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MED444
KING SAUD UNIVERSITY

PHARMACOLOGY
TEAM 444

Drug Metabolism

Lecture no. 3

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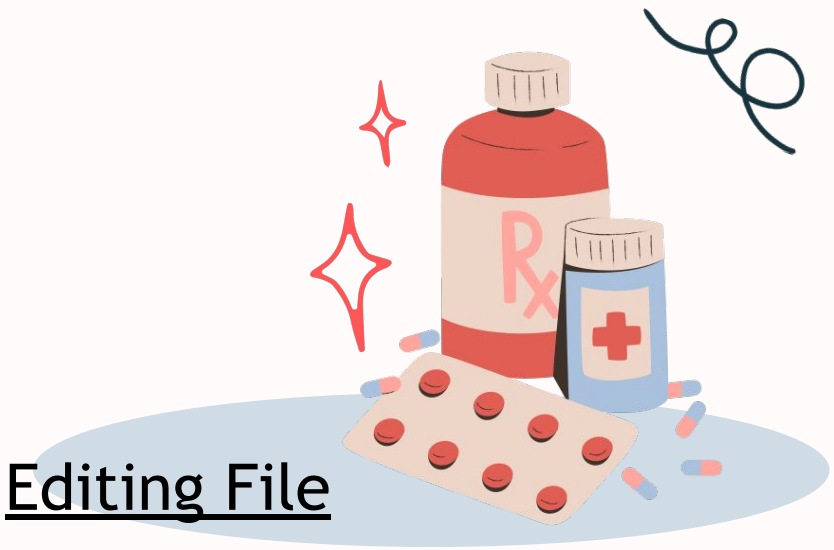

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(اللَّهُمَّ انفَعْنِي بِمَا عَلَّمْتَنِي، وَعَلِّمْنِي مَا يَنْفَعُنِي وَزِدْنِي عِلمًا)

Objectives

- 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 two drugs as enzyme inhibitors.
- Know the impact of first pass metabolism on drug bioavailability.

Drug Metabolism

Definition

Drug metabolism or (Biotransformation) are chemical reactions which occur in the body to change drugs from nonpolar lipid-soluble forms (drugs get absorbed in this form) to polar water-soluble forms that are easily excreted by the kidney.

Importance

- Inactivation or termination of drug action (most drugs).
- Detoxification Biotransformation (change of drug form) is required for protection of body from toxic metabolites. e.g. NAPQI (442note: to prevent accumulation)
- Activation of prodrug (convert inactive form of drug to active form) e.g. levodopa (drug used to treat Parkinson's disease) - carbidopa /dopamine , prednisone – prednisolone.

441note: The patient takes it in the inactive form(prodrug), it becomes active after the metabolism (activation happens inside the body).

Organ sites

- Liver (the major site).(where all metabolic enzymes are formed)
- Intestinal Mucosa and Lumen
- Plasma
- Kidney
- Skin
- Lung

Intestinal Mucosa and Lumen

(where the drug breaks down before it reaches the portal circulation)

➔ Gut Mucosa

- Mono-Amine Oxidase (MAO) , oxidation of catecholamines.

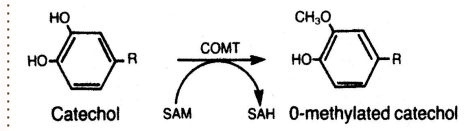
441note:
For drugs with amine groups (introducing one oxygen to amine group in oxidation)
- note: mono → 1

➔ Gut Lumen (bacterial flora)

- Glucouronidas

441note:
produced by bacteria, (breakdown glucuronic acid in drugs)

Plasma

Enzyme (acts on the substrate to metabolize it)	Substrate
Catechol O-Methyl Transferase (COMT) read its name backward → an enzyme that transfers methyl group to the oxygen in catechol  • Polarity increases	catecholamines (e.g. adrenaline) + serotonin
Esterases	Esters Act on drugs as Local anesthetics E.g. Acetylcholine
Amidases	Amides Act on drugs as local anesthetics E.g. Lidocaine

