

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



Pharmacology | Lecture 9

Pharmacokinetics

pt.3



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Bioavailability

❖ The drug has to be significantly lipid soluble to be absorbed (but not too lipophilic)

1. The drug may be too hydrophilic (atenolol), or too lipophilic (acyclovir), to be absorbed easily.
 - ↳ Not well absorbed
 - ↳ (Polar/ionized) Weakly or not we'll absorbed
- 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).

❖ Less absorption -> less bioavailability

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.

- **Efflux transporter (protective mechanism of the body to prevent FOREIGN substances (drugs and toxins) from entering cells)**
- **Transporters like (p-glycoproteins) can be inhibited and they are saturable -> inhibition of this protein causes the influx of the drug**
- **P-glycoprotein is present in the intestinal mucosa and BBB**

Bioavailability

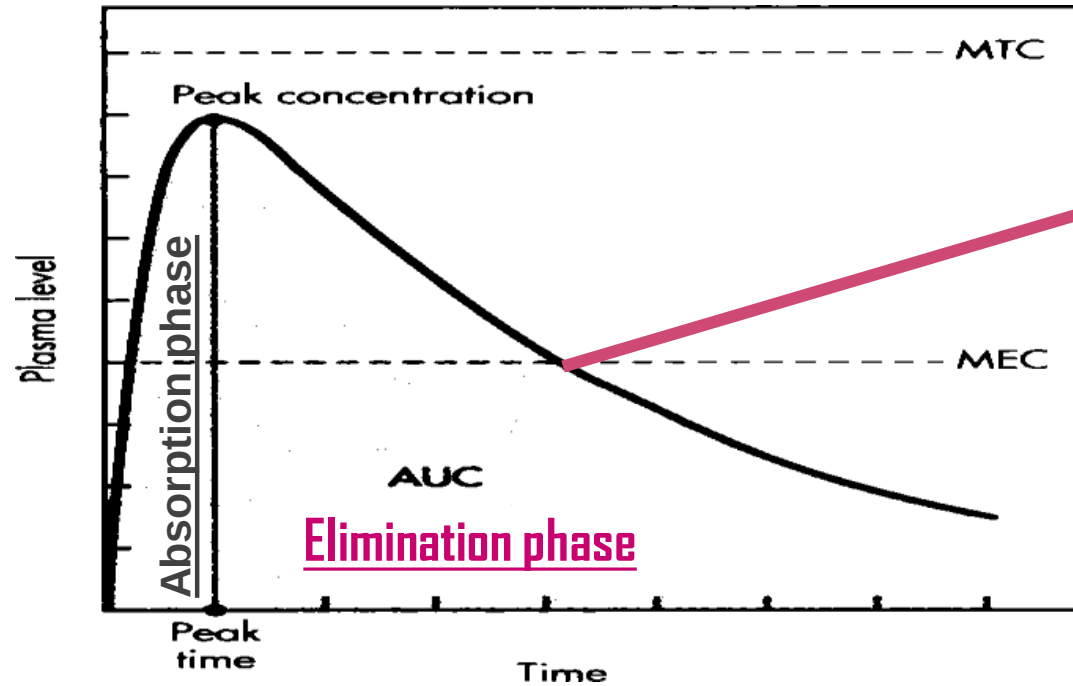
- Inhibition of the reverse transporter by the use of some drugs and **grapefruit juice**, may be associated with substantial increase in drug absorption and thus bioavailability.
- Grapefruit juice also inhibits presystemic elimination of some drugs, and thus, increases their bioavailability.



Grapefruit juice is just like a drug that inhibits P glycoproteins (the efflux transporter) and inhibit metabolism of drugs, we achieve that by what we call a suicidal substrate that we damage the whole enzyme, and it cannot recover only with a synthesis of new enzyme

Both have lots of common substrates and inducers and inhibitors as if they are double the protective mechanisms of the body

First pass and bio availability are related inversely



At this point, the next dose of some drugs is given because the previous one effect decreases by time the new dose is give, before the first effect disappear

