PASSION BATCH
SECOND YEAR

PHARMACOLOGY

LECTURE 5

Assem khatatbeh
Ameera otoom

Pharmacokinetics
Part II

General Pharmacology
M212

Dr. Laila M. Matalqah

Ph.D. Pharmacology

Drug clearance

- **Drugs clearance by:**

1. Hepatic metabolism
2. Excretion (elimination) into the urine or into the bile

- These elimination process cause plasma conc of drugs to decrease exponentially

.

- Clearance include:

1) Clearance by metabolism
.

2) Clearance of elimination by renal or bile routes

- Both of these will not be 100% of clearance because we have clearance by other ways...ex:

1) Saliva
2) Breast milk (for breast feeding mother)
3) mucus secretion
4) sweat

- Clearance of the drug almost reach after few time --->this time depends on the half life time of the drug.

- Half life: means the time needed for the drug concentration to reach the half

- half life يعني ال ١٠٠ حتى تصير ٥٠ في البلازما بدها وقت اسمه
- faster clearance اذا كان العدد قليل نسبيا يعني كمثال ٤ ساعات---<هذا يعني
- half life take longer اذا كان العدد كبير نسبيا يعني كمثال ٢٤ ساعة -----<هذا يعني time to be cleared from our body

- Metabolism is the major route of clearance because most of the drug is eliminated by metabolism.

1. Metabolism

Metabolism: is the process of transforming lipophilic drugs into more polar readily excretable products.

- The **liver** is the major site for drug metabolism, and other tissues, such as the kidney and the intestines

- Some agents are initially administered as inactive compounds (**prodrugs)** and must be metabolized to their active forms.

- What is the fate of the main objective of this metabolism?

1) Mainly to change the drug from active into inactive.
2) To change drug from non-polar into polar to be secreted by urine (urine only secrete polar substances).
3) To change the drug to more active (it is one of the main objective, but not all drugs have this pathway).

- Prodrug: it is a drug that is inactive, administered by oral then transferred to hepatic circulation, and by hepatic circulation will be activated (changed by oxidation, or hydrolysis, or certain mechanism enzymes to more active) and this active drug then is secreted by the liver by bile, then reabsorbed to the blood stream and then do action.

- Logically, this drug is similar to first pass metabolism but it will not metabolized to inactive, instead it is metabolized to the active form.

- Other than that, all the drug metabolized to be eliminated (99% of the drug is eliminated)

Clearance

- **Clearance :** is the amount of drug eliminated from the body per unit time

$$CL = \frac{0.693 \times Vd}{t1/2}$$

- CL: clearance (L/hr) (ml/min)
- Vd: Volume of distribution
- t1/2: half life of drug (the time it takes to reduce the drug plasma conc by half)

- If you don't want to be confused by this equation, you can make it into the original one, which is:

$$t1/2 = \frac{0.693 \times Vd}{CL}$$

- So, half life is proportional to the Vd and half life is inversely proportional to CL

- Vd increases -----> t1/2 increases -----> CL decreases
- Clearance decreases because the drug now is not available in our plasma (it is inside our cells, so it's cleared)

- Liver has enzymes (two phases):

Phase I :
The drug which is lipophilic, will be changed by oxidation to inactive (this involves enzymes, however the other phase (phase II) doesn't involve enzymes).

Phase II :
It does by conjugation... for ex: glucuronic acid (this is polar residue).

- We want to divide the metabolism into two phases (means two types of metabolism): one of the metabolisms depends on the enzymes which is phase I (without enzymes they don't work, and these enzymes are machines, and this machine change the drug from active to inactive by different mechanisms (oxidation, reduction, hydrolysis).

- So we need enzymes in phase I and these enzymes what we call Cytochrome p450 (p450 is the major name, but we have isoenzymes)

Ex: cytochrome 2C9 can metabolize warfarin (مش للحفظ)

- So warfarin go to this isoenzyme (cytochrome 2C9), but other drugs will go to another isoenzyme for Ex: 2A10, so not all drugs are metabolized by the same isoenzyme, but we have certain groups of drugs metabolized by the same isoenzyme.

- Sometimes, drug go out from phase I in inactive form, but still need more polar, so it can go into phase II

- Phases of metabolism:
- Drug can go through phase I only
- Drug can go through phase I and phase II
- Drug can go through phase II only

- Phase II depends on a certain soluble residue (for Ex: acetic acids, amino acids, glucuronic acids), these acids are soluble.

- I conjugate these acids with the drug, so it could be secreted by bile.

- This conjugation is usually inactive (more polar لكن مش بالضرورة يصير)

- In general, we have two objective:

1) To change the drug to inactive (don't have any effect on my body)... if the drug becomes inactive and more polar, it could be eliminated by urine.

2) To change the drug to active...the drug could be more polar but eliminated

---> so generally you can't guess (because it depends mainly on the structure).

