Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 3

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Pharmacokinetics

Mechanisms of permeation of drug molecules:

☺ Lipid diffusion (passive diffusion): follows the concentration gradient .

☺ Aqueous diffusion : follows the concentration gradient .

☺ Special carriers: some follow concentration gradient (facilitated diffusion) , and some don't (active transport).

We will talk about three types of the carriers:

- ATP- binding cassette (ABC) family .
- The multidrug-resistance associated proteins (MRP) transporters.
- The solute carrier family (SLC) .

☺ Endocytosis and exocytosis .

We talked about the first two mechanisms , also we talked about the third one and we will continue with it …

As we mentioned ; **special carriers** transport too large or too insoluble in lipids substances , they are selective "and many of them are less selective " , saturable and inhibitable .

Membrane carriers that are **less selective** are specialized in expelling foreign molecules including drugs ; we will talk about three types of them .

A) ATP- binding cassette (ABC) family :

It includes what is called P-glycoprotein and multidrug-resistance type 1 (MDR1) transporter which are carriers present in many cell types , but it is mainly concentrated in the brain , neoplastic cells, testes and

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intestine , this is very important to us ; because they work to prevent the drug from entering the cell or work to expel the drugs out of the cell once it's in . When you give the patient specific drug and then the drug get absorbed by passing through the membrane , once it is in the cell , to go to the other side it will be expelled like this "using P-glycoprotein" , so the presence of this protein is going to limit the absorption of the drug since it's found in the membrane, it also works the same in brain cells , btw this is a protective mechanism ; as the drug is foreign and there are some mechanisms the cell use to protect itself against them by expelling the drug (efflux – out of the brain) , P-glycoprotein is one of them .

P-glycoprotein and multidrug-resistance type 1 (MDR1) are inducible ; which means that they may exist in low concentration but presence of something could increase their production . This is very important because if there is a high concentration of them because of cancer "for example" it may lead to resistance for chemotherapy; the drug will enter the cancer cell which then will develop P-glycoprotein or MDR1 in high amount that will expel the drug outside and so the cancer cell will be protected and this is the mechanism of resistance of the chemotherapy.

So these carriers affect absorption, the drug's entry to the brain, and response of cancer cells to chemotherapy.

The cell itself will develop the protein, this protein is already existed but the cell increases its concentration to protect itself.

Also this protein has a function in the intestine as it limits the absorption.

B) The multidrug-resistance associated proteins (MRP) transporters:

It is from the ABC family and similar to it, as its name implies the presence of this protein will develop resistance of multidrug, so it is not a selective protein. It mainly functions to excrete and prevent entry of **many drugs** (substances) and metabolites in urine, and this is also present in cancer cells that develop resistance to chemotherapeutic agents.

Drugs are excreted in urine actively by this protein.

C) The solute carrier family (SLC) :

They are different from the two other types mentioned as they are **not** from the ABC family. They are also **NOT ATP dependant,** they're a solute dependant carrier. The SLC family depend on the potential that occurs in the cells as a result of the changes in ions.

They are not selective carriers, but at the same time they are not absolute ones.

Function: they are important in transport of neurotransmitter from nerve cells.

They are responsible for neurotransmitter release or reuptake from nerve cells in addition to cancer cells , they are also important in ureic secretion drugs , moreover ; they protect the brain to cause resistance to cancer cells and also important for the absorption of the drugs .

if you give the patient a drug and it doesn't get absorbed , what may the problem be ??

» maybe this patient has an induced transporter or carrier of these .

* There are substances that affects these proteins and affects their transport mechanisms; substances that we take it as food , fluids or even drugs .

▪ knowing about these mechanisms is very important in clinical practice .

☺ Endocytosis and exocytosis :

This mechanism is specialized for substances that are so large or impermeant, ions and vitamins can also be transported by it .

Example : Vitamin B12 to be absorbed it has to combine with a protein (intrinsic factor) that's secreted from the stomach , then it will go to the terminal part of the ileum (specific part of the GI tract that's specific for vitamin B12) and get absorbed there by **Endocytosis** . While exocytosis is responsible for secretions like hormones and neurotransmitters.

Also ions can be transported by this way like the iron associated with transferrin to RBC's.

First – pass effect:

It means the first passage.

It is applied to drugs which are taken **orally** only.

Why do we call it First-pass?