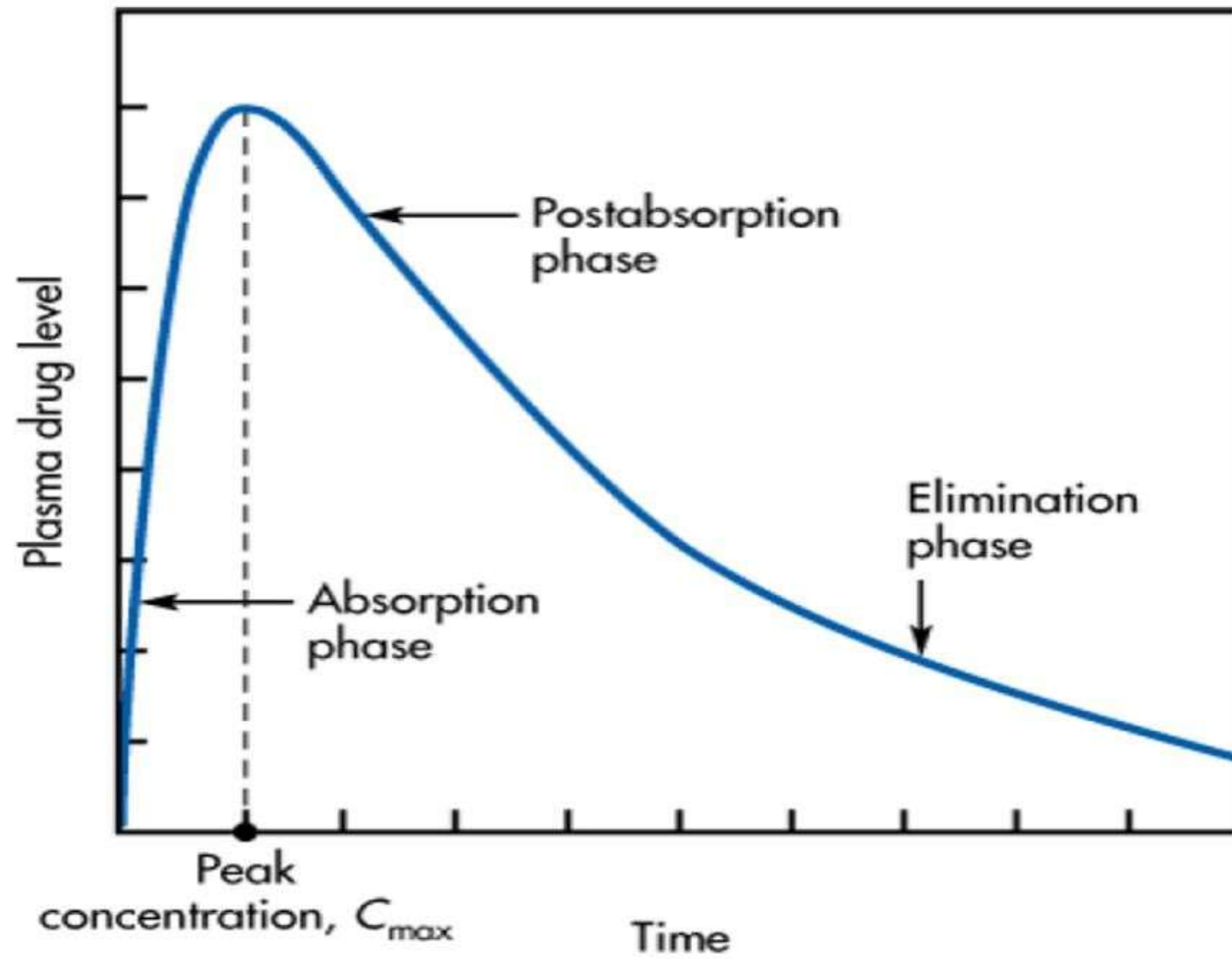


This figure shows a drug that is given orally. (this is a single dose). How did we know the plasma level at zero time? there was a zero drug in the plasma orally taken.

In the absorption phase, concentration is increasing, and the absorption rate is faster than elimination, but both exist.

At the peak concentration rate of absorption equals the rate of elimination.

At the beginning at absorption phase, the absorption rate is higher than the elimination rate and at the end the opposite is true -> the law of mass action. , In the elimination phase, the elimination rate is faster than absorption, but both exist. When prescribing a drug, we need a concentration between these lines if higher, it is toxic, and if less it is a failure of therapy.



Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 6th Edition: www.accesspharmacy.com

Effect of First-Pass Effect on bioavailability

It reduces the bio availability as a part of the drug will be eliminated pre-systemically before reaching the systemic circulation a process called drug extraction

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

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

- When expressing that the drug is 30% bio available means that the extraction ratio is 70%
- Incomplete absorption (not first pass effect) even if both processes have similar effects .

When there is a failure of disintegration in the solution by the activation of gastric acids, and by the presence of the intestinal bacteria that metabolize the drug-> all of these are not related to first pass effect (these only show the incomplete absorption of drug)



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%. $F = 100\%$

If it's metabolized by the intestine and the portal vein and the liver

- 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.