Kinetics of metabolism

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

1. **First-order kinetics (linear kinetic)**

- A constant **fraction** of drug is metabolized per unit of time.
- The rate of drug metabolism is **directly proportional** to drug plasma concentration and drug dose.
- The metabolism of drugs obey **Michaelis-Menten** kinetics:

$$v = rate\ of\ drug\ metabolism = \frac{Vmax\ [C]}{Km}$$

- Kinetics: it is the means of elimination (the rate of elimination)

- If someone takes over toxic dose:

----> mostly, the greater of the concentration of the drug in the plasma, the rate of elimination increase (this protection, because when the overdose increases, the rate of elimination increases by this concentration, means ---> I can decrease the concentration very fast to the subtherapeutic level, but not all drugs follow this way (it depends on factor), so I have two types of kinetics

- Kinetic of elimination has Michaelis-Menten kinetic:

When we talk about the rate of elimination, we talk about enzymes ... and enzymes have a saturation levels, so metabolism can reach maximum when all enzymes are saturated.

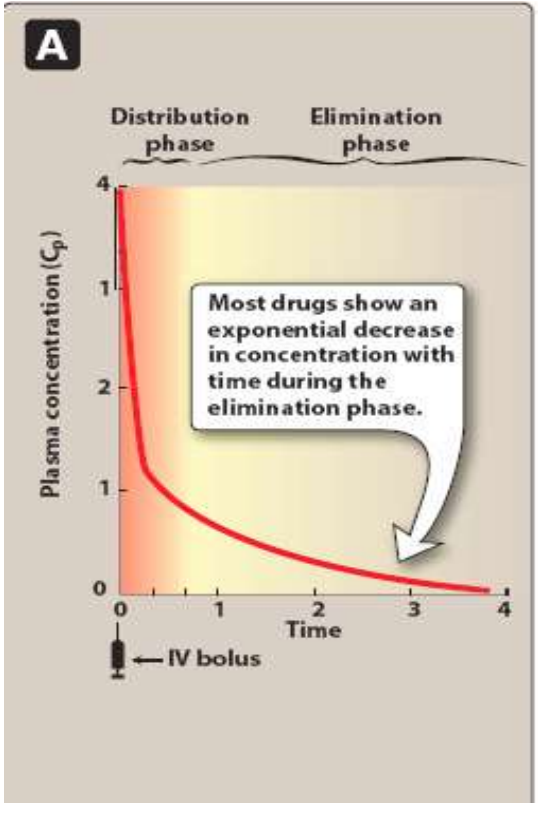
- When all enzymes are saturated, mean I reach the maximum elimination... above this we can't eliminate no more.

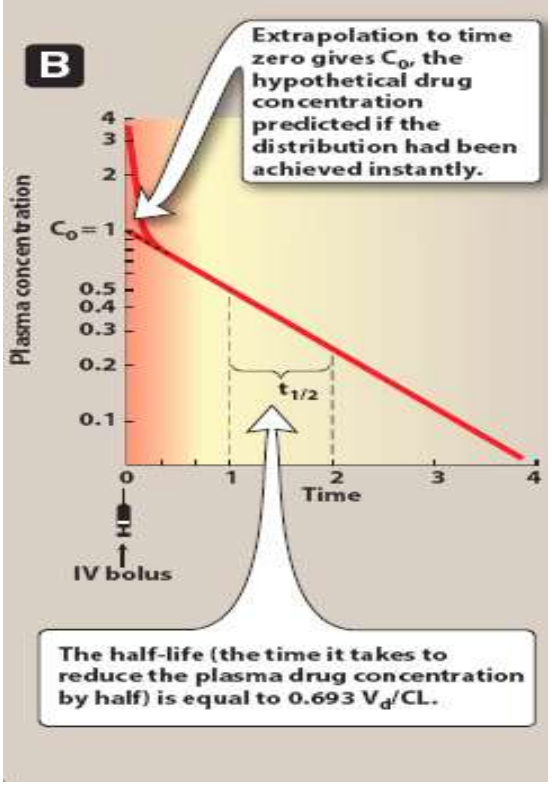
- V max: means the maximum rate of metabolism or the maximum rate of clearance when all enzymes are saturated.
- V max is constant because it happens when all enzymes are saturated and the enzymes are constant.

- Km: is the concentration of the drug at the half elimination rate (means what concentration I need to eliminate 50% of the drug).
- Km is constant too, because it means half of the enzymes are saturated.

- So we can guess by this equation what is the rate of elimination depending on the [C] (because the V max and Km are constants).
- [C] is the concentration of the substrate in the plasma at any time.

After IV Bolus





Kinetics of metabolism

2) **Zero-order kinetics**

- A constant **amount** of drug is metabolized per unit of time.

- The rate of drug metabolism is **independent** of drug plasma concentration and drug dose.

