Drug metabolism

Drug metabolism (biotransformation)

- *A group of* chemical reactions which leads to modification of drugs.
- Drugs are converted from one form to another making them more/less active and finally inactive to leave the body

Sites of metabolism:

A. Liver " Hepatic " (The major site)

B. Extrahepatic sites e.g.

1. **Kidney**
2. **Lung**
3. **Skin**
4. **Plasma (blood)**
   - *COMT (Catechol-O-Methyl Transferase)*
   - *Esterase*
   - *Amidase*
5. **Intestinal mucosa and lumen (GIT)**
   - **Gut flora** :
     - *Glucourindase* (glucourinal drug-glucouronic acid)
     - *Azoreductase*
   - **Gut mucosa** :
     - MAO (Monoamine Oxidase)
     - Sulphatase

Azo- : means linkage between two nitrogen

Liver (Hepatic site):

The three major sites are

1) Microsomes: ER

- Microsomal enzyme system mixed function oxidase → mono-oxygenases
- Its components include: cytochrome P450 and heme binding protein.
  - Flavoprotein (co-enzymes in redox reaction) NADPH
  - Molecular oxygen Mg^{+2} Drug + enzyme +oxygen molecule +NADPH +Flavoprotein
  -

P450 is found all over the body but mainly in the liver and intestinal mucosa.

2) Mitochondria:

By two mechanisms

- MAO (Monoamine Oxidase enzyme)
- Acetylation

3) Cytoplasm:

- Alcohol dehydrogenase

First-Pass Metabolism

- Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entering into the systemic circulation.
- A drug can be metabolized before the drug reaches the systemic circulation so that the amount reaching systemic circulation is less than the amount absorbed.

The first- pass metabolism usually occurs in:

- Liver
- gut wall
- gut lumen
- Portal blood
- Lung (in case of inhaler)

Result:

- Low bioavailability
- Short duration of action
- Decrease in the pharmacological action.
- As morphine**???**

Types of metabolic reaction:

1. Phase 1 reaction (***non synthetic***) → addition or removal.
2. Phase 2 reaction (***synthetic***) → conjugation reaction.

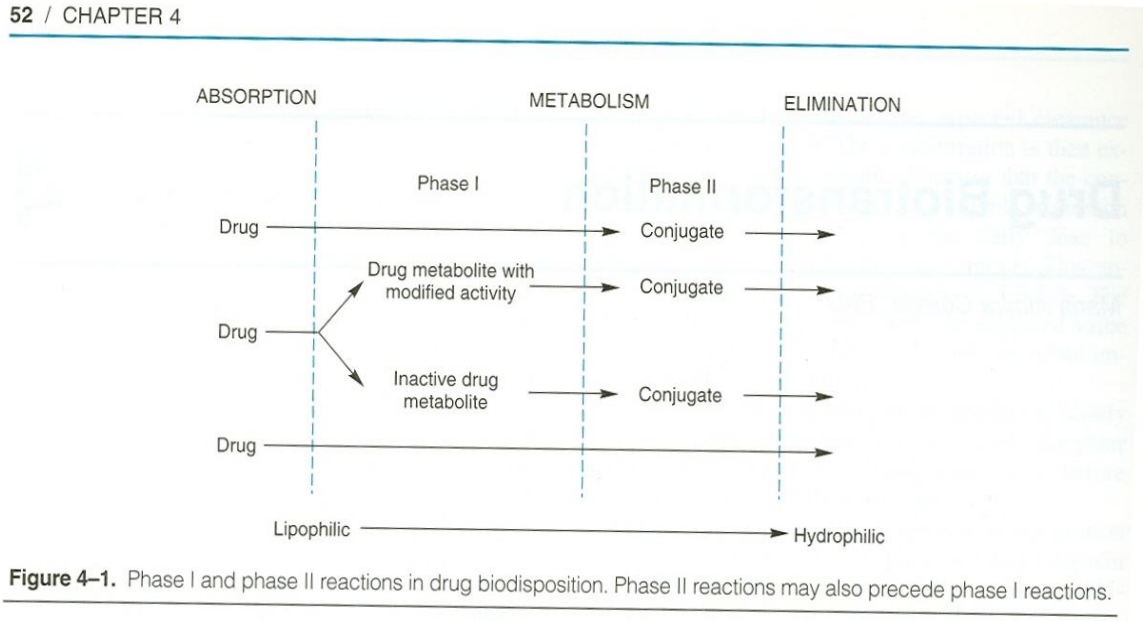

Figure 4–1. Phase I and phase II reactions in drug biodisposition. Phase II reactions may also precede phase I reactions.

