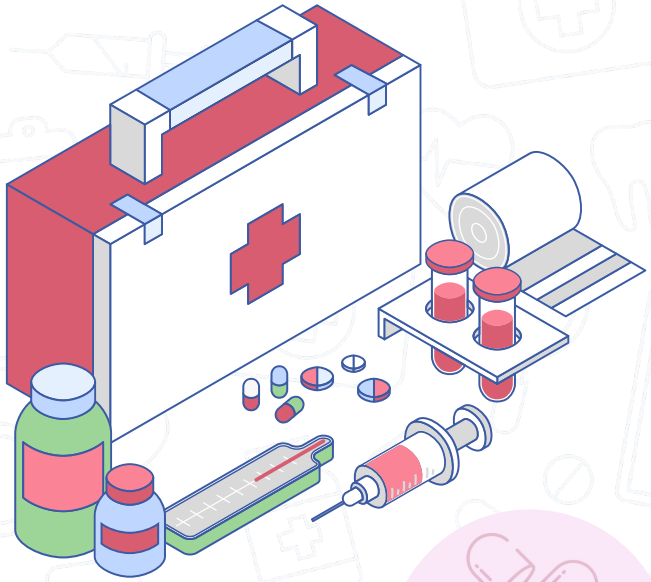


DRUG METABOLISM 442

EDITING FILE

Pharmacology
Team 442

Revised by Mohammad Amr Mahfouz

Important
Main text
Male slide
Female slide
Extra info
Doctor notes

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 inhibitors.
- Know the impact of first pass metabolism on drug bioavailability.

Click for Useful **video**!!

METABOLISM (BIOTRANSFORMATION)

Definition:

Chemical reactions which occur in the body to change drugs from non polar lipid (uncharged-unionized) soluble forms to polar water soluble (charged-ionized)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 product (convert inactive form of drug to active form)**

Sites:

- Liver (**the major site**).
- Intestinal Mucosa and Lumen
- Plasma
- Kidney
- Skin
- Lung

* to be easily excreted in urine and prevent accumulation.
** 441note: The patient takes it in the inactive form, it becomes active after the metabolism (activation happens inside the body).

INTESTINAL MUCOSA AND LUMEN ENZYMES

Gut Mucosa

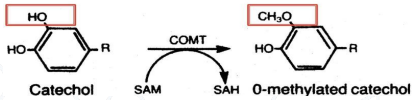
- Mono-Amine Oxidase (MAO).*

Gut lumen (bacterial flora)**

- Glucouronidase

441notes:
*For drugs with amine groups (introducing one oxygen to amine group in oxidation)
**produced by bacteria, (breakdown glucuronic acid in drugs)

PLASMA ENZYMES

Enzyme	Substrate
Catechol O-**m**ethyl Trasferase (COMT)  Adds a methyl group to oxygen in catechol	-Catecholamines E.g. adrenaline+ serotonin
Esterase	-Esters (to alcohol+acid) Act on drugs as local anesthetics E.g. Acetylcholine
Amidases	-Amides (to amine+acid) Act on drugs as local anesthetics E.g. Lidocaine

CELLULAR SITES OF DRUG METABOLISM IN LIVER

Mitochondria	• **N-acetyl transferase:** Introduction of acetyl group (CH3COO-) **Monoamine oxidase enzyme** (MAO): Oxidation of catecholamines as adrenaline
Cytoplasm	• e.g **Alcohol dehydrogenase:** oxidation of alcohol (by removal of H) (NAD+ → NADH) Alcohol → Aldehyde → Acid Ethanol → Acetaldehyde → Acetic acid CH3CH2OH (lipid soluble) → CH3CHO(toxic) → CH3COOH(water soluble)
Microsomes	• **Microsomal enzyme system =** Cytochrome P-450 (responsible of Oxidation). There are more than 20 families e.g. CYP1, CYP2, CYP3 (In humans: only these 3 isoenzyme families are important) Sub-families are identified as A, B, and C etc. Oxidation-cytochrome P-450: ***CYP 3A4***/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**) *dr hanan said omit 5
Lysosomes	

TYPES OF HEPATIC METABOLIC REACTION

TWO PHASES OF HEPATIC METABOLIC REACTIONS:

Phase I (active/inactive metabolite)