Cellular sites of drugs metabolism in liver

01

Mitochondria

- **N-acetyl transferase:**
(it transfers the acetyl group to nitrogen in other compound)
Introduction of acetyl group (CH3COO-)
note → it's polar and uncharged
- **Monoamine oxidase enzyme (MAO):**
oxidation of catecholamines as adrenaline

02

cytoplasm

e.g. **Alcohol dehydrogenase**: oxidation of alcohol (by removal of H or addition of O)
(NAD+) → (NADH)
Alcohol → Aldehyde → Acid
Ethanol → Acetaldehyde → Acetic Acid.
CH3CH2OH(lipid soluble) → CH3CHO(toxic) → CH3COOH(water soluble)

03

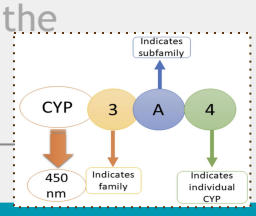
Microsomes (HLM)

Microsomal enzyme system = Cytochrome P-450 (responsible for oxidation).
There are more than 20 families e.g. CYP1, CYP2, CYP3 (In humans, only these three isoenzyme family are important)
Sub-families are identified as A, B, and C etc.

Oxidation-Cytochrome P-450: CYP3A4/5

- Carry out biotransformation of the largest number (30-50%) of drugs.
- Expressed in liver and intestine (responsible for first pass metabolism at this site). - metabolism before it reaches to the circulation

An important picture from male slides



04

Lysosomes

isn't mentioned

Watch this for a better understanding!

Important

Types of hepatic metabolic reactions

two phases

Phase I: active (become toxic) **or inactive metabolites.**

metabolic reactions include:
oxidation / reduction /hydrolysis

Active or nonpolar

Phase II: metabolites are usually **inactive**(water soluble).

- **Conjugation reactions**

(عبارة عن التحام شيئين ببعضهم البعض)

Inactive and polar (conjugated metabolite)

Inactive and polar

Easily excreted by the kidneys.

442Note: The active form of the drug converts to an active metabolite in order to have a long duration of action.
The active metabolite will move to phase II in order to be inactive and water-soluble(polar) for excretion.

Oxidation Reactions

Oxidation:

Is addition of oxygen or removal of hydrogen.

The most important drug metabolizing reaction

Microsomal:

Occurs In **microsome.**

e.g. **cytochrome P450 enzymes** (by addition of O), NADPH(co-factor helps in the oxidation reaction) and oxygen.

Non-microsomal:

occurs in **cytosol** or **mitochondria**

these enzymes include (oxidases & dehydrogenases)

Oxidases:

1) Monoamine oxidase (MAO):

Is responsible for the metabolism of catecholamines as adrenaline and serotonin.

e.g. Moclobemide

Is a monoamine oxidase inhibitor (MAOI).

- It increases serotonin in the brain.(prevents it from breaking down so it can help in treating depression)
- Used as antidepressant drug.

2) Xanthine oxidase:

Is required for the oxidation of xanthine.

Hypoxanthine → (oxidized) xanthine → (oxidized) uric acid

uric acid accumulation → GOUT (النقرس)