Phase-I

- Metabolism brings about a change in the molecule by *oxidation*, *reduction*, *or hydrolysis* and often introduces a chemically active site into it. **The new metabolite may retain biological activity but have different pharmacokinetic properties** e.g. short or long half life, they may become inactive or more toxic. (see below)

Characteristics of Phase I Products (Result of Drug Metabolism)

1) Inactivation:

e.g: Oxidation of phenobarbitol and alcohol, Hydrolysis of acetylcholine

2) Conversion of active drug to another active one:

e.g, Diazepam → oxydiazepam (active)

Hypotonic drugs: they will have long duration of action.

3) Conversion of drugs to toxic metabolites:

e.g: Paracetamol → acetaminophen (hepatotoxic), Halothane → metabolite (hepatotoxic)

4) Activation of pro-drug (inactive → active):

e.g: Chloral hydrate → trichloroethanol, Enalapril → Enalaprilat, Cortisone → hydrocortisone

5) Products may pass to phase 2.

Phase-I Reactions

- Make the drug more polar and more water soluble by oxidation, reduction, or hydrolysis

1) Oxidation reaction:

- The most important
- Introduces or unmasks functional groups such as OH, NH_2, and SH.
- Can be:
  - Microsomal (cytochrome P450).
  - Non microsomal (mitochondria or cytoplasm)

a) Microsomal Oxidation:

Drug + O_2 + NADPH + H → metaoblized drug (polar) + H_2O+ NADP

1) Aliphatic hydroxylation
2) Aromatic hydroxylation
3) Amine oxidation
4) Sulphoxidation .

b) Non Microsomal oxidation:

- Oxidation **by soluble enzymes** in the **cytosol** or **mitochondria** of the cell.
  1) Dehydrogenase and oxidase:
  2) Monoamine Oxidase (MAO)
  3) Xanthine

2) Reduction:

a) Microsomal
b) Non-microsomal

3) Hydrolysis:

- ***All are non-microsomal.***
- **Esters** (-C-O-) and **Amides** (-C-N-)

Phase-II Reactions

- It involves the union of the drug (or metabolites from phase 1) with one of several polar, endogenous molecules to make it **hydrophilic**.
  - Endogenous molecules could be: such as methyl, acetyl, sulfate, amino acid, or glucuronic acid
  - These products of intermediary metabolism **forming a water soluble conjugate** which is **readily eliminated** by the kidney or if the molecular weight is more than 300 in the bile.
  - Phase –II reactions almost invariably **terminate** biological activity.

Conjugation:

By

1. Glucuronide conjugation (the only one which is microsomal)
2. Amino acid (glycin)
3. Acetylation (CH_3-CO)
4. Sulphate conjugation (SO_4)
5. Methylation reactions (CH_3): norepinephrine → epinephrine

Glucuronidation:

- Most common and the most important conjugation reaction.
- catalyzed by enzyme **glucuronyl transferase**
- This type of conjugation is deficient in neonates, making them vulnerable to drugs such as chloramphenicol.

Some drugs may bypass phase 1. Especially polar drugs.

Characteristics of phase II products:

1) Product = conjugate
2) Usually are **pharmacologically inactive**.
3) Polar
4) More readily excreted in urine.