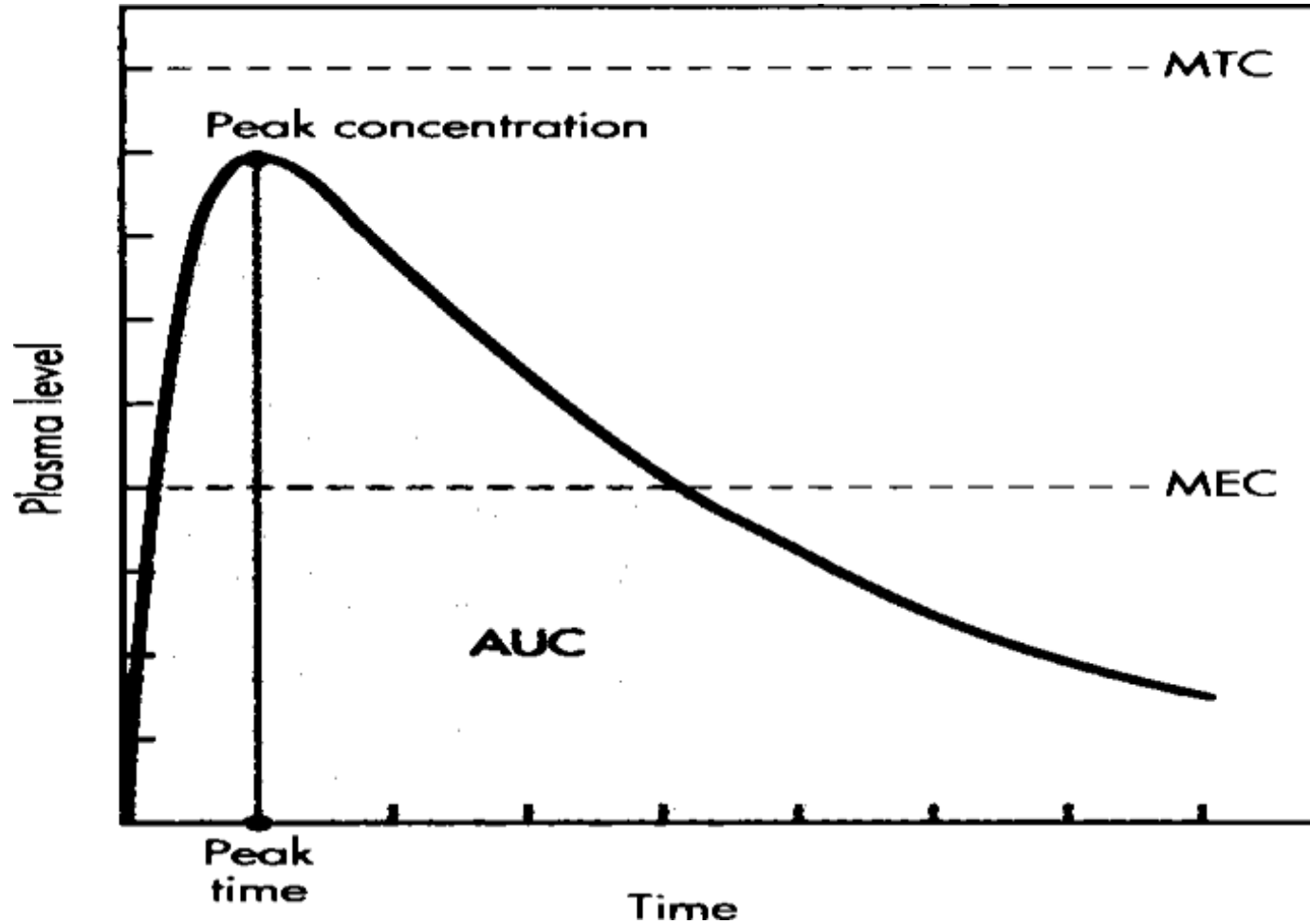
Not all people have the same equal metabolizing enzymes capability .

Drugs that exhibit first-pass metabolism exhibit also high inter-individual variation in drug metabolism, so a drug dose will never be equally effective in 2 people

Bioequivalence

- This term is used to compare the rate and extent of absorption of **different formulations** (or dosage forms) **of the same active drug**. *The same drug from different manufacturing company*
- The extent of absorption is measured by AUC, and the rate is assessed by $C_{\max}$ (peak concentration) and $T_{\max}$ (time to peak concentration).

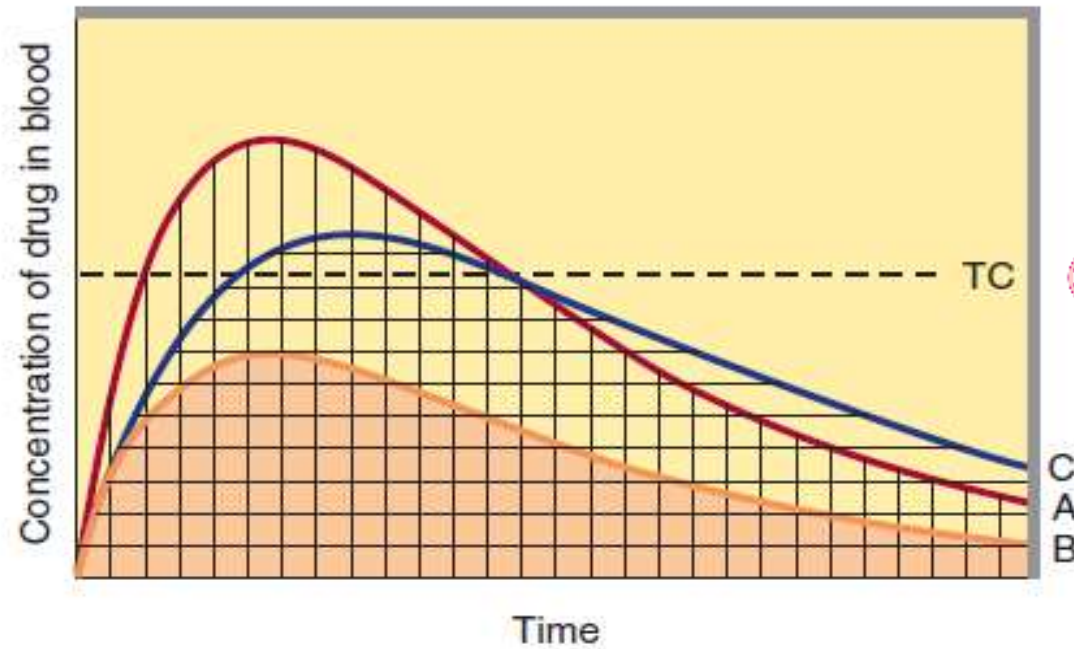
The bio equivalence measurements are compared for the drug from different formulations by having the first existence drug as a standard parameter for comparison (it's called "the originator") and it should have the same efficacy and relative safety as the original so, it can be used as an alternative, and they shouldn't be identical .