Allopurinol: is an inhibitor of xanthine oxidase

- used in the treatment of gout.
  442 note: prevents uric acid accumulation

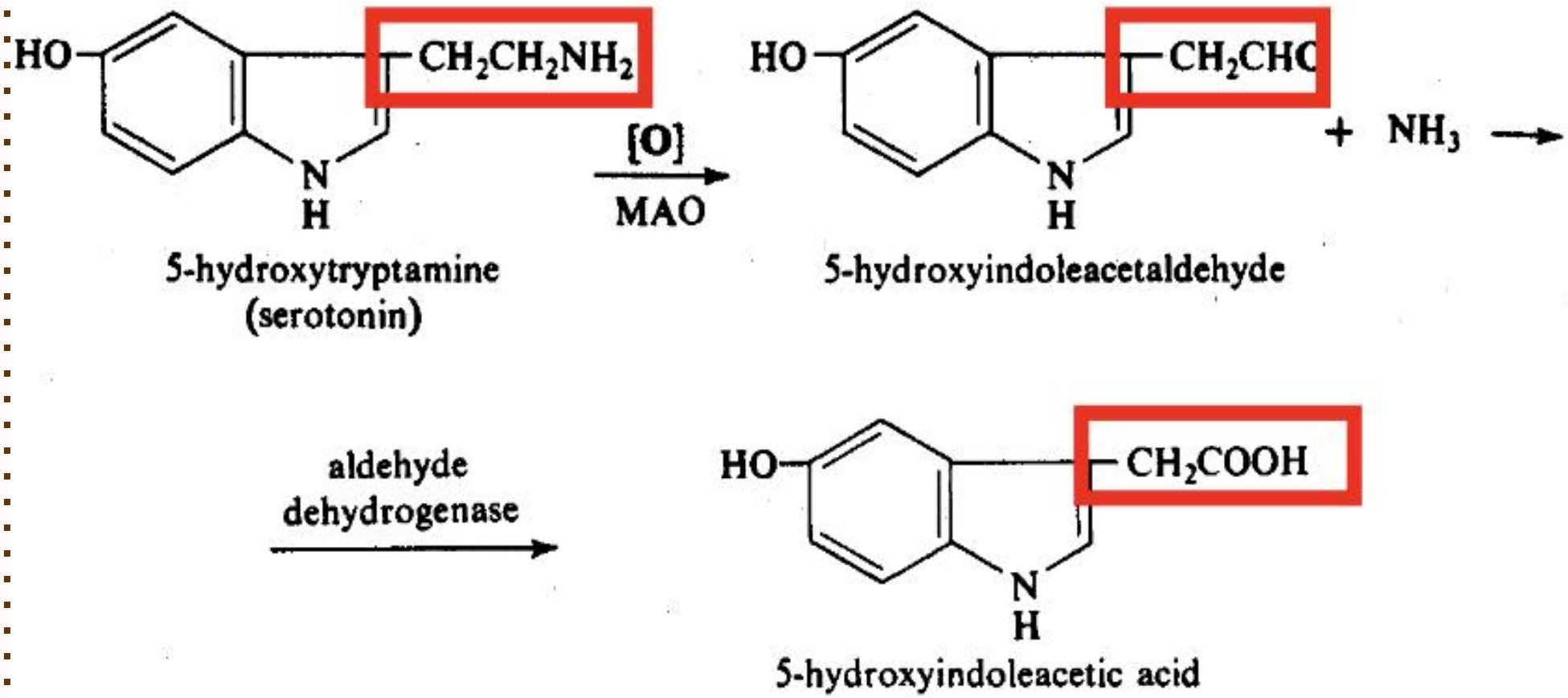
Dehydrogenases:

Are required for oxidation of alcohols.

- e.g. Alcohol dehydrogenase (convert alcohol to aldehyde).
- e.g. Aldehyde dehydrogenase (convert aldehyde to acid).

Oxidation Non-microsomal oxidase (contd...)

Non-microsomal oxidases e.g
Serotonin - Monoamine Oxidase (MAO):



Reduction Reaction

Removal of oxygen or addition of Hydrogen

microsomal or non-microsomal

(Inactive)
L-dopa
Levo= L form
Prodrug

(Active)
Neurotransmitter
Drug

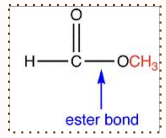
439,441note: Dopamine deficiency will cause Parkinson's disease,and it's treated with levodopa (because levodopa can cross the brain cells barriers while dopamine can't directly)

