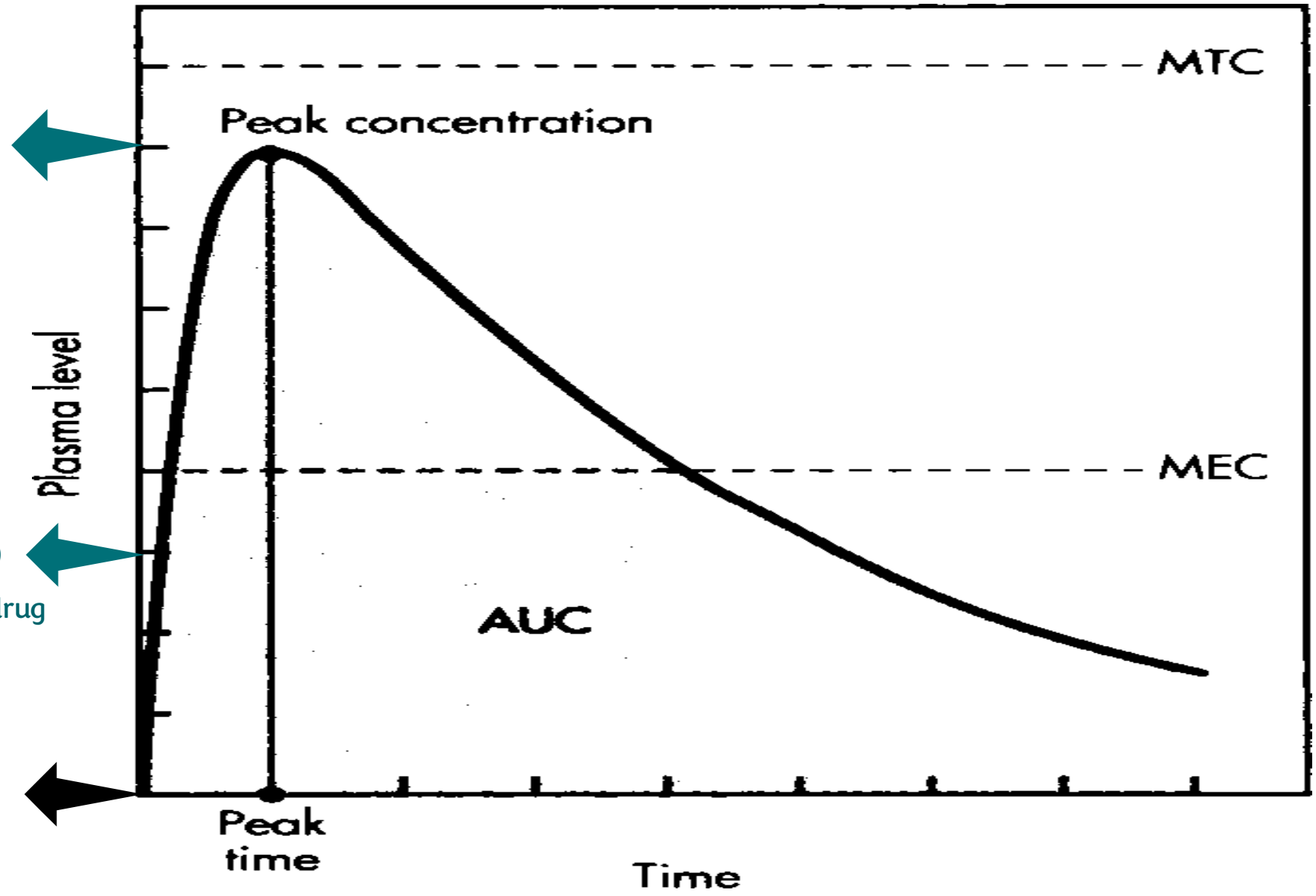
(high)