» Because it has to traverse the gut wall and reach the liver then go to the systemic circulation , since between the gut wall and the liver we have the **portal** circulation not the **systemic** circulation .

☺ **Portal circulation**: it refers to portal vein, which drains the blood from the GI tract into the liver, the drug enters the liver and goes to the hepatic vein then it goes to the systemic circulation, so the passage between the gut and the liver is called portal circulation.

When the drug go from the portal circulation to the systemic circulation it passes many layers ; **gut wall » portal vein » liver » systemic circulation .**

If a patient take a drug , it will transverse these layers .

First-pass effect » means what happens to the drug after oral administration during the first pass before reaching the systemic circulation whether it was in the gut wall, portal vein or the liver.

Systemic circulation » the veins that go to the heart and the arteries that take blood from the heart.

What will happen to the gut wall, portal vein and liver ?

Gut wall can metabolites drugs "drugs can be also metabolized in the epithelial of the portal vein , but this is minor " , and also since the **liver** is the eliminatory of the body , it is the main site of drug metabolism ,although all other cells can metabolize , even the kidney "which secrets " can metabolize also , and the liver "which metabolizes" can also excrete . But if you want to talk about the sum of this ; the liver is the main site of metabolism , so the drugs before reaching the systemic circulation can be changed in these three places at least or excreted by the liver so the drug won't be absorbed in the same amount by the time it reaches the circulation.

How the drug is excreted by the liver ?

In bile. Bile after it is secreted by the liver it goes to the GI tract and then it is expelled through feces to the outside , so drugs can be excreted by the liver through the billiary system "through bile" .

Any of these will lead to incomplete delivery of the dose given to the systemic circulation.

So the drug dose which the patient got now is not complete , part of it was lost through the gut wall , another part in the liver metabolisms and part through liver excretion.

Not all the drugs go through these stages , some don't and also not all of them get metabolized through all of them (gut wall , portal vein , liver metabolism , liver excretion) . All of these 4 stages reduce the amount of the drug that will reach the systemic circulation which results in reduction of **Bioavailability** .

☺ **Bioavailability** : How much of the drug is available to the body "systemic circulation" .

In the figure in slide # 30 you can see the GI tract "Gut Lumen" which is a tube-like structure and then you can see a part of gut wall "dissected" , the wall is drained to the portal vain , the portal vein transports what comes from the gut to the liver , in the liver there will be metabolism or billiary excretion of the drug , then it reaches the systemic circulation and it is called "hepatic vein" .

Part of the drug will be lost through feces , as we mentioned before ; when the drug is taken , it will be disintegrated and as we know there are parts of it that are not liquid , so part of the drug will be lost and it will not be absorbed by the body , but this is **not** considered as First-Pass effect even though it leads to reduction in bioavailability . Same thing happens when some of the drug gets metabolized by the gastric acids or bacteria in the GI tract, which is also not considered a part of the effect. First-Pass effect includes only the 4 stages we've mentioned (gut wall, portal vein, liver metabolism and liver excretion).

First-Pass effect has other names like :

1) First-pass metabolism » this name is implied only when the First-pass effect has only 3 stages "liver excretion is not included".

2) pre-systemic elimination » it is implied if there is excretion , pre-systemic means before reaching systemic circulation.

What is the importance of knowing this ??

Suppose that you want to give a certain drug to a patient , and after doing calculations you decide that the suitable dose for him is 100 milligram and you give him the drug , But the drug doesn't reach his systemic circulation :/ **why does this happen ??**

» Because you forgot about the First-pass effect .

So , you should be careful as you need 100 milligram in the systemic circulation not in the dose . Suppose that the first-pass effect reduce the % of the drug by 30 % and as your calculation says ; you need 100 milligram to reach the circulation . So, if you give the patient 100 milligram ; the amount which will reach the systemic circulation will be about 70 milligram . To avoid this , the dose should contain 150 milligram to result in 100 milligram in the circulation .

Example :

If you have a new drug , and the leaflet tells you that the oral dose is 100 milligram , while the intravenous (IV) dose is 10 milligram , **what does this mean ?**

This means that the drug undergoes **first-pass effect** , so the IV dose is much less than the oral dose. **Why?**

Because when the drug is given intravenously, no part of the dose will be lost , all of it will go to the circulation so the IV dose should be less than the oral one .