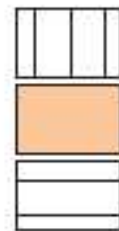
If the curve peak concentration was more to the right (a higher T_{max}), the absorption rate in this case will be lower; even if C_{max} was equal in both cases, we will have an equal but delayed effect.

And the same will apply if the curve peak was lower (lower C_{max}), the rate will also be lower.

And in any of the cases mentioned, we **DO NOT** consider the drug a bio-equivalent.



Target concentration: the concentration that is expected to be achieved for this dosage form to be active



A: Drug rapidly and completely available

B: Only half of availability of A but rate equal to A

C: Drug completely available but rate only half of A

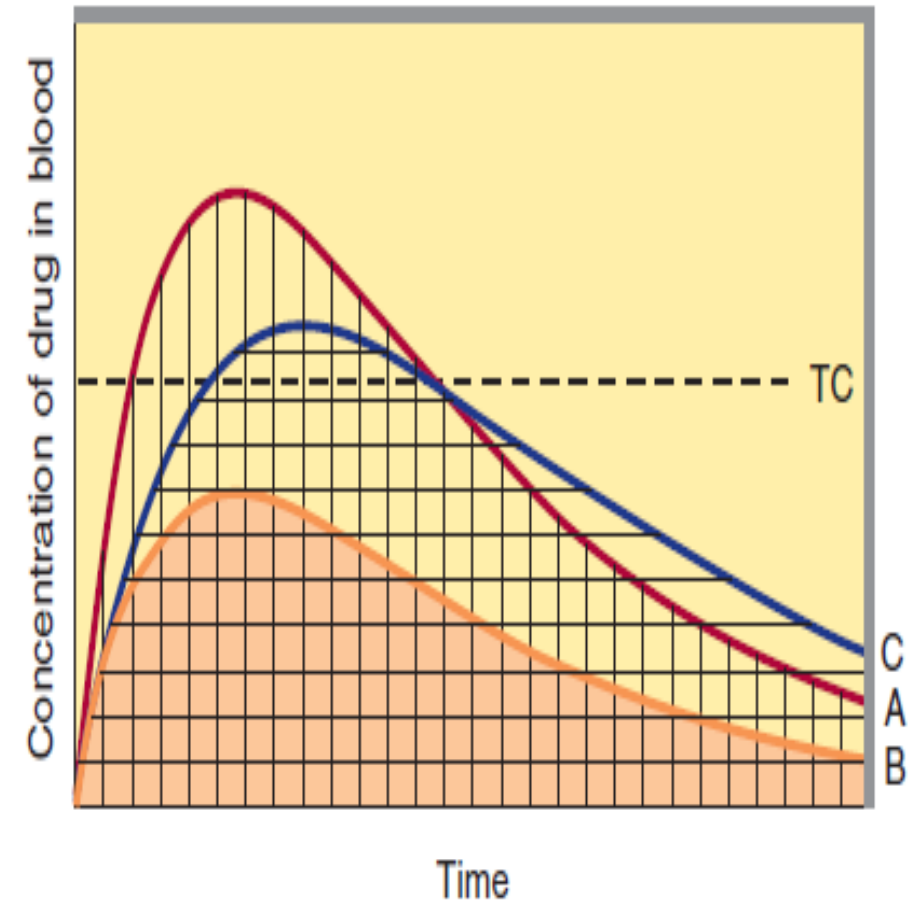
FIGURE 3-4 Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target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

If the bioavailability of a certain drug is 50%, like the yellow one here, never tell the patient to double the dose, because if the patient later buys the drug in the correct formulation, like the red one, doubling the dose could lead to adverse effects. By definition, a drug has a specific dose, which does not change depending on the manufacturer or factory that produces it.

To be bioequivalent, the drug must be equal in C_{max} , T_{max} , and AUC. They should not be higher or lower than the original one, (the one that experiments were conducted on). Any change in these parameters will alter the bioequivalence of the drug.

The lag period is the time needed for the drug to start working, and it is longer in the blue one.

This topic is clinically very important, and you must be aware of it, especially for recent graduates.



Lag time



Lag time is the delay that occurs because the drug needs time for disintegration, dissolution, and absorption before reaching the systemic circulation at a concentration sufficient to achieve the target concentration. This lag time can be short (10–15 minutes) or long (1–1.5 hours).

