Pharmacokinetic, Metabolism

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Pharmacokinetics
Metabolism

What does the body do to the drug?

Absorption
Distribution
Metabolism
Excretion

***The main target of metabolism is producing water soluble drugs to be excreted by chemical modification of drugs, so we call it biotransformation of drugs.**

Drug Biotransformation (METABOLISM)

➢ **The importance of biotransformation is the conversion of unionised drugs to ionised, water soluble metabolite which is easily excreted.**
➢ **The liver is the main organ of metabolism but can occur in other organs like lung, kidney and intestine.**

(Metabolism can occur in any site containing microsomal enzymes).

Consequences of drug metabolism

1. Convertactivedrugtoinactivemetabolite(mostdrugs).

2. Convertinactiveprodrugintoactivedrug
e.g. enalapril >> enalaprilat (active)
***Enalapril: ACE inhibitors (act on converting enzymes (which make inhibition) and also can treat hypertension.**
***prodrug is a type of drug that are inactive in blood, but when liver metabolite it to be water soluble it will be active**

3. Convertactivedrugtoactivemetabolite
E.g. Codeine >> morphine
codeine: which includes synthesis of antitussif drug (inhibit coughing) but it can. Lead to addiction.

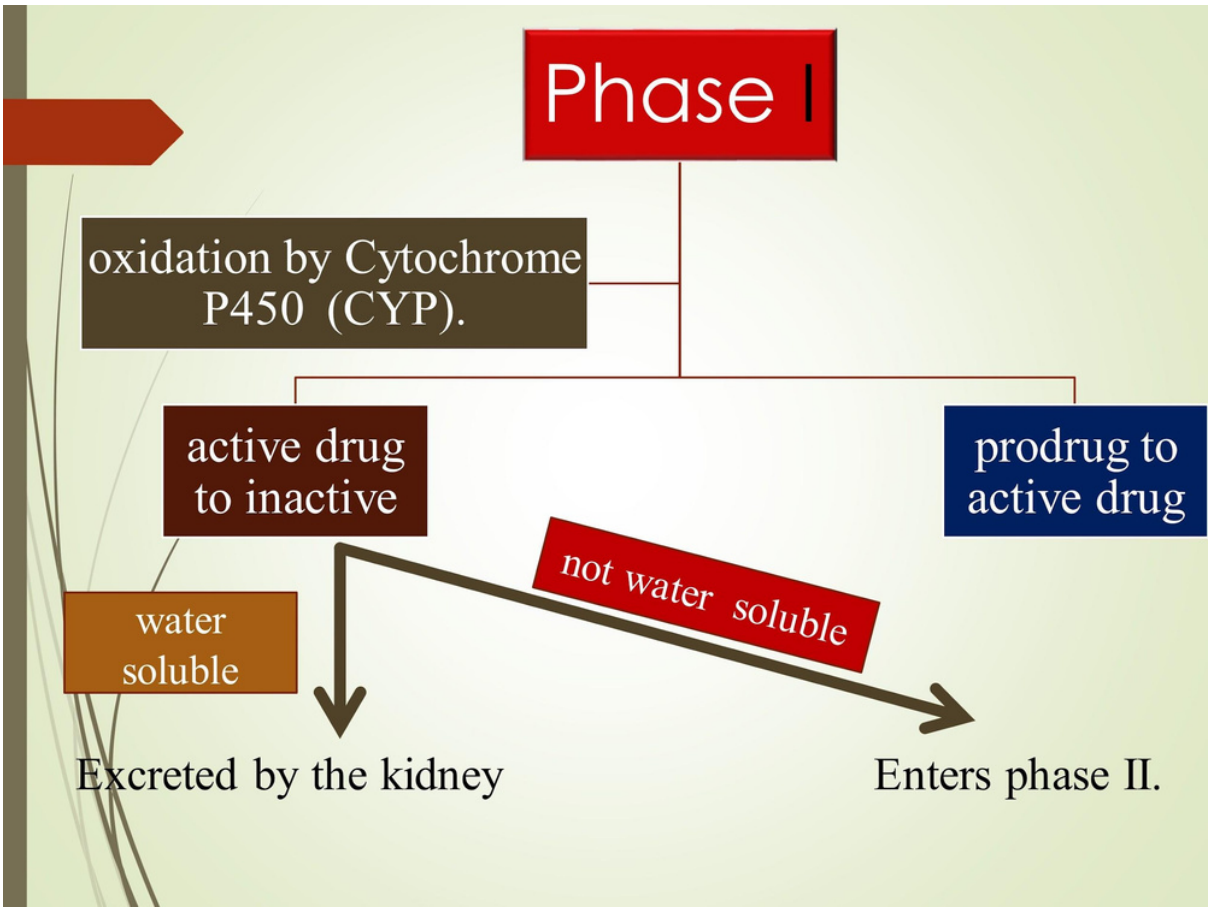
4. Convertdrugstotoxicmetabolites
e.g. Halothane & Paracetamol ---- hepatotoxic
Paracetamol is the most safe drug for pregnancy but if the dose is above 4g/ daily (8 pills) it will be converted to a toxic substance.