If the drug was given orally , it will enter the metabolic pathway and go directly to the liver and get metabolized , but when it is given intravenously , liver will be as any other organ , which means it will get

the drug as any other cell of the body do ; like brain cells , intestine cells , …etc . So the amount of the drug reaches the liver through the blood in the circulation will be less and the metabolism will be less comparing with the case when the drug is given orally .

This is also implies when the drug taken is inactive and it needs to be metabolized firstly to be active. In this case , IV will not be efficient , because it would take very long time till the drug reaches the liver and converted into the active form plus that the amount of the drug which reaches will be small .

Example :

If the patient has **liver Cirrhosis (fibrosis in the liver)** , the blood will bypass the portal circulation , which means that the drug will go directly from intestine to the systemic circulation without passing through the portal vein .

In this case; if you give a large dose orally (taking in consideration the first pass effect) , you may kill the patient. **Why?**

Because the First-Pass isn't present here , no first-pass metabolism , no accessory elimination . In other words , the drug changes its path , so the dose in the case of liver cirrhosis should be less , otherwise ; the drug will become toxic and may kill the patient .

Example :

Morphine which is used as analgesic , affects the CNS and suppresses respiration, this drug **isn't** given orally , it is given intravenously , intramuscularly or subcutaneously **, why ??**

Because if it was taken orally, 67% of its amount will be removed by the liver "First-pass effect" .

We calculate what we call **extraction ratio (ER)** which is defined as : How much of the drug dose is excreted .

If the patient takes the morphine orally, two thirds of the dose will be eliminated by the liver because of First-Pass elimination, so its bioavailability is 33%.

But there is cases at which we give the morphine orally with higher dose, if we want to give it to a patient who suffer from permanent illness like; cancer patients because they have pain, **why ?**

Because it is very painful for them to keep injected as well as they already suffer from pain. Giving the drug orally in a higher dose is simpler, easier and more convenient.

Clinically related fact…

When using Drugs that have high extraction ratio or drugs that goes through First-Pass metabolism, we notice great interindividual variations upon drugs response, which means that same dose can produce different effects in different people **due to two reasons:**

1) Drug metabolism and amount of enzymes among people is not identical.

2) Hepatic blood flow among people is not identical, also.

The extraction ratio is affected by genetic metabolism and by the blood flow to the liver and this is how we calculate the First-Pass effect using these parameters.

Because of these differences in blood flow and the capacity of the liver metabolism of the drugs between people , there will be interindividual differences in the First-Pass metabolism and drug response because these variables affects the effects of the drugs and so the action of the drug .

As we mentioned; First-Pass effect reduces the **Bioavailability**, so what is **Bioavailability?**

Bioavailability is what is available of the drug to the systemic circulation, so it is the fraction of the dose given that reaches the systemic circulation intact and active after any type of administration. Intact means; not metabolized and active means; can produce action.

Usually Bioavailability value is 1 or 100% after intravenous administration, the dose is totally absorbed, **why?**

» Because you put the dose directly in the systemic circulation.

On the other hand; bioavailability value is 1 or less after oral administration ; between (0% and 100%) , which means that the does is either completely absorbed or not , **why ?**

☺ **Many reasons :**

▪ First-Pass effect.

▪ Incomplete absorption .

▪ Incomplete disintegration and dissolution .

» If the drug is not completely disintegrated it will not get absorbed completely .

▪ Destruction of drug within the GI lumen by gastric acid, bacteria , ..etc .

» As we mentioned before , this is not considered as a part of First-Pass effect but it reduces **Bioavailability** . The metabolism here is done by gastric acid and microorganisms present in our GI tract , like bacteria .

Example : there are drugs used in cardiology "like; digoxen " , 10% of people metabolize it by the bacteria present in the GI tract , if a

person take antibiotic , that drug will be overdose and will result in toxic effect , because antibiotic inhibit the metabolism by killing the bacteria and that will increase the concentration of the drug in the systemic circulation and cause adverse effects or toxic effects .

▪ Faulty manufacturing of the dosage form .