Hydrolysis reaction

All are non microsomal

occurs by addition of water molecules in presence of enzymes as (esterases & amidases)

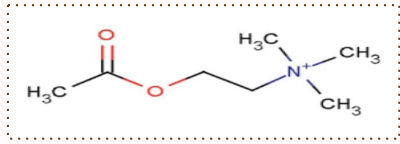
Esterases: hydrolyze drug that are esters →



Ester + H_2O → Acid + Alcohol

e.g.: Acetylcholine (Ach)

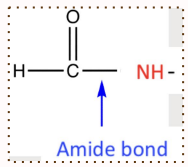
(Neurotransmitter)



Esterase

Acetylcholine → acetate + choline

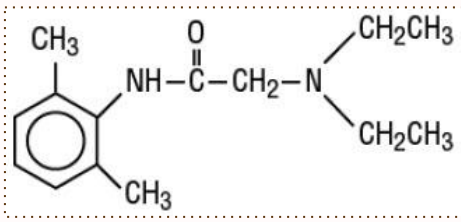
Amidases: hydrolyze drugs that are amides →



Amide + H_20 → Acid + amine

e.g.: Lidocaine (used as local anesthetic)

(مشتق من الكوكايين)



Phase I reaction can result in :

1. Activation of pro-drug
   e.g. levodopa to dopamine

443note: prodrug is an inactive form or the drug

2. Inactivation of drug (termination of action)

3. Conversion of active drug to active metabolite
(442note: long duration of action)

4. Conversion of nontoxic drug to toxic metabolite
Paracetamol (Panadol) → hepatotoxic metabolite (hepatic necrosis),
(N-acetyl-p-benzo-quinone imine; NAPQI)

- NAPQI: is a toxic metabolite caused by paracetamol overdose and it results in liver toxicity/damage.

5. Product might undergo phase II

Phase II Conjugation Reactions

Conjugation of:

metabolite coming from (phase I)

Endogenous substance (inside the body)

Methyl group

Acetyl group

Sulphate

Amino acid

Glucouronic acid

To produce a conjugate that is:

water-soluble and easily excreted in urine or bile

Types of conjugation reactions

Important

Conjugation reaction	Enzyme required
glucouronide conjugation (most common- the only microsomal)	Glucouronyl transferase
Acetylation (CH3 COO -)	N-acetyl transferase
Sulphation (SO4--)	Sulfo transferase
Methylation (CH3)	Methyl transferase
Amino acids conjugation	Glycine conjugation

Note:ENZYME REQUIRED make CONJUGATION REACTION inactive and polar

Phase(1)
Oxidation, reduction → microsomal, non microsomal
Hydrolysis → non microsomal
Phase(2)
Non microsomal (except: glucouronidation)

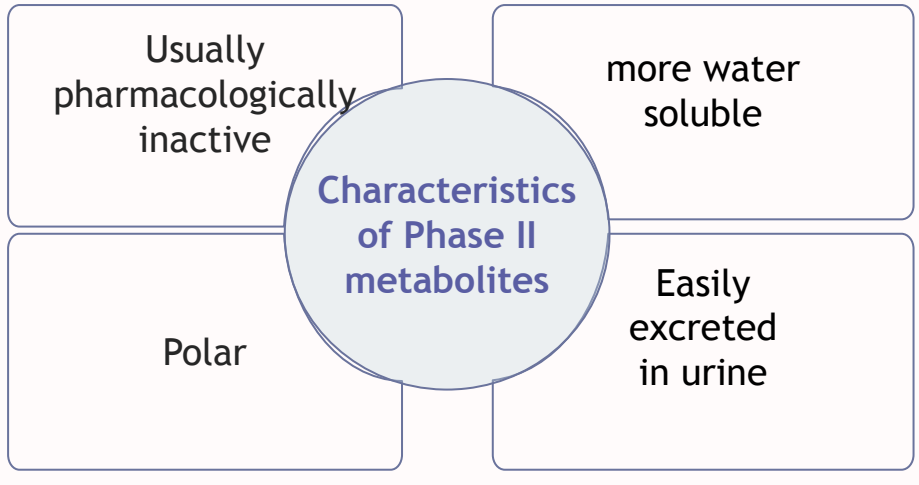
Phase II metabolic reactions:

All are: non microsomal except glucouronidation

Glucouronide conjugation is a microsomal process (the most common of phase II reactions).