Explanation:
In the normal state paracetamol is converted to toxic form, but glutathione (a substance formed from amino acids in our bodies) eliminates its effect.

-glutathione autable substance (قابل للاشعاع) so if paracetamol increases in the body, glutathione cannot remove all toxicity.
+if someone suicide by using paracetamol, may lead to acute liver failure in patient.

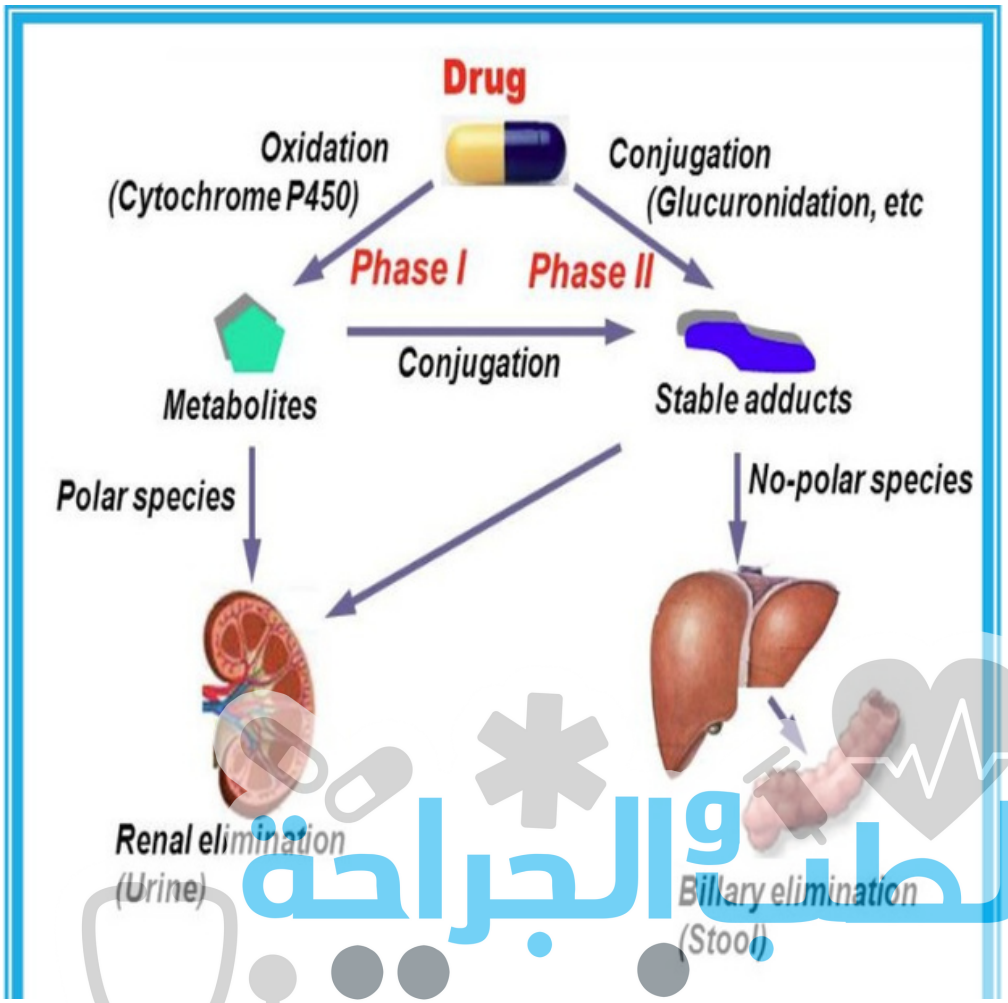
Biotransformation reaction
Phase 1: oxidation (adding oxygen molecule to the drug in presence of NADPH) , **reduction hydrolysis.**
Phase 2: Biosynthetic reactions "conjugation" (adding specific group like acetyl group, mathyl,....)