» Wrongly manufacturing . If the company manufacture the drug wrongly , it will not be absorbed "completely" and this results in low **Bioavailability .**

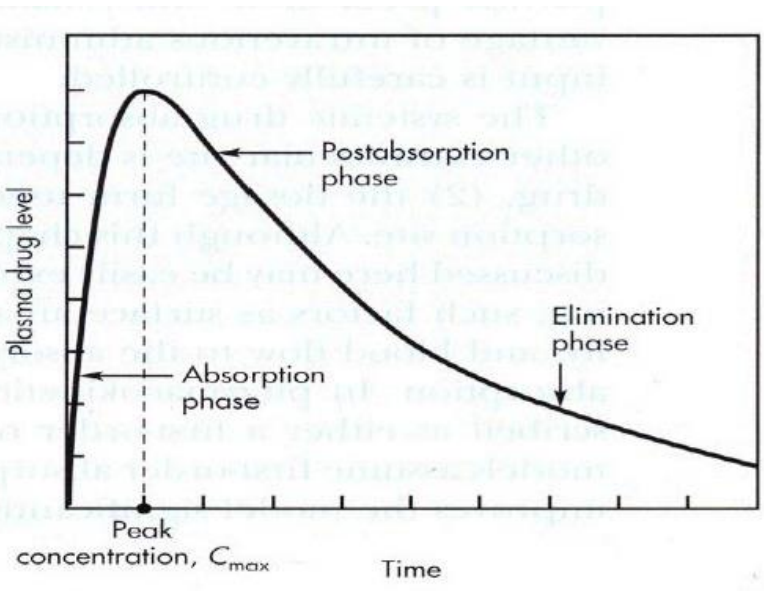
▪ Enterhepatic cycling .

» We will talk about it later .

How can we measure Bioavailability ?

By giving a null dose as a reference , then we take serial samples of the blood in different times and calculate the concentration of the drug in each sample then you draw the relation between time and concentration then you will get a curve .

Look at the figure below …



This curve results after taking different samples from the blood of a patient who took a drug orally. It shows how the concentration of the drug in the blood changes with time.

☺ **There are 3 phases appears in the curve :**

▪ **The absorption phase :** at which the rate of absorption is higher than the rate of elimination .

▪ **The postabsorption phase :** forget about it .

▪ **The elimination phase :** at which the rate of elimination is higher than the rate of absorption .

» So you should know that this curve doesn't represent sequent steps, in other words, this curve doesn't mean that absorption occurs firstly then elimination.

Explanation: When the drug enters the body, its molecules will get absorbed and then go to the systemic circulation. The low of mass action is applied here, which means that: after the drug is taken, it will act in different ways;

▪ If the drug hits the receptor it will introduce effects.

▪ If it hits the metabolizing enzymes it will get metabolized. (elimination process).

▪ If it goes to the kidney it will be excreted.

These things are not applied to all drugs.

***** Refer to the previous figure **…**

- At the beginning , at zero time , the concentration of the drug in the blood equals zero .

- Then , the drug will reach the intestine and the concentration of it will be high and the absorption rate will be more than the elimination rate , **Absorption phase .**

- The drug concentration will reach its max value **(C_{max})** and this is represented by a peak in the curve, after that, the concentration will not increase anymore because what is getting absorbed of the drug equals what is getting eliminated. The time at which the concentration reaches it max value is known as **(T_{max}).**

- Then the elimination will predominate , and this is called ; **Elimination phase** . In this phase , there is absorption but its rate is low in comparison with the rate of elimination .

Again ; This curve <u>doesn't mean</u> that at the beginning the drug works efficiently then it becomes toxic …

Now , we will complete the answer of the previous question; **how can we calculate Bioavailability ?**

Measurements that relate to Bioavailability has two aspects :

1) **Extent Bioavailability** » The Area Under the Curve (AUC) , we can find it mathematically.

2) **Rate of Bioavailability** » it depends on the concentration of the drug " Directly proportional " and the time "inversely" . Reaching the maximum concentration faster means higher rate of bioavailability.

The rate of bioavailability can be calculated using C_{max} and T_{max} .

- T_{max} is the time at which the C_{max} is achieved, the time at which the peak concentration is achieved .

- C_{max} is achieved when absorption rate = elimination rate .

- Higher concentration means higher rate and higher extent .

- Higher time means lower rate .

☺ **Bioavailability** : how much of the drug will reach the systemic circulation .

Extent of bioavailability » the area under the curve

Rate of bioavailability » we calculate it using Cmax and Tmax

☺ Causes of reduction of the extent of the absorption :

1) The drug may be too **hydrophilic** (like; atenolol) or too **lipophilic** (like; acyclovir) .

Explanation :

▪ Too hydrophilic drugs can **Not** cross lipid membrane easily.