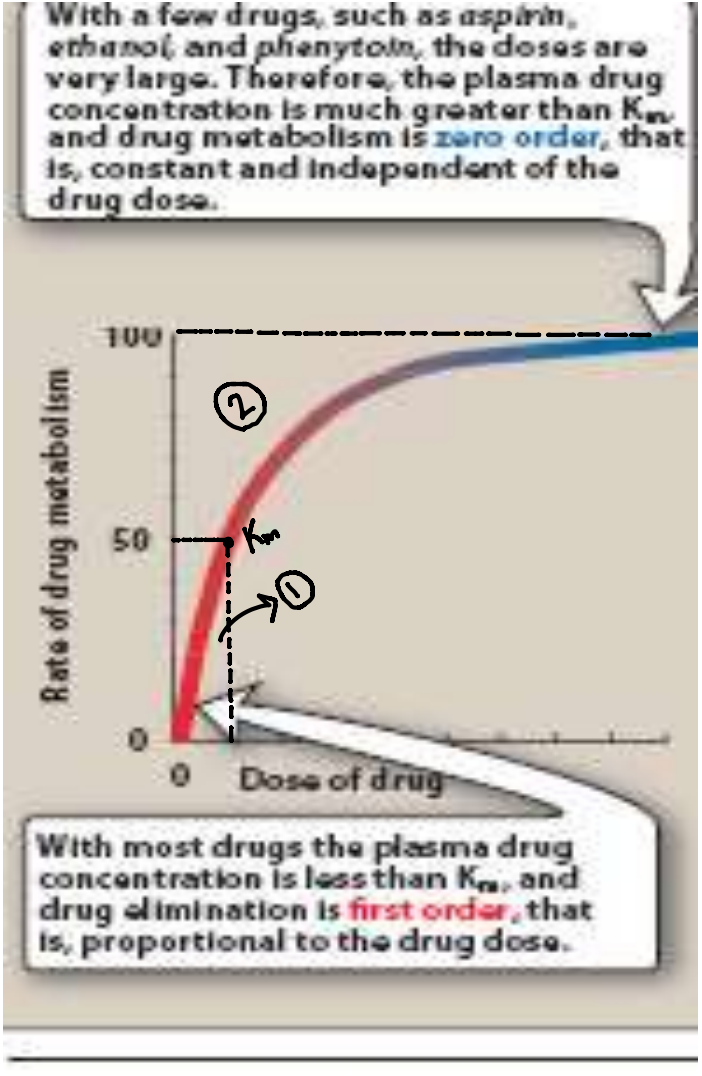
- The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time

Kinetics of metabolism

2) **Zero-order kinetics: (nonlinear kinetics).**

- E.g., a few drugs, such as **aspirin, ethanol, and phenytoin**

$$v = rate\ of\ drug\ metabolism = Vmax$$


With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, the plasma drug concentration is much greater than K_m, and drug metabolism is zero order, that is, constant and independent of the drug dose.
100
50
0
Rate of drug metabolism
K_m
2
1
0
Dose of drug
With most drugs the plasma drug concentration is less than K_m, and drug elimination is first order, that is, proportional to the drug dose.

① : is almost linear
② : is almost plateau (constant)

- When we give the drug at low concentration and most of the drugs are given in low doses.
- يعني احنا كأطباء الجرعة اللي بنعطيها عادة عشان تشفي المريض ما بنعطيها بالجرعات العالية ---> يعني مستحيل جرعة توصل لل saturation الا قليل
- The effective dose will not reach the saturation level of the enzyme

- Most of the drug is described in part ①

- Will the concentration of the drug be less than Km or more?

Less than Km

- If it is less than Km which one now is bigger, Km or substrate?

Km is bigger

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

- This equation used in phase I
- [C] is negligible so the equation will be:

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

- First order: means when the drug is at low concentration, and normally the drug at first order of the kinetics that means that the rate of metabolism depends only on concentration---> means when the concentration of plasma increase, the rate of elimination increase, and it is logic because the enzyme still unsaturated, so more drug means more elimination.

- Now, what is the effect when the dose is higher than Km? For EX: to give (phenytoin, aspirin) at high doses?

We give aspirin at low doses for cardiovascular disease (80 mg), and we give it in high doses for anti-inflammatory drug (350 mg)---> so we give it in different concentrations, most of the concentrations exceed the saturation level, so then our drug will be in phase II

- At first, Aspirin will follow first order of kinetics, but when it's concentration in plasma becomes more than Km (Km<S) then V will be constant----> Vmax= V
- So, when the drug concentration is more than Km, it is then in phase II, so any more increase in drug concentration will not increase the drug elimination

- The Best choice of drug is to be at phase I, because if the drug is at phase II (Zero order):

1) we can't predict the action
2) we can't predict the half life
3)we can't predict the time of elimination

→ Because this doesn't depend on the concentration

- If we give a drug and the concentration of this drug in plasma was 100 mg, after 6 hours it will be eliminated by half, when this drug will be totally eliminated from the body?

