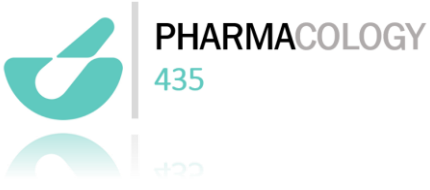
PHARMACOLOGY

Drug Metabolism

OBJECTIVE:

- Recognize the importance of biotransformation
- Know the different sites for drug metabolism
- Define the major phase I and phase II metabolic reactions.
- Describe the modulation of liver microsomal enzymes by inducers and inhibitors
- Mention two drugs that are known as enzyme inducers and inhibitors.
- Know the impact of first pass metabolism on drug bioavailability.



Drug Metabolism:

It is the chemical reactions which occur in the body to change drugs from nonpolar lipid soluble forms to polar water soluble forms that are easily excreted by the kidney.

Importance:

- Inactivation or termination of drug action (most drugs).
- Detoxification Biotransformation is required for protection of body from toxic metabolites
- Activation of prodrug (convert inactive form of drug to active form)

  e.g. levodopa - carbidopa, prednisone – prednisolone

Organ sites of drug metabolism:

1- Liver **(the major site).** 2- kidney 3- skin 4- lung

5- Intestinal Mucosa and Lumen:

Gut Mucosa: MonoAmine Oxidase (MAO) .

Gut lumen (bacterial flora): Glucouronidase.

6- Plasma:

Enzymes	substrate
Catechol o-methyl transferase (COMT)	catecholamines (adrenaline)
Esterases	Esters (Local Anesthetics)
Amidases	amides (Local Anesthetics)

Cellular sites of drug metabolism:

1- Cytoplasm:

e.g. Alcohol dehydrogenase: oxidation of alcohol

Alcohol ⟶ Aldehyde ⟶ Acid

2- Mitochondria: - Monoamine oxidase enzyme (MAO):

oxidation of catecholamines as adrenaline

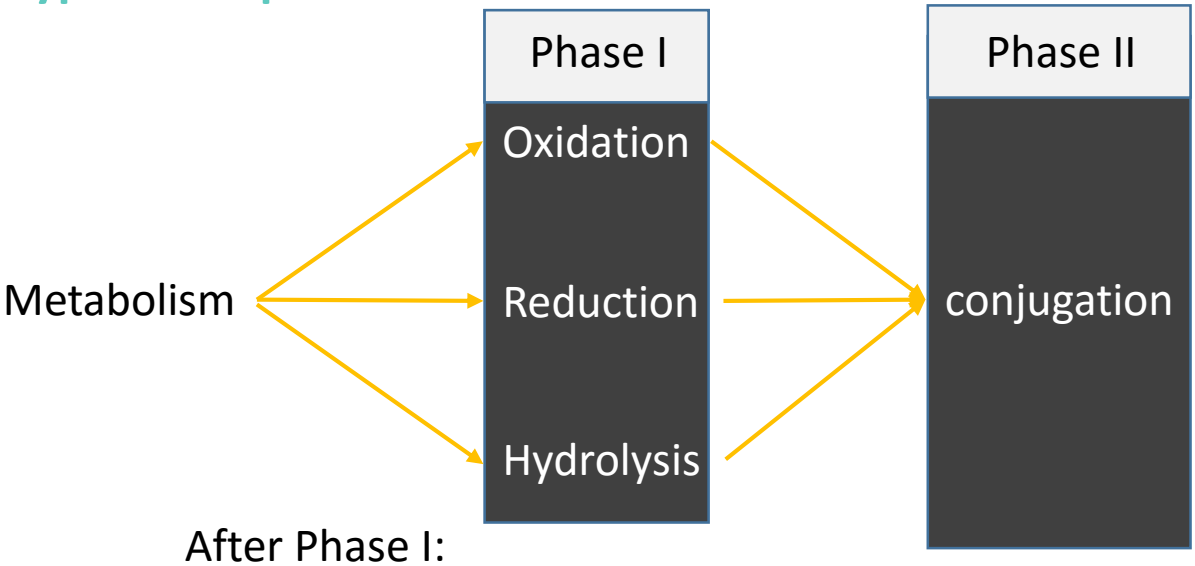
- N-acetyl transferase: Introduction to acetyl group