▪ Too lipophilic drugs are **Not** water soluble enough to reach the membrane "to cross the water layer adjacent to the cell ".

2) Drugs may not be absorbed because of the presence of a reverse transport like (P-glycoprotein), where the drug reaches the cell wall but these proteins pump the drug out of the gut wall cells back into the gut lumen, decreasing bioavailability.

It is very important to know this; **why?**

Because some drugs and even plants like grapefruit (its juice) , inhibit the P-glycoprotein , this inhibition will result in increasing in drug absorption and thus bioavailability .

Example : if a patient takes a drug with a dose of 100 milligram and he drinks grapefruit juice , this will result in toxic effects as the grapefruit inhibits P-glycoprotein and so increase the absorption of the drug .

Sometimes , you "as a doctor" may tell your patient to drink grapefruit juice with drug , **when do you do this ?**

» If your patient has deficiency in absorption.

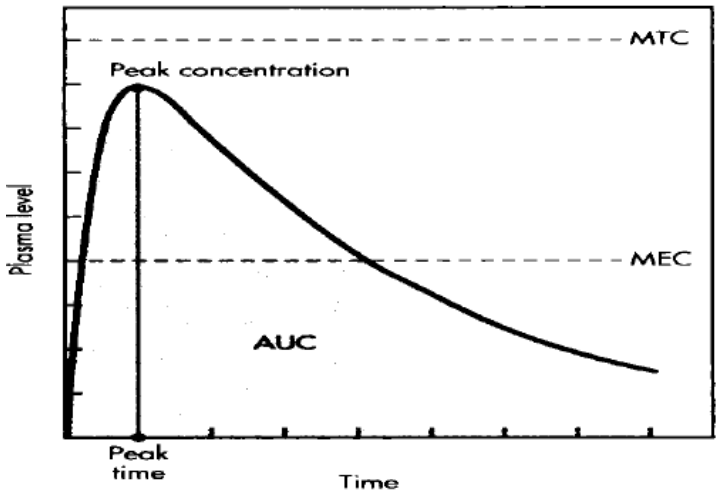
Result :

▪ In general , The drug is expelled from the liver cells by the P-glycoprotein and metabolized by liver cells , so the absorption will decrease and the drug concentration which reaches the systemic circulation will be less .

▪ If you take grapefruit juice , the P-glycoprotein will be inhibited and so will not expel the drug out which results in inhibition of metabolism , consequently ; the drug will reaches systemic circulation with higher concentration .

» so grapefruit is considered as a drug and it causes drug-drug interactions .

Look to the figure below …



This figure is similar to the previous one, but we add two new terms:

1) MEC : Minimal Effective Concentration .

2) MTC : Minimal Toxic Concentration .

- The concentration of the drug must reach the MEC to introduce effects , below the MEC there is no effects .

- The drug become toxic if its concentration reaches MTC .

☺ **So, for a drug to be efficient , its concentration must be at the range between (MEC) and (MTC) .**

According to this, where does the drug start introducing effect? At the time where it reaches MEC, **Not** at zero time.