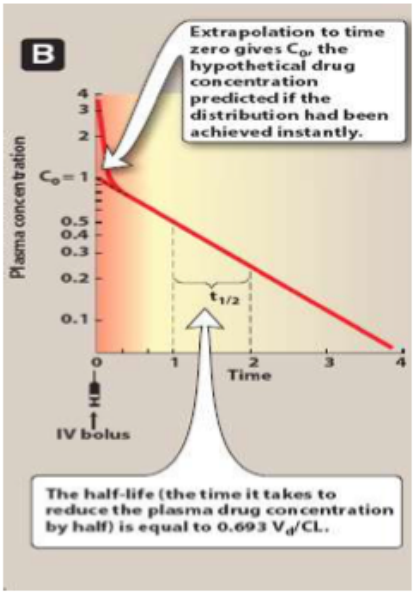
$100 \xrightarrow{6} 50 \xrightarrow{6} 25 \xrightarrow{6} 12.5 \xrightarrow{6} 6.25 \longrightarrow$ etc.. nearly 2 days

If I said, 10 mg is eliminated from a 100 mg drug per 6 hours?
100/10= 10---> 10*6= 60 hours

- Which one is more accurate... percentage or amount?

Percentage---> لانه بالنسبة للكمية ممكن ال 10 بهذا الوقت ما ينزلوا كلهم اما النسبة المئوية بضل نسبة من اللي ضل فهو fraction

- First order has constant fraction of drug eliminated per unit of time (when we say 50% eliminated by unit of time, this fraction means rate of metabolism is proportional to the drug concentration, and it becomes constant concentration is increased.



In linear relationship, the slope is constant at any time, so I can calculate the half life

First order kinetics have constant half life (means have fixed time to eliminate the action of the drug per unit of time)---> لهيك التعامل مع أسهل لانه رح نكون قادرين على: first order الادوية بال

1. Predict when the drug will be act
2. Predict when the drug will be eliminated

من الأخطاء الشائعة انه بفكر اذا اخذت الدواء ثاني يوم بروح من جسمي, وهذا خطأ...مثال: البعض عنده acne vulgaris ويستخدم retin A وهذا الدواء بضل بالجسم من ٦ أشهر الى سنة حتى يصيرله elimination وهذا لانه very fat soluble لهيك ممكن يصيرله تخزين بال adipose tissue

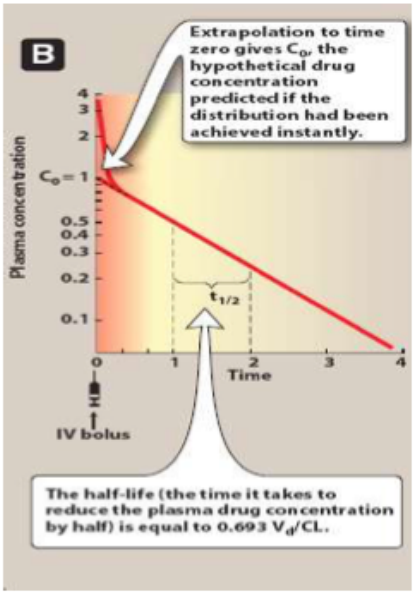
مثال: اذا فيه بنت مقبلة على الزواج وكانت توخذ دواء مانع للحمل وتوقفت عن استخدامه... ما رح تحمل من وقتها لمدة سنة لانه الدواء رح يضل بجسمها وحتى لو توقفت عن استخدامه...وهذا يعني اذا توقفنا عن استخدام دواء معين ما بطلع من الجسم في نفس الوقت

- Prediction when the drug is eliminated is used in CNS drugs.
- في بعض الأدوية ما بقجر اعمل shift من دواء لدواء حتى أضمن انه الدواء الأول راح لانه رح يصير synergistic action وممكن يكون مميت
- Drug interaction will occur when the drug is in my body

- Summary:

When the drug is in the plasma, the it will be distributed, if you give IV bolus there will not be phase of absorption, so it will be distributed immediately.

هل الدواء بستنى حتى يتوزع عشان يصيرله eliminaton؟ الجواب لا ممكن يصيرله elimination اول ما يصل الدم من البداية



Extrapolation: means elimination starts from [C.]

[C.] is the first concentration we want to start with... we find than constant fraction secreted by unit of time----> so it should be first order to predict the half life

Zero order means that rate of elimination is constant

الأدوية اللي بصير الها zero order :

1) Aspirin
2) phenytoin
3) ethanol (for alcoholic drunk)

بصير معهم hepatotoxic لانه لو اخذنا كمية قليلة من ethanol رح يتحول ل aldehyde وال aldehyde رح يتحول ل acetic acid

احنا بنحكي عن يلي بيوخذوا الكحول orally فشو ما كانت الكمية يلي رح يشربها رح تكون oversaturation وهذا بعمل hepatotoxic لانه ال saturation enzymes فضلوا ال ethanol which will attack hepatocytes and make hepatotoxic

EX: phenytoin is a first line for epilepsy and it is a narrow therapeutic index, if we increased the dose of this drug a little it will be toxic because it reaches the saturation very fast.