2. Intramuscular (IM)

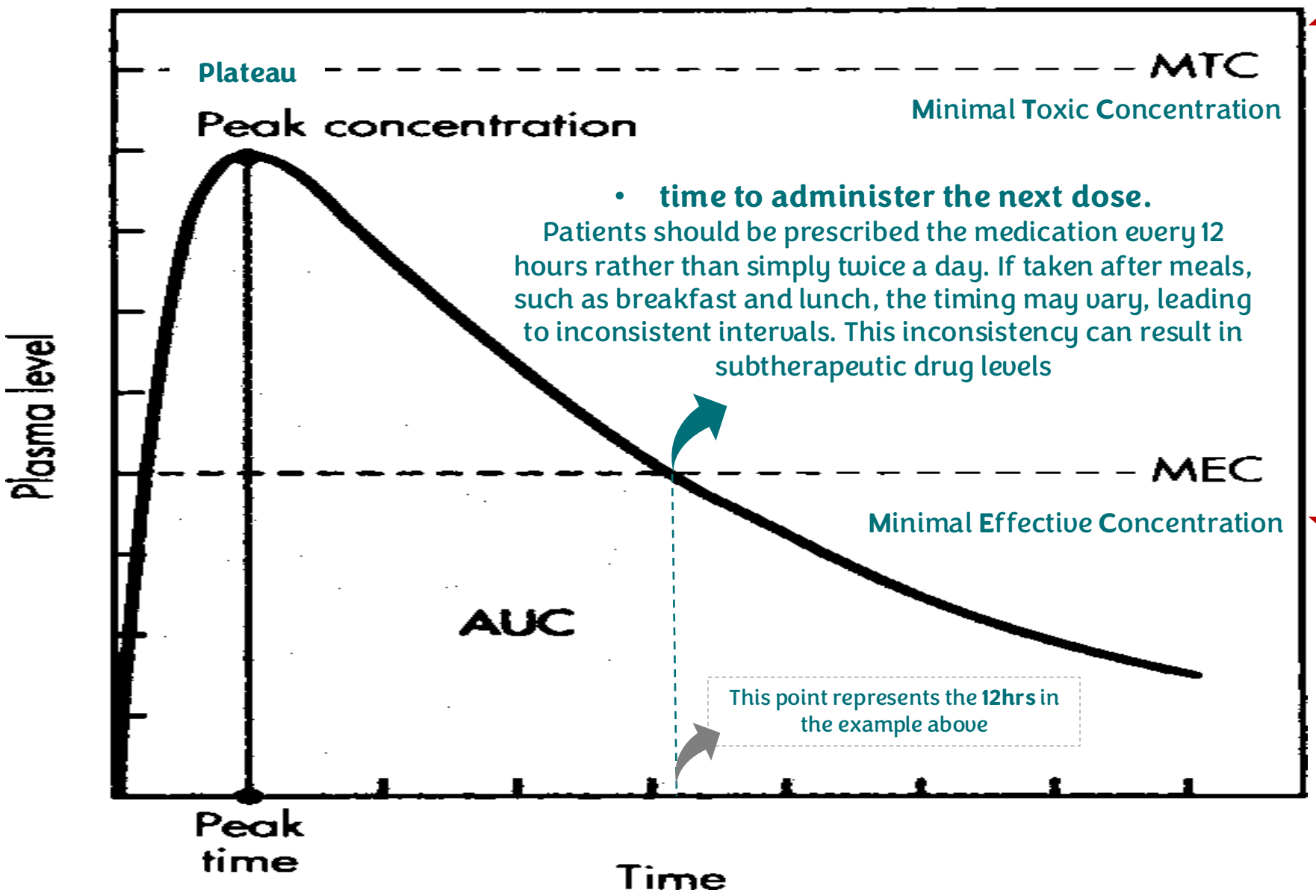
It contains BVs -> some of the drug enters immediately

(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



above MTC = **Toxic** reaction

- **time to administer the next dose.**

Patients should be prescribed the medication every 12 hours rather than simply twice a day. If taken after meals, such as breakfast and lunch, the timing may vary, leading to inconsistent intervals. This inconsistency can result in subtherapeutic drug levels