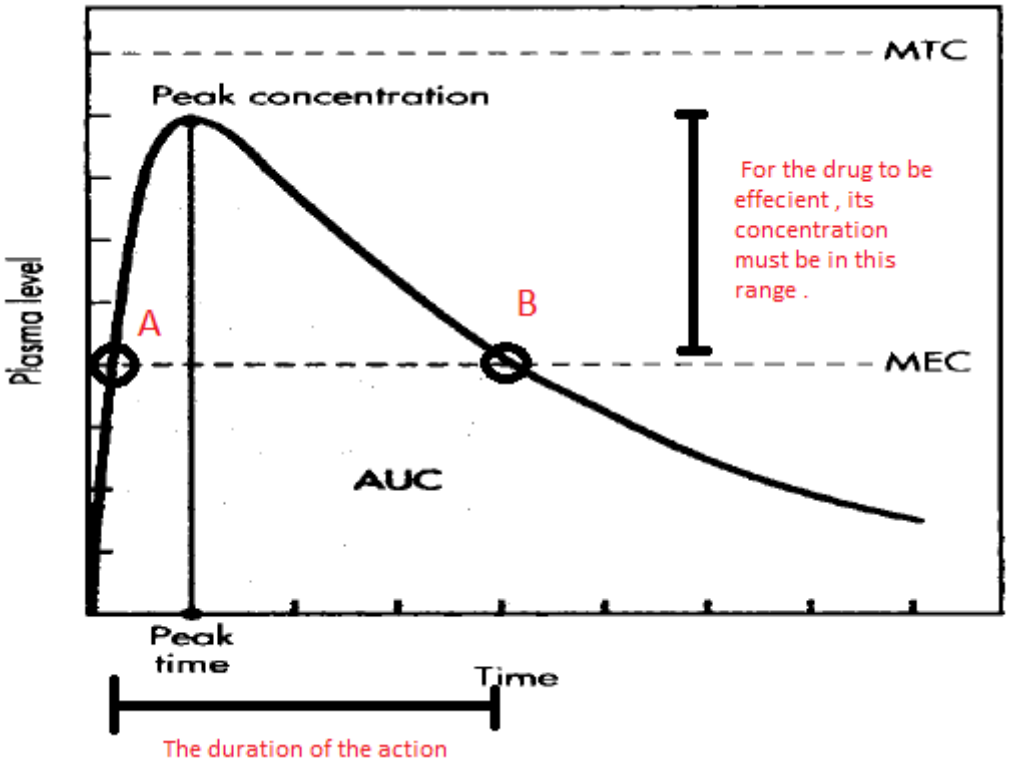
So , the drug reaches the MEC and start introducing effect , then its concentration will start increase more and so the action will also increase until it reaches MTC . After that , the concentration will decease and the action will decrease , also . This reduction of action will continue as the concentration continues reduction until it becomes less than MEC again "look to the right side of the curve" , after this , there will be **no action** .

☺ **The duration of the action lasts from the moment when the drug starts the action (as its concentration reaches MEC) to the moment when it stops it (as its concentration becomes less than MEC) .**

» That is why the drug is taken with more than one dose ,the subsequent dose is given just before the previous dose stops its action (before it drops below MEC) so the new dose won't take time re-reach the MEC.

Example : a certain drug is given in a dose of 5 milligram , 2 times a day … **why ?**

» In order to keep the concentration of the drug within the therapeutic rate .



The action of the drug begins at A and stops at B

Bioequivalence :

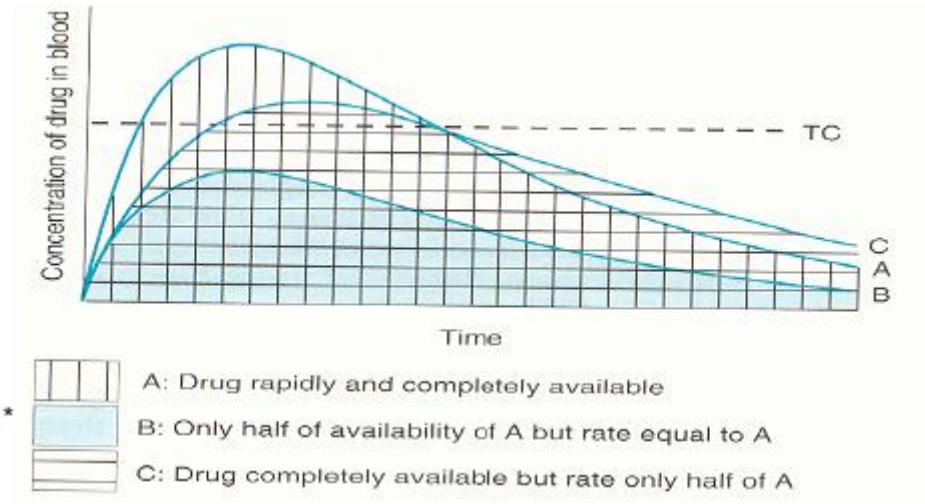
- This term is used to compare the rate and extent of absorption of different formulations of the **same** active drug .

- As we mentioned before ; the extent of absorption is measured by AUC , and the rate is assessed by C_{max} (peak concentration) and T_{max} (time of peak concentration) .

Explanation: Many companies can provide pharmacies with the **same** drug , one drug can have more than one source from more than one company, **are they identical ? If you go to a pharmacy and demand specific drug and it was not there and then the pharmacist told you that there is a substitute , are they identical ? Do they have the same rate and extent bioavailability ? How can we check this ?**

» By doing experiments and observing the concentration vs time

Look at the figure below …



As you can see , we have the **same drug** manufactured by three companies A, B, C .