- When the drug in zero order, we can't remove the toxicity of the drug if we took overdose---> toxic effect of the zero order is high

- Zero order drugs don't have fixed half life, and we can't predict when the action will start and when it will stop (it's not constant and it's not predictable)

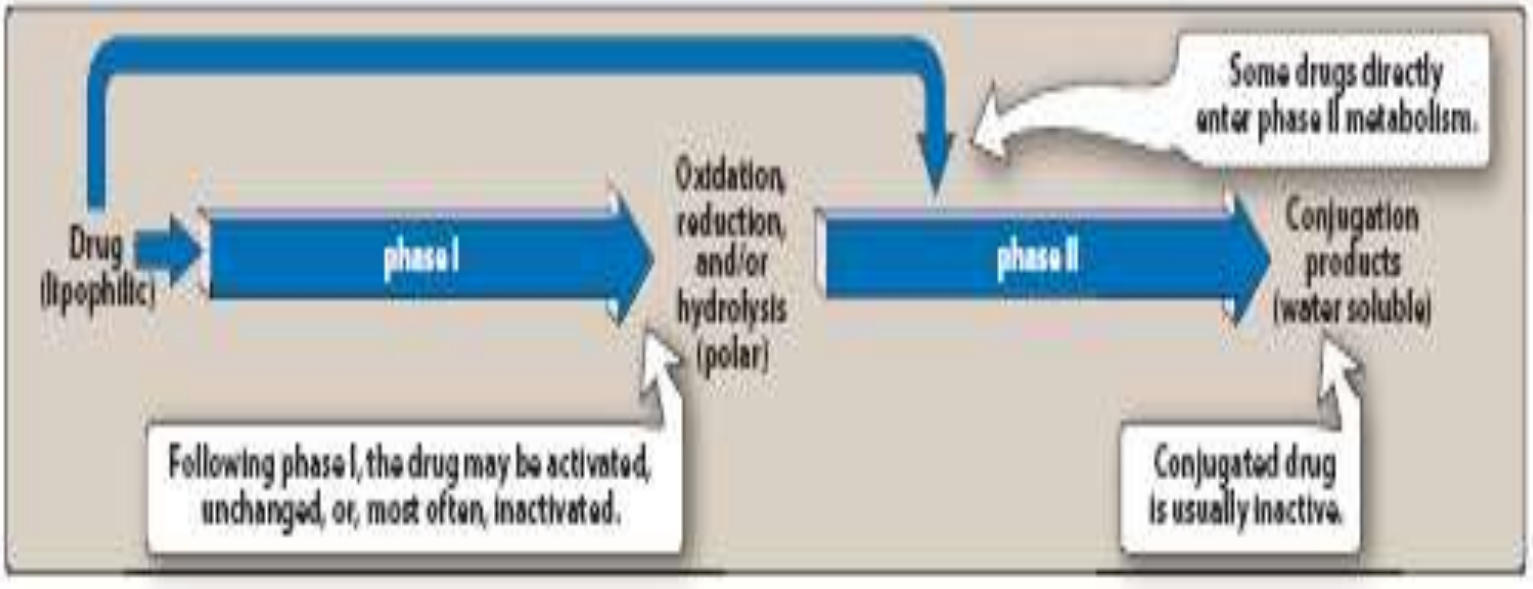
- First order:

*linear (more concentration, more elimination)
*we can predict half life
*half life is fixed

- Zero order:

*constant (plateau)
*doesn't depend on concentration
*we can't predict the half life

Reactions of drug metabolism



- zero order بس مش كلها بتكمل ل first order كل الأدوية بتبلش ب
- At low doses the drug is at first order kinetics because saturation level doesn't reached
- At the zero order the dose is vey high (more than saturation level)
- Any drug should be at zero order or first order depending on the dose
- Generally, most of the drugs don't exceed the 50% because they are given at doses lower than Km.

- Some drugs are polar, means I need to convert it to inactive by glucouridenation
- Some drugs are non-polar and active---> can go into the two phases

Reactions of drug metabolism

1. **Phase I reactions:**

- to convert lipophilic molecules into more polar molecules

A. **Phase I without P450 system**: oxidation, reduction or hydrolysis reactions. Example ethanol oxidation

B. **Phase I metabolism using cytochrome P450 system**

- Cytochrome P450 (CYP450), is composed of many families of isozymes that are located in the liver and GI tract

- Phase I: most of it use cytochrome p450---> means it uses enzymes
- 90% of metabolism need enzymes, whereas 10% doesn't need (it could go through hydrolysis...EX: esters salts could be hydrolyzed in any media such as PH (hydrolysis doesn't need enzymes for example: ethanol oxidation)
- Ethanol follows phase I and phase II (we have both..saturation and non-saturation enzymes)
- Oxidation of ethanol doesn't need enzymes
- We have another pathway which is glutathione which needs enzymes

Reactions of drug metabolism

1. **Phase I reactions:**

Six isozymes are responsible for the majority of P450-catalyzed reactions:

- **CYP3A4/5**
- **CYP2D6**
- **CYP2C8/9**
- **CYP2C19**
- **CYP2E1**
- **CYP1A2.**

مش حفظ.. فقط كأمثلة

CYP 3A4/5 metabolize certain drugs but other drugs need CYP2D6

- Isoenzymes: are a collection of enzymes which are available in hepatic cells and can be metabolized