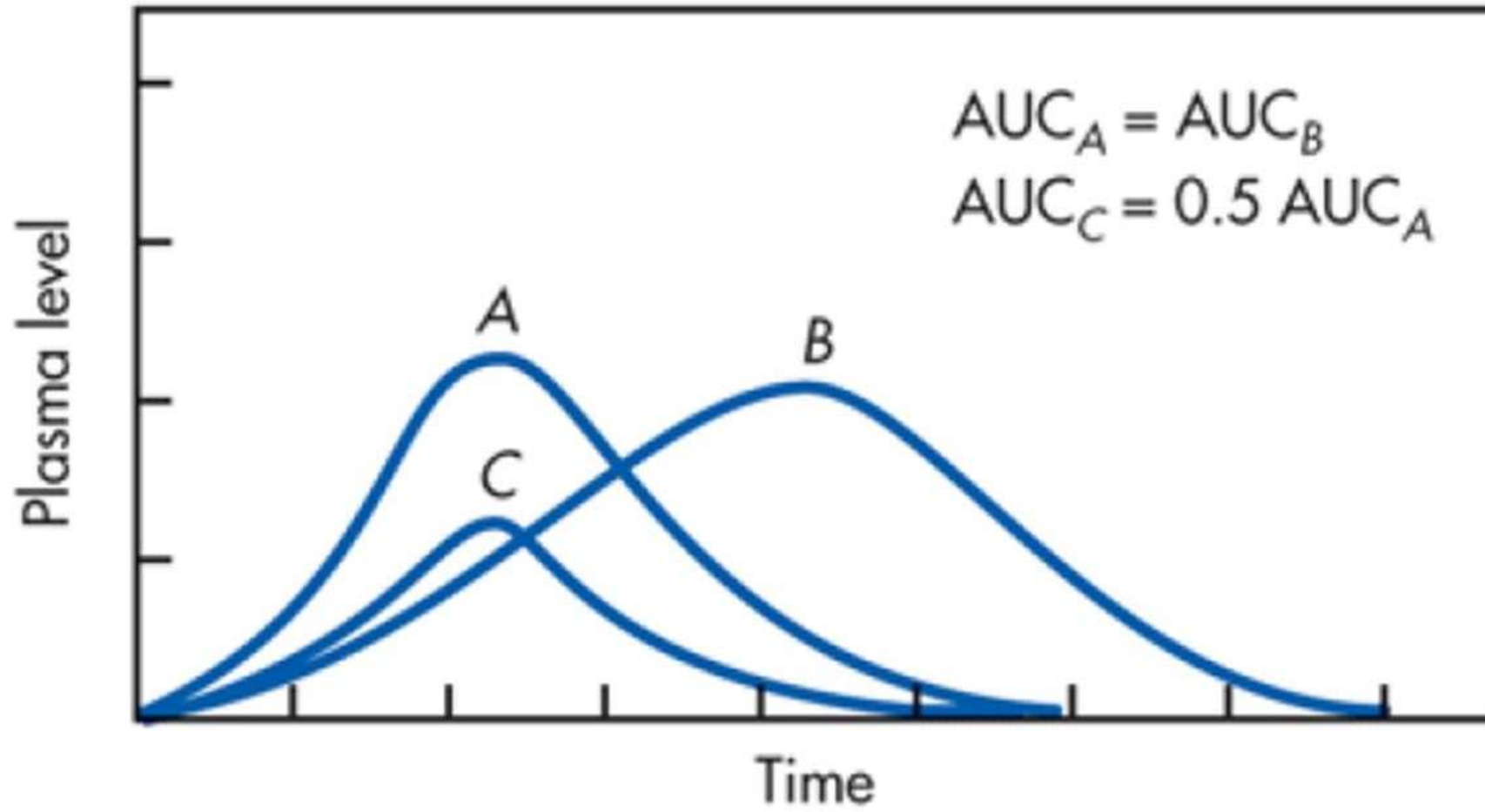
During the first dose, lag time can affect the onset of the drug's effect. However, with multiple dosing, the second dose is often taken before the first dose reaches the target concentration. In this case, there is effectively no lag time, because there is already drug present in the body, and the new dose simply adds to the existing concentration, helping reach the therapeutic level faster.

The original drug is the one on which the experiments were conducted. Another formulation of the drug may reach the same C_{max} but at a longer T_{max} . In this case, we call it late bioavailability. These formulations are equivalent in extent but not in rate which is undesirable because it increases lag time.

In simple cases, like treating a headache, lag time is less important.