3- Microsomes:

- Microsomal enzyme system = Cytochrome P-450.
- There are more than 20 families CYP1, CYP2, CYP3
- Sub-families are identified as A, B, and C etc.
- In human: only 3 isoenzyme families are important CYP1, CYP2 and CYP3

4-Lysosomes

Types of hepatic metabolic reaction:



After Phase I:

1. **Active** = lipid soluble > Phase II
2. **Inactive** = water soluble (excreted)

Phase I

Oxidation:

Addition of oxygen OR Removal of hydrogen .
It's the most important drug metabolizing reaction .

Microsomal

- Occurs in **Microsomes**

E.g. Cytochrome P450 enzymes, NADPH , Oxygen

Non-microsomal

- Occurs in **cytosol OR Mitochondria**

E.g. Oxidases & Dehydrogenase

Non-microsomal occurs Either dehydrogenase OR Oxidases.

1. Dehydrogenase: Alcohol dehydrogenase and aldehyde dehydrogenase

2.Oxidase:

A. Xanthine oxidase

- metabolism of xanthine .
- Hypoxanthine ⟶ xanthine ⟶ uric acid ⟶ uric acid accumulation ⟶ GOUT
- Allopurinol is an inhibitor of xanthine oxidase and used in treatment of gout.

B. Monoamine oxidase (MAO)

- metabolism of catecholamines as adrenaline and serotonin .

E.g. Moclobemide is MAO inhibitor and used as antidepressant since it increases serotonin in brain.

Phase I

Reduction:

Removal of oxygen or addition of hydrogen.

- May be microsomal or non-microsomal

E.g.: levodopa

Levodopa(DOPA) —**DOPA- decarboxylase**→ Dopamine

Hydrolysis:

occurs by addition of water molecules in presence of enzymes
All are non-microsomal

Esterase: hydrolyze drugs that are esters e.g. **acetylcholine** (neurotransmitter).

Acetylcholine → acetate + choline.

Amidases: hydrolyze drugs that are amides e.g. **lidocaine** (used as local anesthetic)

Phase I result in:

- Activation of pro-drug e.g. **levodopa to dopamine.**
- Inactivation of drug (termination of action).
- Conversion of **active drug** to **active metabolite.**
- Conversion of **nontoxic drug** to **toxic metabolite.**

  Paracetamol → hepatotoxic metabolite (hepatic necrosis)
- Product might undergo phase II

Conjugation:

coming from (phase I) with endogenous substance to produce conjugate that is water soluble and easily **excreted** in urine or bile.

Conjugation reaction	Enzyme required
glucouronide conjugation	**Glucouronyl transferase**
Acetylation	**N-acetyl transferase**
Sulphation	**Sulfo transferase**
Methylation	**methyl transferase**
Amino acids conjugation	**Glycine Transferase**

Phase II:

- All are non microsomal except glucouronidation
- **Glucouronide conjugation** is a microsomal process (the most common).
- Deficieny of **glucouronyl transferase** enzyme in neonates may result into toxicity with chloramphenicol **(Gray baby syndrome)**.

Characteristics of Phase II product:

- Usually pharmacologically **inactive**.
- **Polar**
- more **water soluble.**
- **Easily** excreted in urine.