- cytochrome p450 عبارة عن isoenzymes كل ال

A. Enzyme Induction

- **Substrate:**
  Drug is metabolized by the enzyme system

- **Inducer:** Drug that will increase the synthesis of CYP450 enzymes
- It may induce the activity of these enzymes by inducing the expression of the genes encoding the enzyme or by stabilizing the enzymes

- **metabolism at the same substrate** ممكن طبيب يوصف دوايين لشخص, وهذول الدوايين ممكن يصيرلهم

- **Substrate inducer: (محفز)**

isoenzyme لقوا انه فيه مجموعة من المواد ممكن تزيد من تشغيل ال

- **Substrate activator: (مثبط)**

isoenzymes مواد تقوم بتثبيط ال

- **Drug A which is an inducer, make the machine (isoenzyme) to work more and this will metabolize B more, so B will decrease In concentration in the plasma and then it will reach the subtherapeutic**

A. Enzyme Induction

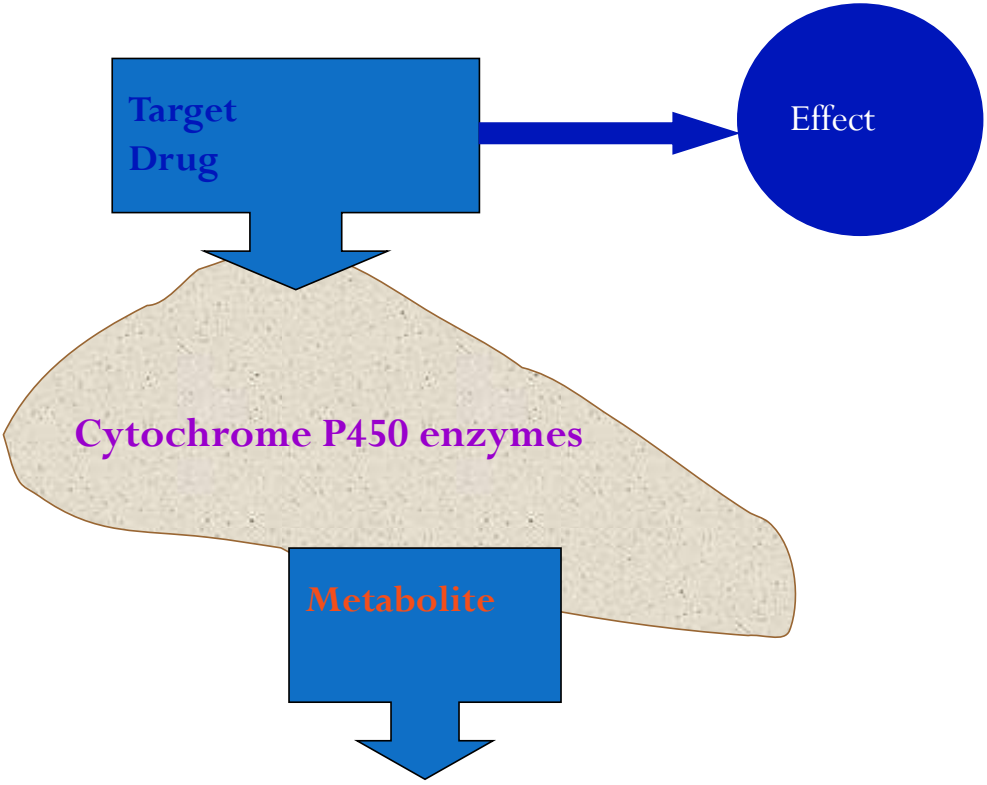
The Overall effect is :

1. increased biotransformation of the substrate drugs
2. significant decreases in plasma drug concentrations
3. Decrease in effect of the substrate drug (Target) if the metabolite is inactive
4. Decreased therapeutic drug effect.