- **Oxidation | Reduction | Hydrolysis**

Active or non-polar

Inactive and polar

Phase II (usually inactive metabolite)

- Conjugation(يلتحم مع بعض)

Inactive
polar (conjugated metabolite)

Easily excreted by the kidneys

Note: 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 2 in order to be inactive and water soluble(polar) for excretion

OXIDATION REACTIONS

Oxidation:
Addition of O or removal of H

The most important drug metabolizing reaction

Microsomal: occurs In microsome

-cytochrome P450 enzymes(by addition of O),NADPH (cofactor) and Oxygen

Non-microsomal: occurs in **cytosol** or **mitochondria**

(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**
- It increases serotonin in the brain (يمنع تكسره)
- Used as antidepressant drug

Xanthine oxidase:
Is required for the oxidation of xanthine.

Hypoxanthine $\xrightarrow{\text{Oxidase}}$ xanthine $\xrightarrow{\text{Oxidase}}$ uric acid
uric acid accumulation→ GOUT (النقرص)

★Allopurinol: is a xanthine oxidase **inhibitor**
- used for treatment of Gout (prevent uric acid accumulation) (xanthine can be found in meats that's why GOUT used to be called ملك الأمراض ومرض الملوك)

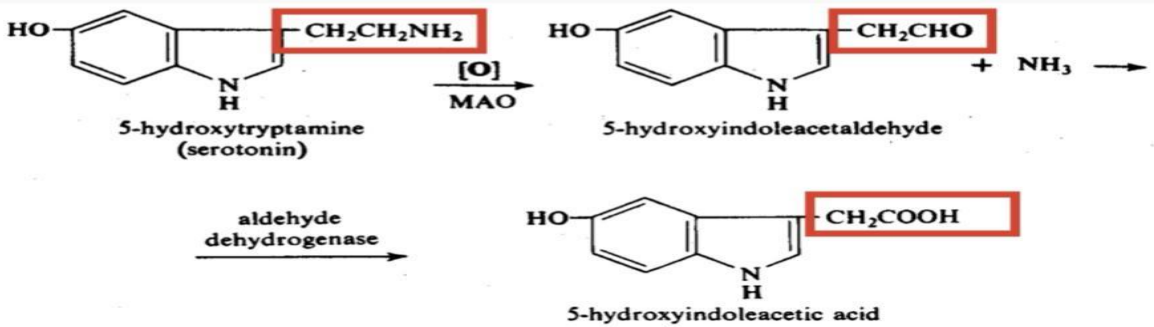
Dehydrogenases:

Are required for oxidation of **alcohols e.g:**

Alcohol dehydrogenase: converts alcohol to aldehyde

Aldehyde dehydrogenase: converts aldehyde to acid

OXIDATION NON-MICROSOMAL OXIDASES [CONTD...]



Non-microsomal oxidases e.g:

Serotonin – Monoamine Oxidase (MAO):

Dr hanan noted: للتوضيح فقط
لا داعي للحفظ

REDUCTION REACTION

Removal of oxygen or addition of Hydrogen

microsomal or non-microsomal

Levodopa (DOPA) (inactive)
L-dopa
Levo= L form

Dopamine (active)

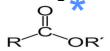
439,441note:Dopamine deficiency will cause Parkinson's disease, and it's treated with levodopa (because levodopa can cross the brain cells barriers while the dopamine can't directly)

HYDROLYSIS REACTION

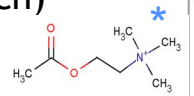
All are non microsomal

Occurs by addition of Water in presence of enzymes as

(esterases & amidases)

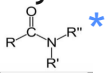
Esterases: hydrolyze drugs that are esters→ 

Ester + H_20 → Acid + Alcohol

e.g.: Acetylcholine (Ach) (Neurotransmitter)→ 

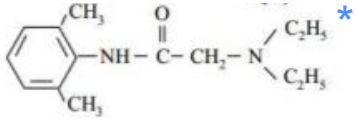
Esterase

Acetylcholine → acetate + choline

Amidases: hydrolyze drugs that are amides→ 

Amide + H_20 → Acid + amine

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



*:pictures from male slides

PHASE I REACTIONS RESULTS

- Activation of pro-drug
  - e.g. Levodopa to Dopamine
  - Pro drug= inactive form of the drug
- Inactivation of drug (termination of action)
- Conversion of active **drug** to active **metabolite** (long duration of action)
- Conversion of nontoxic drug to toxic metabolite
  - Paracetamol (Panadol) → hepatotoxic metabolite (hepatic necrosis)
- Product might undergo **phase II**