Deficieny of glucouronyl transferase enzyme in neonates may result into toxicity with chloramphenicol (Gray baby syndrome).

441note: It is forbidden to give chloramphenicol to children under 2 years



Factors affecting metabolism

Age: ↓ rate of metabolism in neonates (newly born) and elderly

Diseases:↓ rate of metabolism in liver diseases (+kidney)

Degree of Protein Binding: ↓ rate of metabolism (increase in protein bound drugs will make it trapped in the blood circulation resulting in decreasing the metabolism in the liver)

Concurrent use of drugs: Induction and inhibition (in liver microsomal enzymes)

Nutrition: malnutrition ↓ rate of metabolism

Genetic polymorphism: Metabolism may vary from population to another due to the existence of different forms of the metabolic enzymes

E.g. metabolism of **isoniazid (Anti-TB)** (acetylation by acetyl transferase)	Slow acetylator phenotype	decrease in isoniazid metabolism	accumulation of isoniazid	risk of peripheral neuropathy
	Rapid acetylator phenotype	increase in isoniazid metabolism	results into excess metabolites produced (toxic)	risk of hepatitis

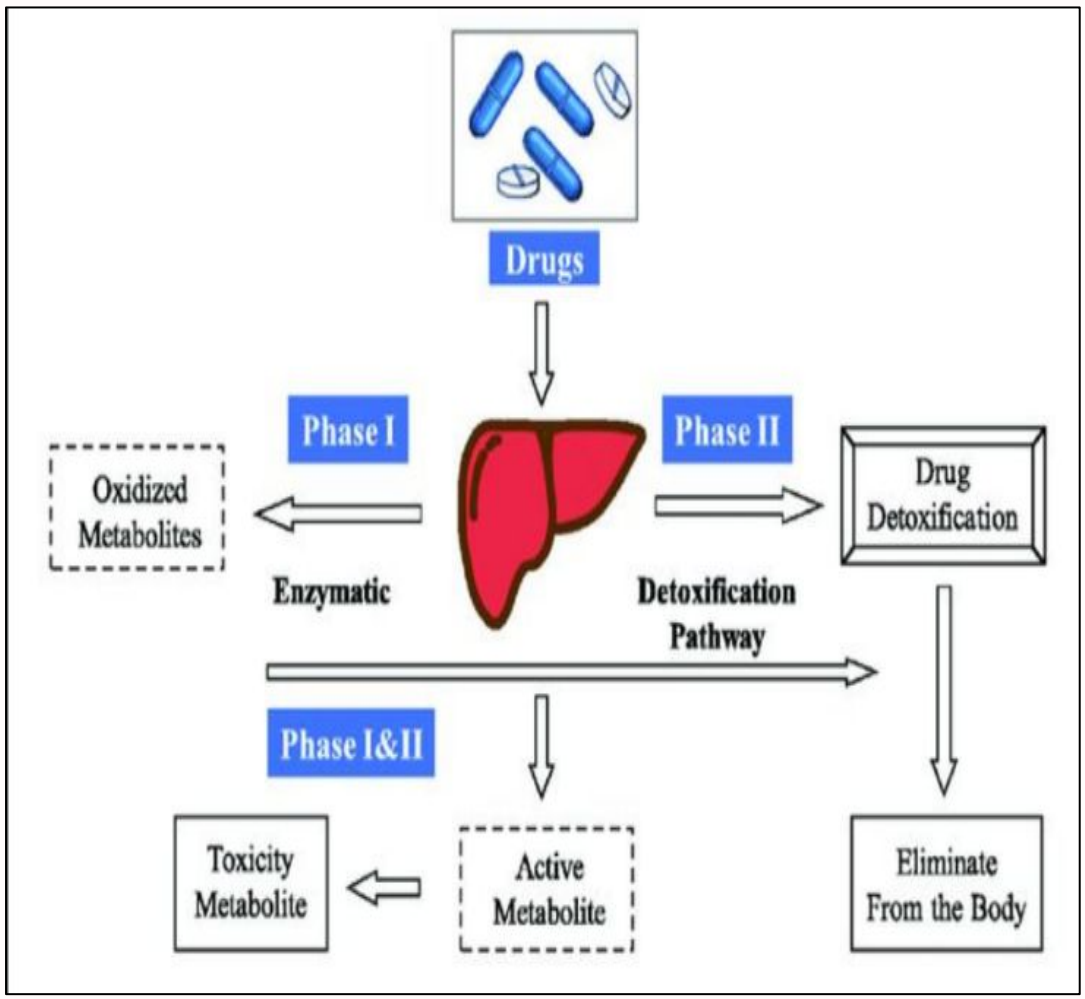
Enzyme induction & Inhibition (table is cont. in next slide)