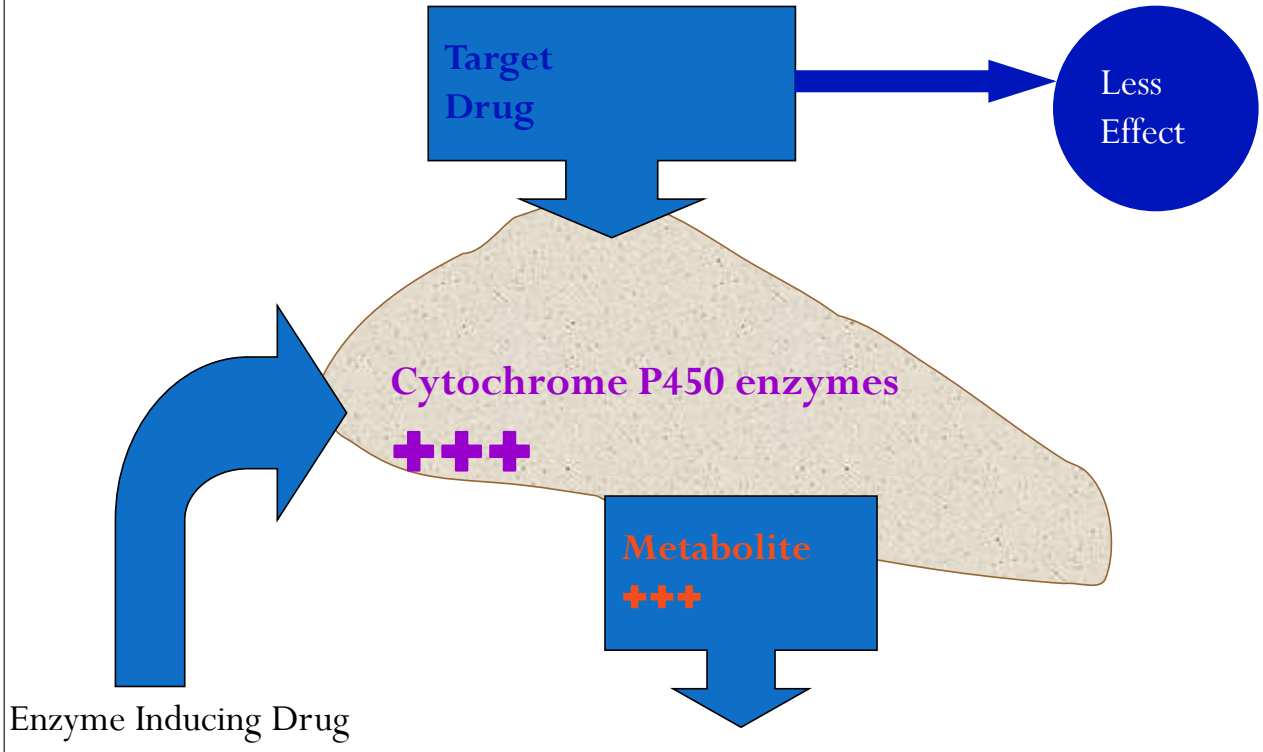
How to solve this problem:

- To get the same effect from the target drug, you may need to INCREASE the dose of the target drug

Drug metabolism



Enzyme inducers reduce the effect of the target drug



- Target drug = A ---> this drug wants to be metabolized and then eliminated (normal)
- If we give the enzyme inducer drug for EX: rifampin ---> this drug induces the cytochrome p450 ---> so the rate of metabolism will increase and the metabolites will be secreted very fast

- يعني مثلا عندي دواء بشتغل ٦ ساعات, بعد ساعتين طلع ----> رح يصير عندي gap وهذا رح يعمل treatment failure <--- انا بعطي الدواء ولكن دون مفعول والتأثير رح يصير أقل, شو لازم نعمل؟

If you guess that and you can't stop any one of them, you have to increase the dose of the target drug (A)---> اذا زدت الجرعة رح ازيد الشغل

(حفظ)

Enzyme Inducers: Examples

- Rifampicin → **For Tb patient**
- Phenobarbitone
- Carbamazepine
- Phenytoin
- Cigarette smoking

→ **For epilepsy**

- If the therapeutic index = 2, this means:

If we double the dose it will be lethal

- The normal dose is 50mg and I gave him 100mg ----> 100/50= 2

Narrow therapeutic index
(اخذ حبتين وتوفى)

- Therapeutic index = lethal dose/therapeutic dose

- Therapeutic index can't be one because that means therapeutic dose = lethal dose

- If the therapeutic index= 100---> that means the frug is very safe, and it means if the dose is 500 mg, you should give the patient 50 g to kill him

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin *Phenytoin* *Ibuprofen* *Tolbutamide*	*Phenobarbital* *Rifampin*

- **The inducer will affect only these substrates**
- **Autoinducer** لحالهم واسمهم **inducing** فيه أدوية بتعمل