PHASE II CONJUGATION REACTIONS

Conjugation of:

metabolite coming from (phase I)

endogenous substance

- 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

Conjugation reaction	Enzyme required
glucouronide conjugation (most common- the only microsomal)	Glucouronyl *transferase*
Acetylation (CH_3 COO –)	N-acetyl *transferase*
Sulphation (SO_4 – –)	Sulfo *transferase*
Methylation (CH_3)	Methyl *transferase*
Amino acids conjugation	Glycine conjugation

Phase(1)
Oxidation, reduction→ microsomal, non microsomal
Hydrolysis→ non microsomal

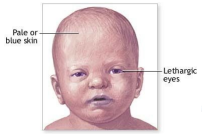
Phase(2)
Non microsomal (except: glucouronidation)

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

CHARACTERISTICS OF PHASE II METABOLITES

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

FACTORS AFFECTING METABOLISM

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

Not predictable

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) (زي سالفة الباندول)	risk of **hepatitis**

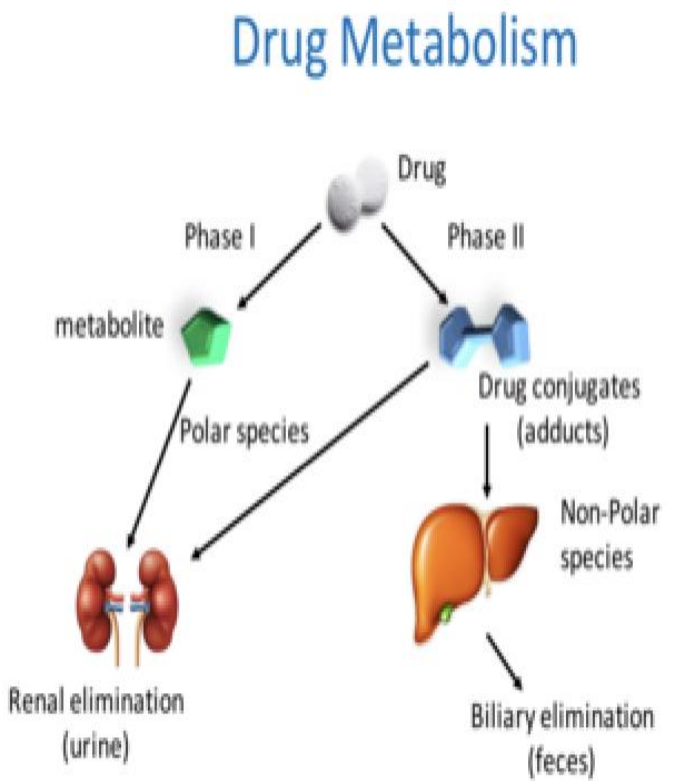
	Enzyme Induction	Enzyme inhibition
Liver microsomal enzymes	inducers:	Inhibitors:
	drugs that **increase activities** of liver microsomal enzymes and **increase** the **metabolism** of drug itself and other drugs taken with the inducer at the same time	drugs that **decrease activities** of liver microsomal enzymes and **decrease** the **metabolism** of the drug itself and other drugs taken 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) (يتم تكسير الدواء من قبل نشاط الإنزيمات العالي قبل أن يؤدي فعاليته المطلوبة)	↑Increase (**Prolong**)
May occur	**Tolerance**: decrease in the pharmacological action of the drug by continuous or **repeated administration**	