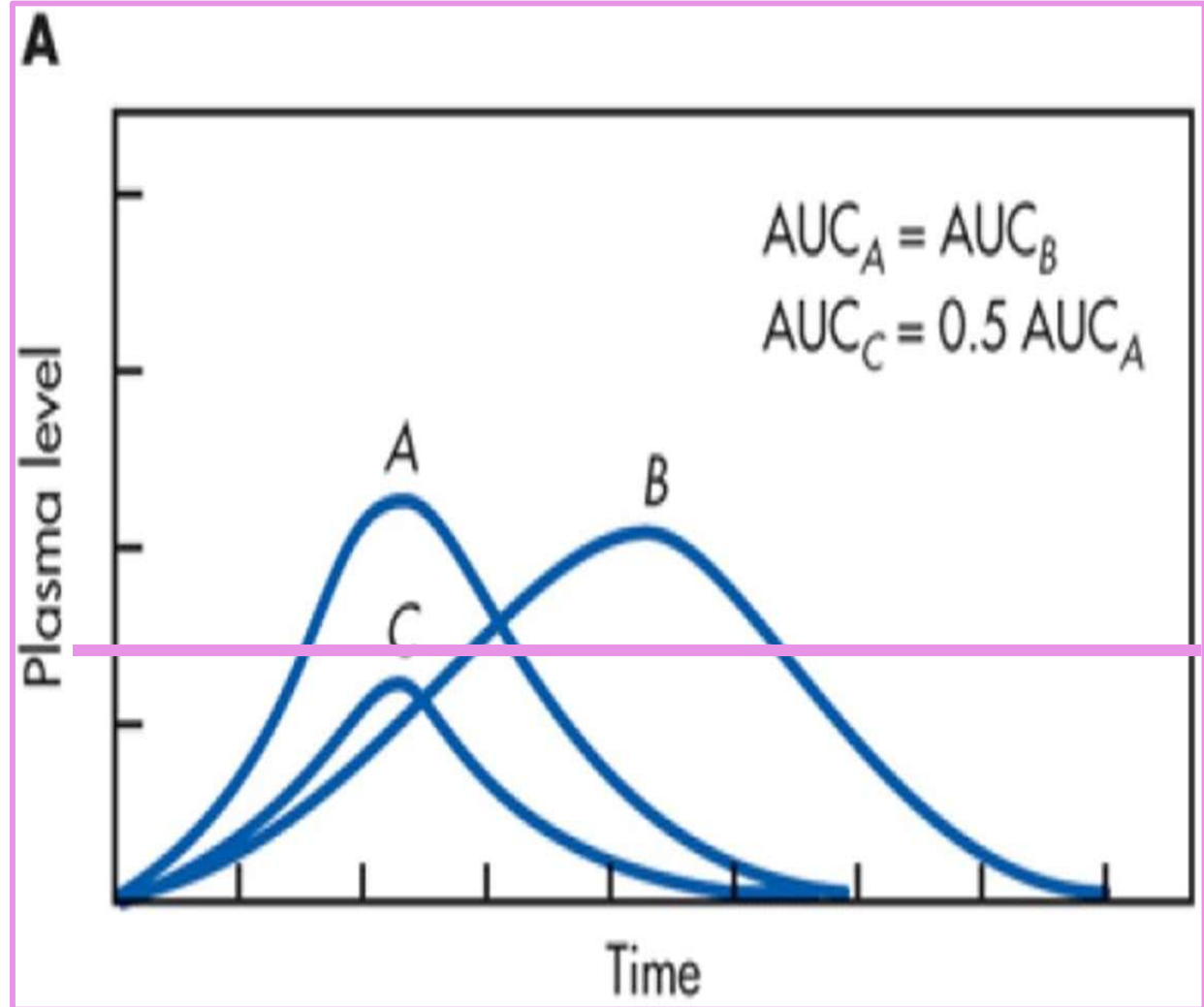
However, in emergency situations, we want the lag time to be as short as possible to ensure a rapid therapeutic effect

A



Considering the target concentration:

- A is the best option.
- B has delayed bioavailability, so although the extent of absorption may be sufficient, the bioequivalence is not accepted
- C is poor in all parameters and is therefore unacceptable.



Enterohepatic Cycling of Drugs

- **After oral administration and absorption, a drug can be excreted in bile before reaching the systemic circulation, go back to gut lumen, and then reabsorbed again.**
- **This is called enterohepatic cycling of the drug.**
- **It reduces drug bioavailability and prolongs its half-life of elimination.**