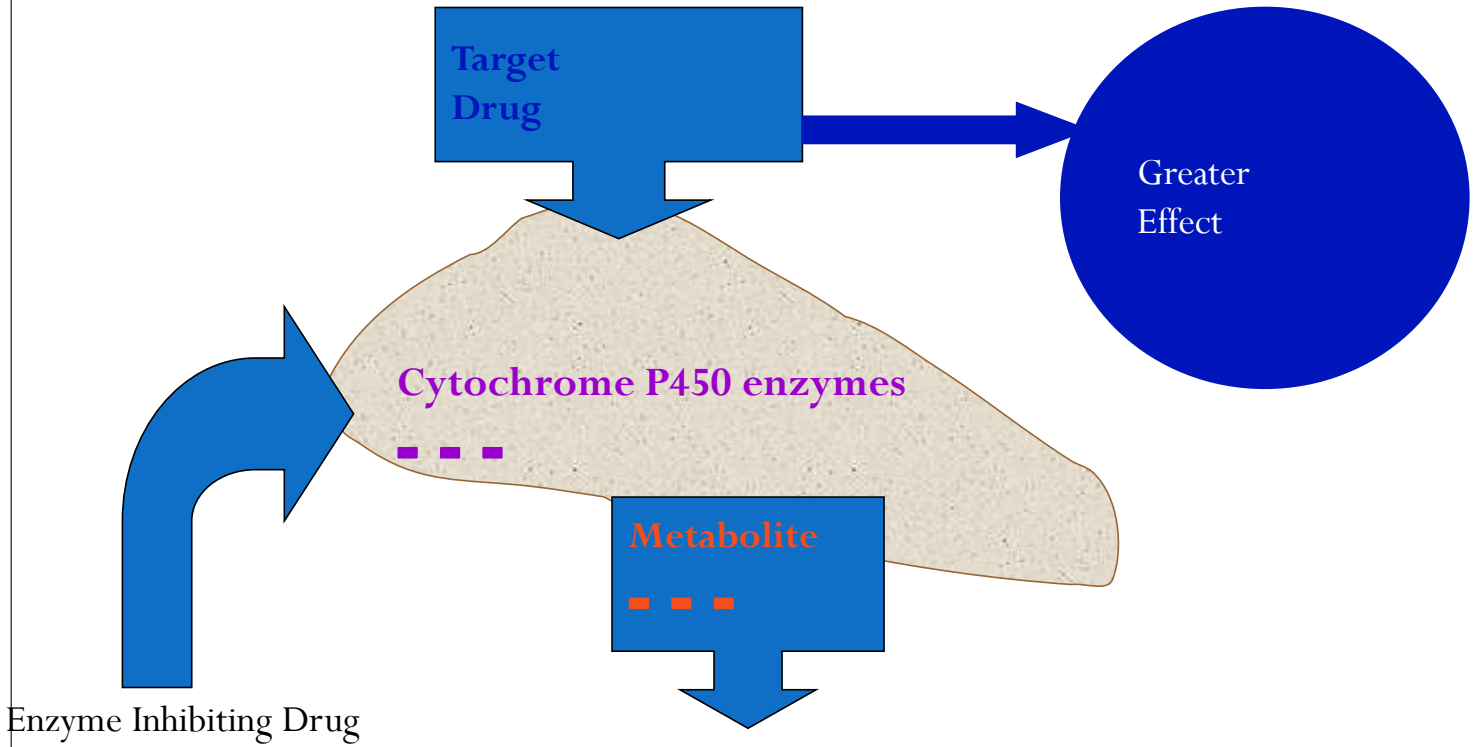
- **Phenytoin: (inducer+substrate)** هذا يؤثر ويتأثر بغيره...يعني يعتبر
- **Ibuprofen:** مسكن
- **Tolbutamide:** دواء للسكري

- **If we take warfarin and rifampin for a patient to prevent angina--->** يمكن بعد اسبوع ييجي معاه جلطة ويدخل المشفى---> هذا طبيعي لأن ال **rifampin** يعتبر محفز **(inducer)** لل **warfarin** وبالتالي ال **warfarin** بيدخل من هون ويطلع من هون---> **will not reach the therapeutic dose** <--- وممكن يصير عنده جلطة خصوصا يلي عندهم عملية قلب مفتوح واللي عندهم زراعة صمام فممكن يحدث **clot** على الصمام المزروع

B. Enzyme Inhibition

- **Inhibitor:** Drug that will decrease the metabolism of a substrate
- Inhibition of CYP isoenzyme activity through competition for the same isoenzyme.
- This drug interactions can lead to serious **adverse events**
- *Example: omeprazole is a potent inhibitor of CYP* isozymes responsible for *warfarin metabolism*.
- ***what is the result of this drug–drug interaction?***

Enzyme inhibitors increase the effect of the target drug



Enzyme Inhibition

- Overall effect is an increase in effect of the target drug
- To get the same effect from the target drug, you may need to DECREASE the dose.
- For example, omeprazole is a potent inhibitor CYP isozymes responsible for warfarin metabolism. If the two drugs are taken together, plasma concentrations of warfarin increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions.

Enzyme Inhibitors

Inhibitors	Substrate
Omeprazole دواء للمعدة	Warfarin
Cimetidine دواء للمعده, والأفضل نستخدم ranitidine	Warfarin Theophyllin دواء للأزمة
Erythromycin(Antibiotic)	cyclosporine دواء لزراعة الأعضاء
ketoconazole(Antifungal)	cyclosporine
Grapefruit	*Nifedipine, simvastatin* دواء للقلب / دواء للكوليسترول

- If you give a patient warfarin and an inhibitor??

The effect will increase----> it's important to know if the drug is a narrow therapeutic index(المريض رح ييجي ومعاه نزيف)

- narrow therapeutic ولكن في الجدول فقط ال drugs يوجد العديد من ال inhibitor لكل index

- Warfarin: it should be given at exact concentration and dose--> if it's increase it will cause bleeding, and if it decrease it will cause clot

- If the patient take inhibitors with another drug??

The inhibitor will decrease the metabolism ---> so the drug will stay in our body longer and the patient will be already took the other doses, so the drug will be accumulated ---> greater effect ---> then it will reach the toxic effect especially if the drug is a narrow therapeutic index.