	Enzyme Induction	Enzyme inhibition
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(*نشاط الانزيمات العالي للـphenytoin جعل مانع الحمل أيضًا الـmetabolism له عالي فالبتالي يتكسر بسرعة قبل أن يعطي التأثير المطلوب، واستمرار المرأة بأخذه بنفس 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)(*نشاط الانزيمات المنخفض للـwarfarin الـmetabolism يجعل أيضاً الـerythromycin منخفض، فبالتالي يقل تكسيره فلا يتم التخلص منه بسرعة، وبقاؤه في الجسم طويلًا يسبب زيادة تأثيره ويجلس بالجسم اطول ويسبب نزيف)
Examples of Enzyme inducers/inhibitors (حفظ)	Alcohol - Phenytoin(antiepileptic) Phenobarbitone (hypnotic)-Cigarette smoking - Rifampicin(Anti TB)	Grape fruits - Erythromycin(antibiotic)-Ketoconazole(antifungal) – Cimetidine

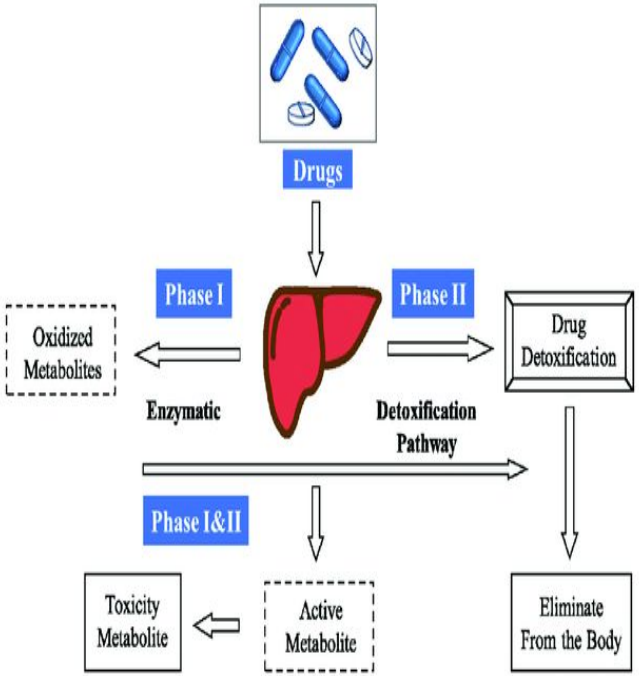
Quizlet

SUMMARY AND REVISION

I-CLICK FOR USEFUL VIDEO!!
2-CLICK "PHARMACOKINETICS DRUG METABOLISM".



- Drug metabolism
- Phases of metabolism
  - Phase I reactions - Oxidation
  - Reduction/hydrolysis reactions
- Phase II reactions - conjugation
  - Glucuronide
  - Sulfate
  - N-acetylation
  - Methylation
  - Glutathione/amino acid
- Drug interactions involving metabolism
  - Enzyme induction
  - Enzyme inhibition
- Factors affecting metabolism
- First-Pass effect



MCQ

Q-1 Which of these is an enzyme inducers?			
A-Allopurinol.	B-Ketoconazole.	C-Rifampicin.	D-Grapefruits
Q-2 Which of these affect metabolism?			
A-Age.	B- Metabolism of Isoniazid.	C-Diseases.	D- All of the above
Q-3 Where is MAO metabolized?			
A-Cytoplasm	B-Mitochondria.	C-Microsomes.	D-Lysosomes
Q-4 Example of a prodrug			
A-Moclobemide.	B-Warfarin.	C-Levodopa.	D-None of the above

1-C

2- D

3-B

4-C

SAQ

Q-1 What is the name of Xanthine oxidase inhibitor?

Q-2 What is an example of a an antiepileptic?

Answers

1-Allopurinol

2-Phenytoin

SAQ

Q-3 list 3 of Phase I Reactions Results?

Q-4 What are the cellular sites of drug metabolism in liver

Answers

1-slide 10

2- microsomal
Cytoplasm
lysosomes
Mitochondria

DONE BY THE AMAZING TEAM

You GOT THIS!

Shahed Bukhari
Kadi aldossari
Hend Almogary
Razan Almohanna
razan almanjomi
Noura bin hammad
Lina alyahya
Tharaa Alhowaish
Reema Aljubreen
Reema Alhussien
*OUR AMAZING Q BANK
Renad Alayidh

Mohammed Alrashod
Mohammed aloraini
Musaed almutairi
Mohammed al-zeer
Ibrahim alharbi
Hamad Alotaibi
Ahmed Abdualaziz

Leader | Khalid Al Rasheed | Reema Alquraini

Contact us:Pharmacology442@gmail.com