TC : Therapeutic concentration . ☺

- **The drug of company A »** has the higher extent and rate bioavailability, it is available completely and rapidly .

- **The drug of company C »** has a rate lower than the rate of A (notice the peak) and a shorter duration , but as you can see it reaches the TC so it does the action but there is a delay , so this drug is available completely and its rate is only half of A .

- **The drug of company B** » doesn't do the reaction as it doesn't reach the TC .

A is good product , B is bad one and C is between them .

So a patient may change a drug of certain company to one of another company , and then the new drug do nothing with his disease , why ?

Because the concentration of the new drug will not reach the TC .

How to avoid this ??

»In company A "for example" ,all the drugs which do the same action should undergo **Bioequivalent study** , what does it mean ?

This means that this company have to prove that all its products have equal bioavailability values which equals to the bioavailability of the first drug was manufactured .

☺ Drugs with the same bioavailability can be exchangeable .

Look at the figure below …

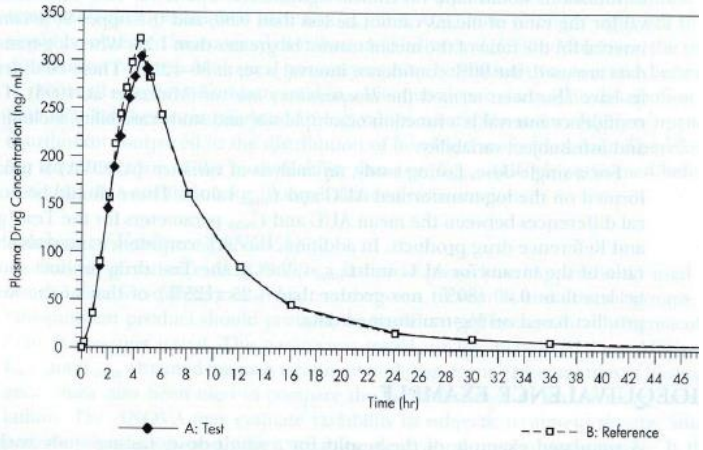
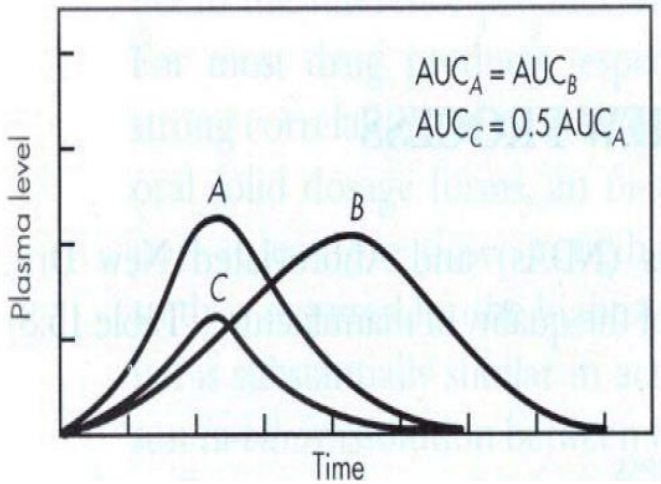


Figure 15-8. Bioequivalence of Test and Reference drug products: mean plasma drug concentratio

This figure shows the same drug from two companies . As you can see , they have almost equal bioavailability "very small difference" .

Look at this figure which represents 3 products of 3 companies "for the same drug" …



▪ AUC of product A equals AUC of product B.

▪ AUC of product C equals half of AUC of product A .

☺ AUC : Area Under Curve .

▪ A is good product and C is bad one , **what about B ??**

» B is equivalent to A ; as they have the same extent bioavailability .
A and B differs in the rate , **Is this important ?**

It depends ; if the disease is critical and the drug is also critical , so yes it is important ; they should be equal in rate and extent . On the other hand , if the conditional is chronic and the condition is not that critical , so you can accept it , but there will be a delay .

Example : Someone has headache "not severe" , and after 30 minutes of taking the drug the headache gone away , now in the case of taking another drug the effect may need 45 minutes "not that important" .

☺ Be careful that you accept a drug with different rate (small difference) , but you can't accept a drug with different extent at all .

"when life puts you in tough situations , don't say : "why me" ; just say : "try me" …. ☺ "

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