*not all drugs enter 2 phases, some drugs are converted to water soluble by phase 1 only or phase 2 only or by entering phase 1 and phased 2.



Oxidase enzymes are 2 types:
-microsomal enzymes in smooth endoplasmic reticulum.
-non microsomal enzymes in the cytoplasmic

Phase II (biosynthetic) "conjugation" reactions
❖ **An endogenous substrate e.g. glucuronic acid, sulphate, glutathione amino acids, or acetate is conjugated with the parent drug or its phase I metabolite.**
❖ **This results in formation of water soluble and rapidly eliminated conjugates..**



BOTH PHASES THEIR NOT RESULT IN ELIMINATION BY KIDNEY.

Factors affecting biotransformation

1. Physiologicalfactors:age,Sex.

Age: the maturity of the enzymes differ in children from adults. Example: chloramphenicol (antibiotic) if it is given to children, it will accumulate in the body because it can't be metabolite causing grey babies syndrome.

Sex: females make more metabolism than males because her hormones (oestrogen and progesterone) meke enzyme induction.

2. Pathologicalfactors:livercellfailure.

3. Pharmacogeneticvariationinmetabolisingenzymese.g.slowandfastacetylators. (

In phase 2)

- Theacetylationprocessisfasterthanothersdependingongeneticvariationsuchas: hydralazine (antihypertensive drug) / ionised (for TB) these drugs metabolite by acetylation. So if the patient is a slow acetylator he will get a high adverse effect from ionisation because the drug will metabolise slowly and accumulate in the body.

4. **Enzyme induction & enzyme inhibition.**

Enzyme induction

❖ **Many drugs are able to induce (increase activity and number) of microsomal enzymes resulting in increased rate of metabolism of the inducing drug as well as other drugs metabolised by the same microsomal enzymes.**

❖ **Some inducing drugs : Phenobarbitone, phenytoin, nicotine, rifampicin, carbamazepine.**

For epilepsy: Phenobarbitone, phenytoin,carbamazepine.
TB: rifampicin.
- Nicotinesmokingcausesenzymeinduction.

Consequences of enzyme induction:

1. Increasemetabolismoftheinducingdrugs.Thisleadstotolerancee.g. phenobarbitone.

2. Druginteractions:
(That causes drug failure, although the drug is taken in excellent dose but increasing its rate in metabolism lead to fast elimination of the drug so the drug does not make the target effect.)
❑ **Rifampicin enhances metabolism of warfarin. >> cause blood coagulation.**
❑ **Antiepileptics increase the metabolism of each other. >> who has epilepsy doesn't take only one drug.**

3. Prolongeduseofenzymeinducersmayproducerickets(children) orosteomalacia (adults) due to increased metabolism of vitamin D.

❖ **Enzyme induction is reversible. It occurs over a few days and passes off over 2 - 3 weeks after withdrawal of inducer.**

Enzyme inhibition

Many drugs inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.e. potentiate their pharmacological actions.

Some enzyme Inhibitor drugs
❖ **Erythromycin, Clarithromycin, Cimetidine, Contraceptive pills (the mechanism similar to pregnancy, so no ovulation occurs. It should be taken at the same time daily / if the female is a smoker it will cause high failure of contraceptives because these agents will inhibit its metabolism).**

Consequences of enzyme inhibition on metabolized drugs

1) Exaggerated pharmacological actions.
2) Exaggerated adverse effects.
3) Drug interactions.

انت الذي تجاهد نفسك بالدراسة،انظر الى أطباء غزة كيف يكونون نوراً بين كل هذا الظلام
كذلك أنت بعلمك واجتهادك تستطيع أن تكون هذا النور
انت الآن في مرحلة الاستشعار لعظمة الله في دقة خلقه
لكن لابد أن تكابد وتجتهد لتشعر بذلك .
فقد كابدوا المجد حتى مل أكثرهم وعانق المجد من أوفى ومن صبرا.
ادرس لأجل أن تكون نوراً وسط الظلام !!

اللهم اجعل هذا الطريق حُجة لنا لا حُجةً علينا
لا تنسوا إخوانكم في غزة من صالح دعائكم