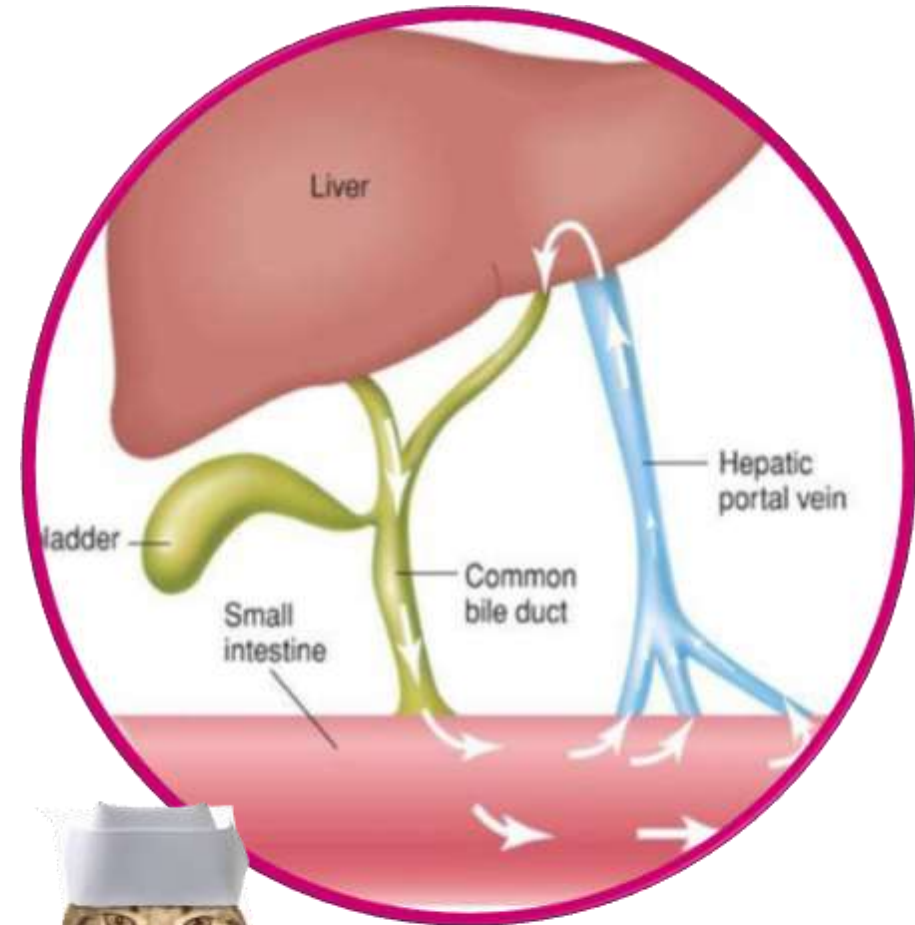
When the drug reaches the gut, it is absorbed and it then passes through the portal vein to the liver, where part of it may be metabolized and some may be secreted into the bile. From the bile, the drug returns to the intestines and can be reabsorbed. This process, known as enterohepatic circulation, prolongs the half-life of the drug.

intero = Gastrointestinal (GI) tract

Hepatic = Liver

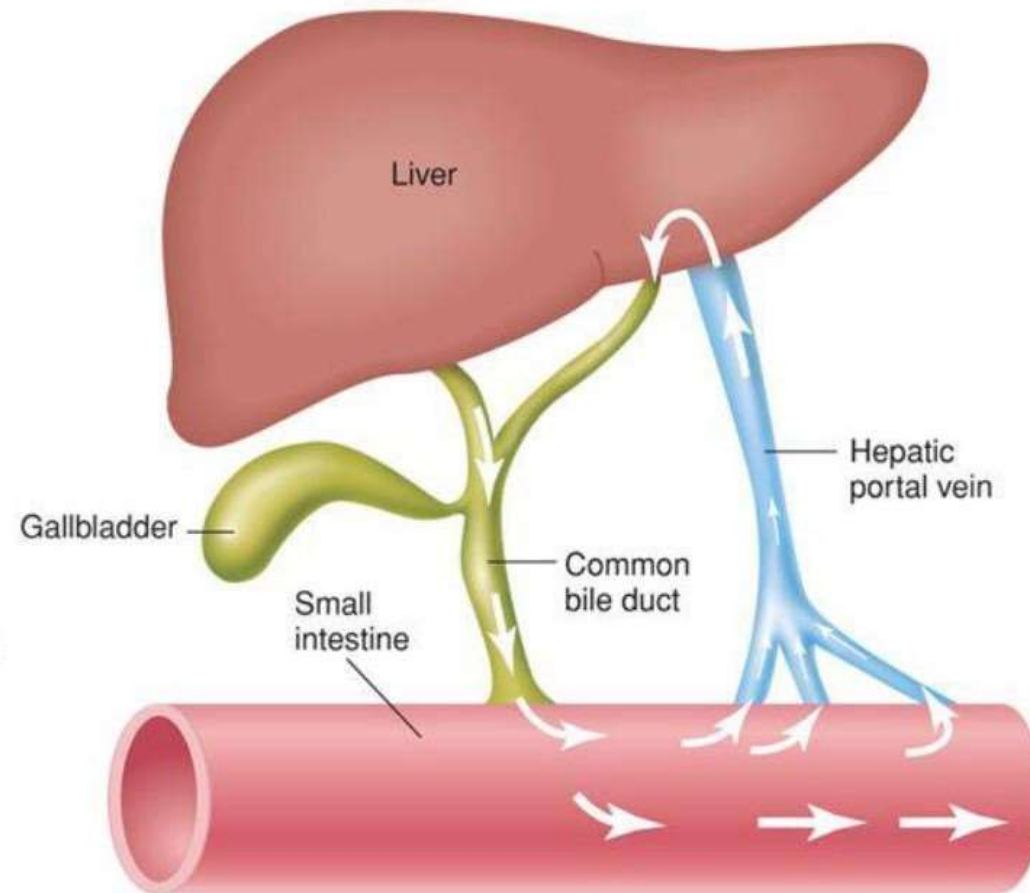
The drug cycle describing is enterohepatic circulation, which is the recycling of a drug between the liver and the intestine.

Gut → Portal vein → Liver → Bile → Gut → Portal vein → Liver → Bile → Gut ...