This point represents the **12hrs** in the example above

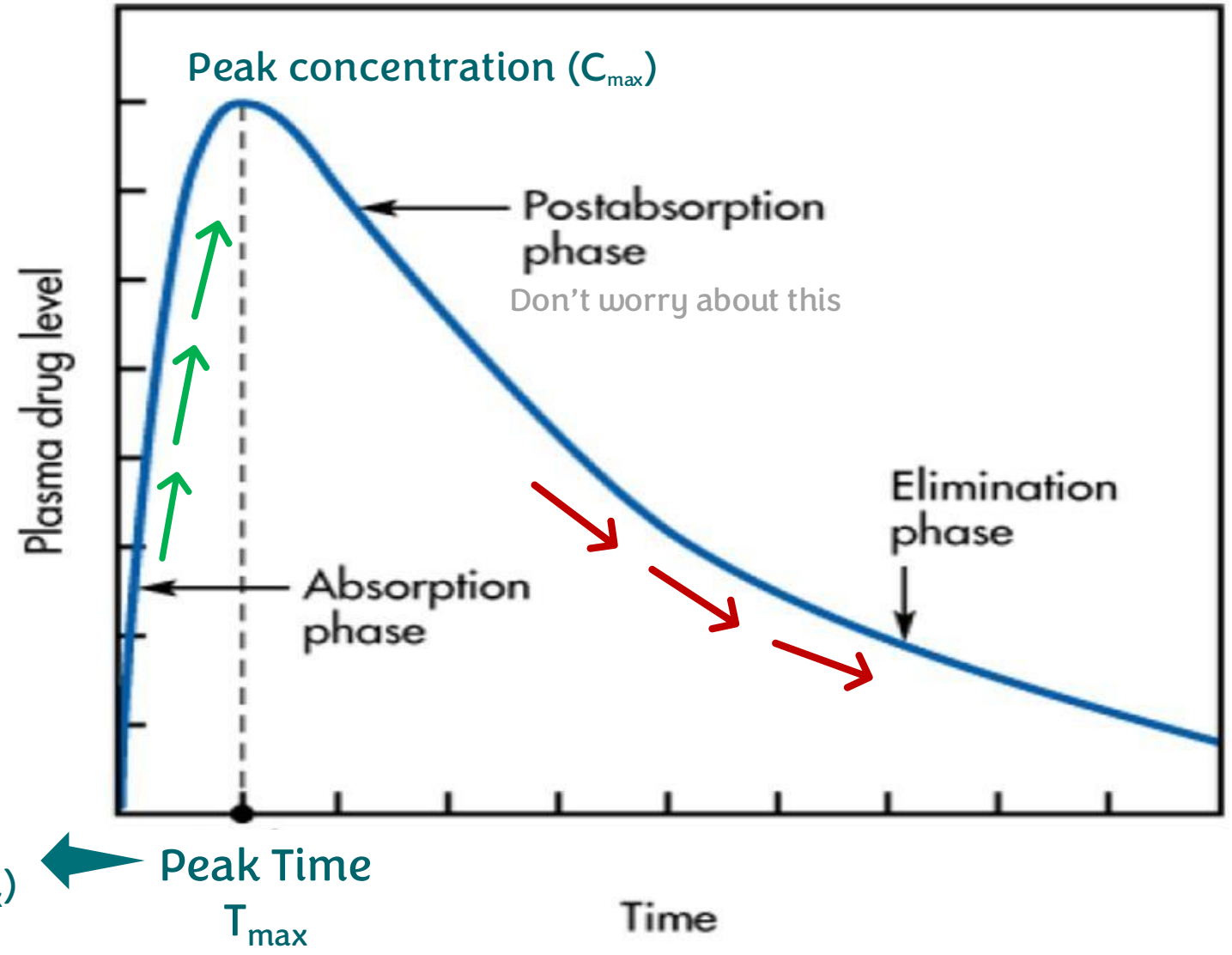
Recall : therapeutic window in pharmacodynamics

Below MEC = **no** therapeutic effect

- 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})