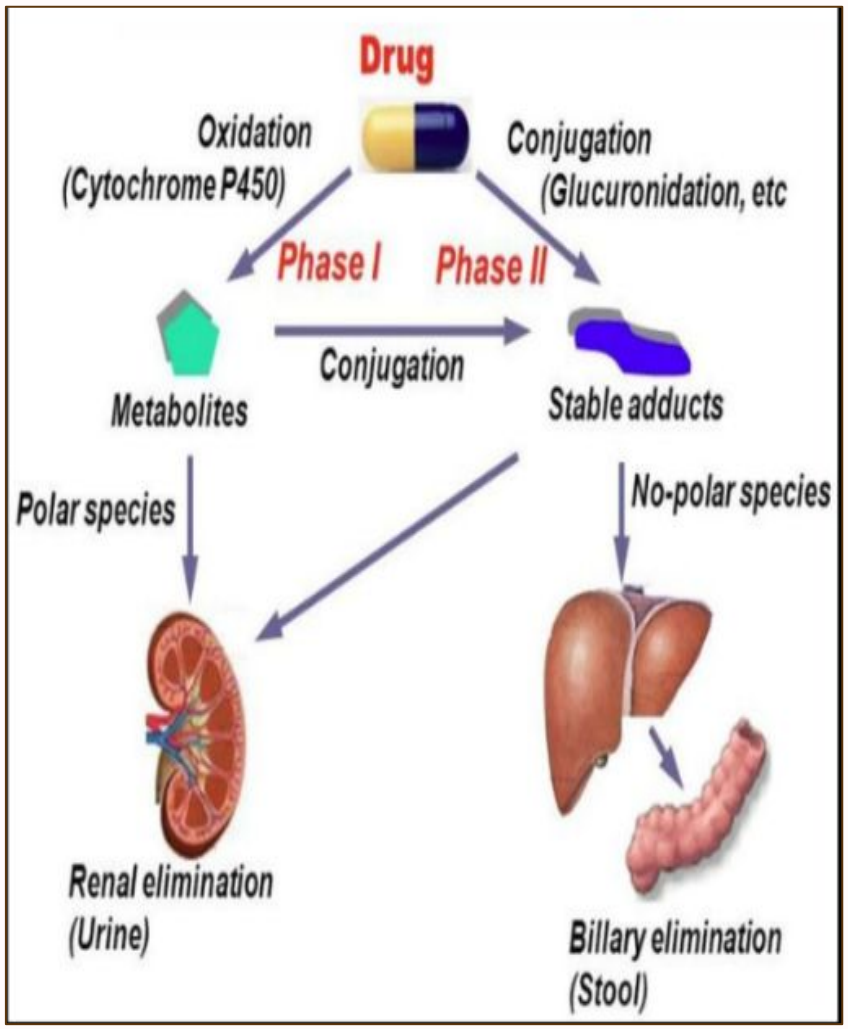
Team 443:

	Enzyme Induction Inducers:	Enzyme Inhibition Inhibitors:
Liver microsomal enzymes	drugs that **increase** activities of liver microsomal enzymes and **increase** the metabolism of drug itself and other drugs taken with the inducer at the same time.	drugs that **decrease** activities of liver microsomal enzymes and **decrease** the metabolism of drug itself and other drugs taken with the inducer at the same time (concurrently).
Metabolism and Excretion of the drug itself and co-administered drugs	↑ Increase	↓ Decrease (delay)
the action of the inducer drug itself and co-administered drugs	↓ Decrease (short duration of action)	↑ Increase(prolong)
May occur	**Tolerance:** decrease in the pharmacological action of the drug by continuous or repeated administration	

	Enzyme Induction Inducers:	Enzyme Inhibition Inhibitors:
Drug interactions	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 • oral contraceptives + phenytoin → induce contraceptive metabolism → Failure of oral contraceptive → pregnancy 442: نشاط الإنزيمات العالي للـ phenytoin جعل مانع الحمل أيضًا الـ metabolism له عالي بالتالي يتكسر بسرعه قبل أن يعطي التأثير المطلوب ، واستمرار المرأة بأخذ نفس الجرعة بلا اعتبار للتأثير الحاصل - بسبب أخذ الدوائين بنفس الوقت - يؤدي للحمل	e.g. warfarin + erythromycin (inhibitor) -Inhibition of warfarin metabolism may lead to increase its **anticoagulant effect (risk of bleeding)** • warfarin + erythromycin → inhibit warfarin metabolism → increase anticoagulant effect →bleeding 442: نشاط الإنزيمات المنخفض للـ erythromycin يجعل أيضًا الـ metabolism للـ warfarin منخفض، بالتالي يقل تكسيره فلا يتم التخلص منه بسرعة، وبقاؤه في الجسم طويلاً يزيد تاثيره و يسبب نزيف
Examples of Enzyme inducers/inhibitors **حفظ**	• Alcohol • Phenytoin(antiepileptic) • Phenobarbitone (hypnotic) • Cigarette smoking • Rifampicin(Anti TB)	• Grape fruits • Erythromycin(antibiotic) • Ketoconazole(antifungal) • Cimetidine

Revision


Drugs
Phase I
Oxidized Metabolites
Enzymatic
Phase II
Drug Detoxification
Detoxification Pathway
Phase I&II
Toxicity Metabolite
Active Metabolite
Eliminate From the Body


Drug
Oxidation (Cytochrome P450)
Conjugation (Glucuronidation, etc
Phase I
Phase II
Conjugation
Metabolites
Stable adducts
Polar species
No-polar species
Renal elimination (Urine)
Billary elimination (Stool)

MCQs

1)Microsomes consist of a microsomal enzyme system called:			
a) Amidases	b) COMT	c) Cytochrome p-450	d) MAO

2)What are the reactions that occur in phase II of hepatic metabolic reactions?			
a) Oxidation reactions	b) Conjugation reactions	c) Reduction reactions	d) Hydrolysis

3)In phase II , All are non-microsomal <u>except:</u>			
a) Glucouronidation	b) Acetylation	c) Hydrolysis	d) Oxidation

4)Which one is an endogenous substance in phase II ?			
a) Acetyl group	b) phosphate group	c) Fatty acid	d) Butyl group

Answers:

1) C
2) B
3) A
4) A

↑increase the metabolism and excretion of the inducer drug itself and co-administered drugs.

Give one of the results that enzyme induction may cause :

1- Inactivation of drug

2- Activation of pro-drug

Mention two important results of phase I reactions?

SAQS

Team Leaders:

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