Factors affecting metabolism :

- AGE: ↓ rate of metabolism in neonates & elderly.
- DISEASES : ↓ rate of metabolism in liver diseases.
- Degree of Protein Binding : ↓ rate of metabolism.
- Concurrent use of drugs : Induction & inhibition.
- Nutrition : malnutrition ↓ rate of metabolism.
- Genetic polymorphism : Existence of more than one phenotype due to genetic variation in rate of metabolism. E.g. **Isoniazid** (anti- tuberculosis drug)

  Slow acetylator phenotype → peripheral neuropathy

  Rapid acetylator phenotype → hepatitis

Enzyme Induction & inhibition:

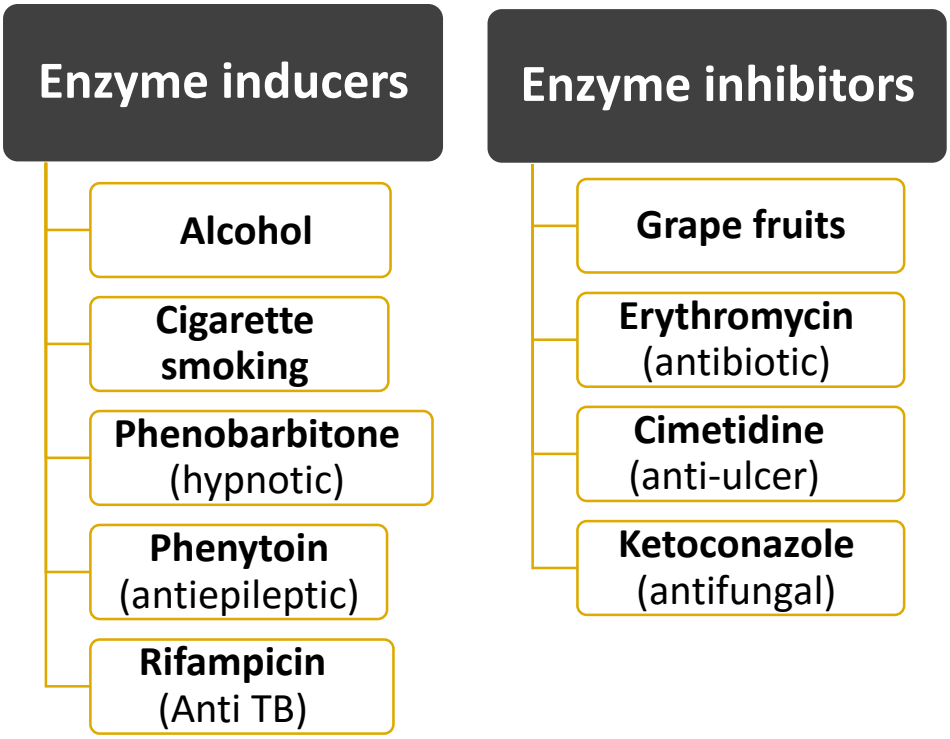
Liver microsomal enzymes inducers :

drugs that **increase** activities of liver microsomal enzymes & increase the metabolism of drug itself and other drugs taken with the inducer at the same time.

Liver microsomal enzymes inhibitors :

drugs that **decrease** activities of liver microsomal enzymes & decrease the metabolism of the drug itself and other drugs.

Enzyme



Enzyme induction may result in:

- ↑ the metabolism and excretion of the inducer drug itself and co-administered drugs.
- ↓ the action of the inducer drug itself & co-administered drugs.
- **Tolerance may occur:** decrease in the pharmacological action of the drug by repeated administration .
- **Drug interactions may occur:** decrease in action of one drug by administration of another drug. e.g. oral contraceptives & phenytoin(inducer)

(Failure of oral contraceptive may lead to pregnancy if combined with phenytoin.)

Enzyme inhibition may result in:

- ↓ Delay the metabolism and excretion of the inhibitor drug and co-administered drugs.
- ↑ Prolong the action of the inhibitor drug & co-administered drugs.

  e.g. warfarin & erythromycin (inhibitor).
- Inhibition of warfarin metabolism may lead to increase its **anticoagulant effect** (bleeding).

THANK YOU FOR CHECKING OUR WORK

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