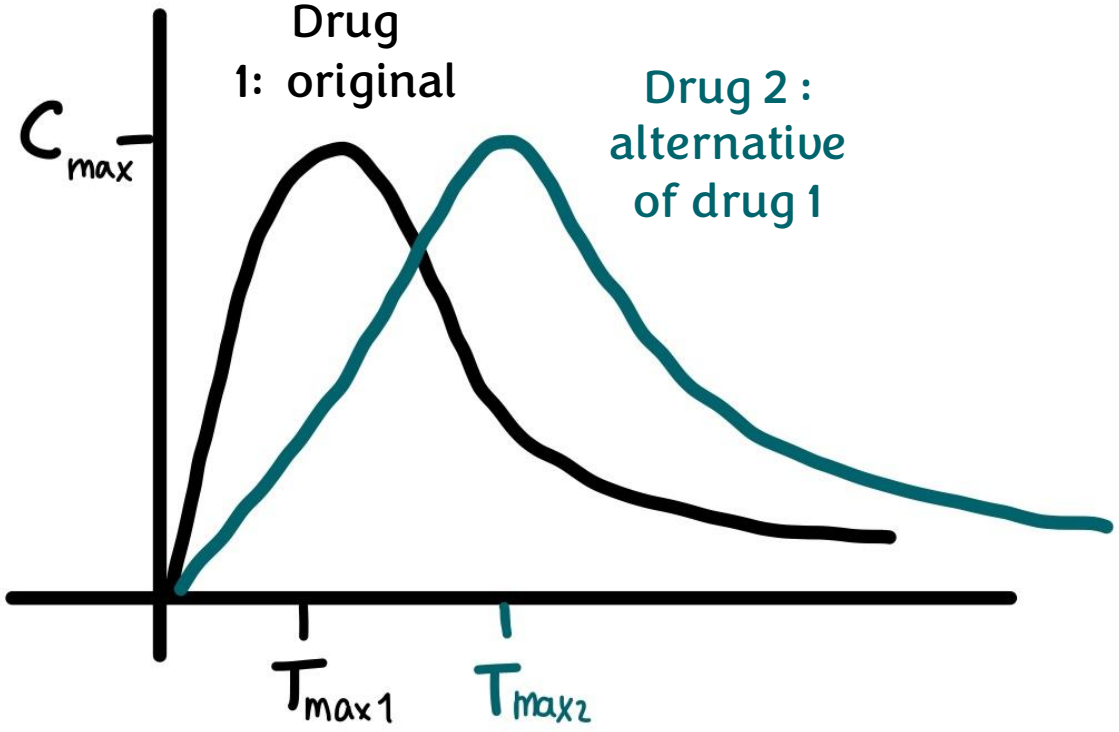
Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com "Textbooks aren't facts. " Dr Yaqoub :)

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 concentration 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.**

Due to first pass effect

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

Fraction absorbed

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

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	Slide 3 Slide 4 (For example,…is used) Slide 6 Slide 6 Slide 12 Slide 13 Slide 20	Added information Color code corrected (Grey) Iron binds to transferrin, allowing it to enter developing RBCs Color code corrected Cytochrome P453 Added information in grey Further additional explanation is added in grey	Recall in the previous lecture… Color code corrected (Teal) Iron binds to transferrin, allowing it to enter developing RBCs <u>via endocytosis</u> P450 (CYP3A4) You need additional…
V1 → V2			

Additional Resources:

Extra References for the Reader to Use:

1. Summery of Drug absorption (4min)

رسالة من الفريق العلمي:

اللهُم كُن لأهل غزة عونا ونصيرا يا رب العالمين اللهم نستودعك أهالي غزّة وفلسطين فانصرهم واحفظهم بعينك التي لا تنام، واربط على قلوبهم وأمدهم بجُندك وأنزل عليهم سكينتك وسخر لهم الأرض ومن عليها

يقولُ اللَّهُ تَعالَى: أنا عِنْدَ ظَنِّ عَبْدِي بي، وأنا معهُ إذا ذَكَرَنِي، فإنْ ذَكَرَنِي في نَفْسِهِ ذَكَرْتُهُ في نَفْسِي، وإنْ ذَكَرَنِي في مَلَإٍ ذَكَرْتُهُ في مَلَإٍ خَيْرٍ منهمْ، وإنْ تَقَرَّبَ إلَيَّ بشِبْرٍ تَقَرَّبْتُ إلَيْهِ ذِراعًا، وإنْ تَقَرَّبَ إلَيَّ ذِراعًا تَقَرَّبْتُ إلَيْهِ باعًا، وإنْ أتانِي يَمْشِي أتَيْتُهُ هَرْوَلَةً.

الراوي : أبو هريرة | المحدث : البخاري | المصدر : صحيح البخاري

Quick reminder :
1 day left for mid exam :)