Enterohepatic Circulation

- ▶ Is recirculation of compounds between liver and intestine
- ▶ Many compounds are released in bile, reabsorbed in SI, and returned to liver to be recycled
- ▶ Liver excretes drug metabolites into bile to pass out in feces



The liver excretes drug metabolites (products of drug breakdown in the body) into bile. Sometimes, the drug can be reabsorbed from the gut and return to the liver, and the liver excretes it again. Other times, the metabolite cannot be reabsorbed, so the liver does not excrete it again. This cycle may repeat as long as the drug is reabsorbable, or it stops if the metabolite is non-absorbable or excreted in urine.



Can a metabolized drug be reabsorbed? It depends on the type of metabolism: if the drug was conjugated (chemically linked to another molecule, usually to increase water solubility), it can be reabsorbed. However, if it was hydroxylated or reduced, it cannot be reabsorbed. Once a drug or metabolite is not reabsorbed, it will not enter enterohepatic circulation again

This happens because the intestinal flora can break the conjugate and release the parent drug, which can then be reabsorbed. The intestinal flora is therefore very important in this process.

For example, a woman takes oral contraceptives, which are metabolized by conjugation. She then develops tonsillitis and takes a broad-spectrum antibiotic. This antibiotic can disrupt the intestinal microflora, preventing the reconversion of the conjugated drug back to its active form and reducing absorption. As a result, the contraceptive may become less effective, and the woman could become pregnant despite taking the medication.



Enterohepatic Cycling of Drugs

Application:

- This phenomenon can be taken advantage of in cases of drug overdose, to enhance drug elimination from the body.
- Activated charcoal can **adsorb** many drugs and chemicals (except ionized ones, and petroleum distillates) into its surface.

Charcoals or Ion Exchange Resins



Adsorb: to stick molecules or particles onto the surface of a material without entering it.

Example: Charcoal adsorbs toxins on its surface, trapping them without chemically changing them.

It is like magnets attracting paperclips. The paperclips stick to the surface of the magnet, but they don't merge with it or change their shape—they simply cling to it.

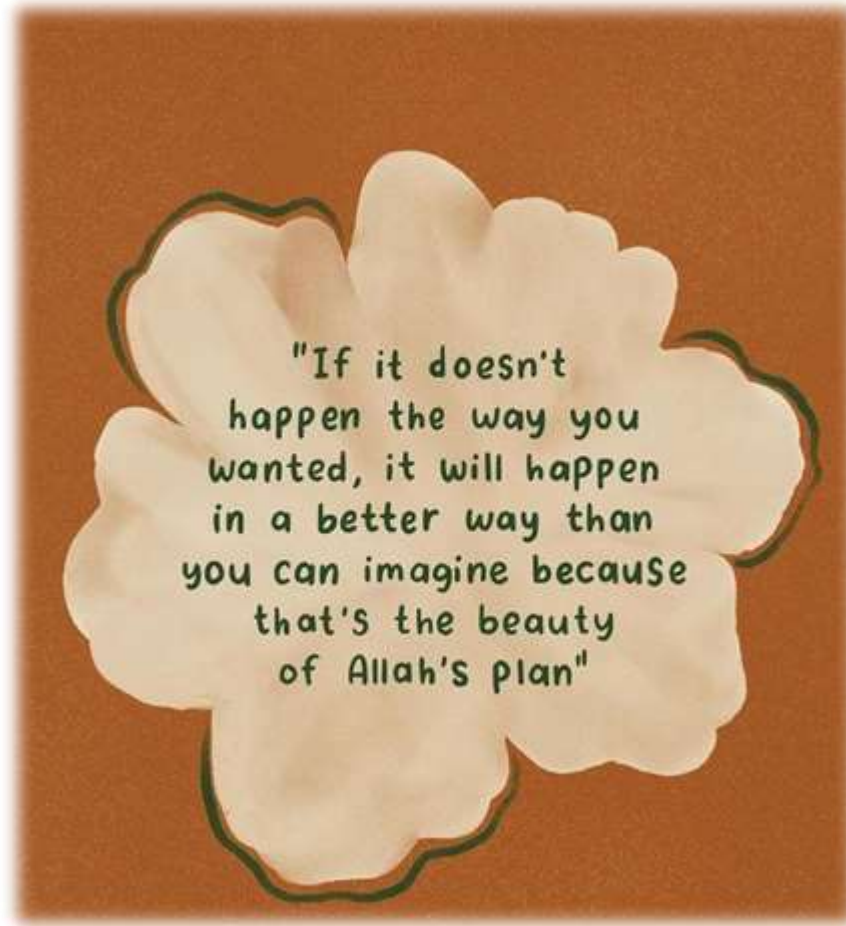
It prevents reabsorption. Activated charcoal is cleaned and free from debris, and processed to have a very high surface area. It is not in tablet form, but a very fine, soft powder, which is usually mixed with juice to make it easier to take orally.

Enterohepatic Cycling of Drugs

- If we give activated charcoal orally in cases of drug overdose, Or it secreted along with intestinal secretions and the drug undergoes enterohepatic cycling, then the portion of the drug that is excreted into the gut through bile can be trapped and prevented from reabsorption back into the systemic circulation.
- This will accelerate drug elimination from the body and reduces its half-life of elimination.

Additional Resources:

رسالة من الفريق العلمي:



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			