Factors affecting metabolism: Modulation of liver microsomal enzymes:

1) Induction
2) Inhibition

Liver Microsomal inducers (MCQ)(IMP):

- Alcohol
- Cigarette smoking
- Barbiturates (phenobarbitones hypnotic)
- Phenytoin (antiepileptic → most of them are inducers)
- Rifampicin
- Griseofulvin (antifungal)
- Spironolactone

Use of inducers result in

1. **Increase the metabolism of the inducer.**
2. **Tolerance :** Decreases the inducer's pharmacological action.
3. **Increase the metabolism of co-administrated drugs (drug interaction)**
   - E.g. Barbiturates and warfarin → thrombosis.
   - Phenytoin and oral contraceptive (the woman gets pregnant)
4. **Increase tissue toxicity by metabolite.**
   - E.g. Paracetamol , phenacetin .
5. **As therapy.**
   - E.g. Phenobarbitone (given to babies with physiological jaundice to induce liver microsomal enzymes) and hyperbilirubinemia.

Liver microsomal inhibitors: (MCQ)(IMP)

- Cimetidine (anti-peptic ulcer)
- Erythromycin (antibiotic)
- Ketoconazole (antifungal)
- Grapefruit
- Probenecid

Use of inhibitors result in:

- Impede the metabolism and excretion of the inhibitor and Co-administered drugs, thus increasing $t_{1/2}$.
- Prolong the action of the inhibitor and co- administrated drugs → increased pharmacological activity

Factors modifying drug action:

They are factors that can alter or change the effect of drug on various

They include

- Physiological factors.
- Pathological factors.
- Genetic factors.
- Environmental factors.
- Interaction with other drugs

1) Physiological factors:

Age, sex, pregnancy, lactation.

A- Age:

1- Newborn: **-MCQ**

- Low acid secretion (gastric secretion).
- low microsomal enzymes (glucuronyl transferase).
- Low plasma protein binding.
- Low glomerular filtration and tubular secretion(Elemination).
- Immaturity of BBB in neonates.
- All the previous factor are responsible for increasing the bioavalability of drug → produces greater and more prolonged effects

2- Old age:

- ↓ liver functions
- ↓ kidney functions
- Increase sensitivity to CNS depressants (e.g. diazepam, morphine).
- ↓ plasma protein binding.(more free drug → wide range of distribution)
- All the previous factor are responsible for increasing the bioavalability of drug → produces greater and more prolonged effects

B- Sex:

- testosterone increases the rate of biotransformation of drugs.
- Decreased metabolism of some drugs in female (diapzam)

C- Pregnancy:

- Inc cardiac output, leading to increased renal blood flow and glomerular filtration and increased renal elimination of drugs.
- Maternal plasma albumin concentration is reduced → so, increased free drug (bioavailability) and hence prolong the action of drug

- Lipophilic drugs cross placental barrier + slowly excreted.
- Inc metabolic rate of some drugs
- Inc GFR and renal elimination .

2) Pathological Factors:

A- *Liver Disease*: -MCQ-

- prolongation of action. →Inc Half life of drugs ($T_{1/2}$).
- Decreased plasma protein binding for drug → adverse effects (increased free form → increase action).
- Decreased hepatic blood flow → decreases clearance of drug, especially drugs with high molecular weight.
- Impaired liver microsomal enzymes (see page 3) → decreased metabolism → increase action

B- Renal Disease:

- Dec GFR → less elimination → longer duration of action.
- Dec tubular function
- Dec plasma albumin .

C- ***Malnutrition:***

- Dec plasma protein binding of drugs.
- Dec amount of microsomal enzymes.

➔ Inc portion of free unbound drug → can u tell the effect ??

3) Genetic Factors:

Pharmacogenetics:

- Is the study of the relationship between genetic factors and drug response
- Abnormal drug reaction due to genetic disorder (idiosyncrasy, see below).
- genetic polymorphism (more than one form) : is the existence in a population of 2 or more phenotype with respect to the effect of a drug

4) Environmental Factors:

microsomal enzyme inducers or inhibitors: explained above

5) Interaction with other Drugs.

DRUG COMBINATION (Drug-Drug Interaction)

- When 2 or more drugs are taken at the same time (drug-drug interaction).
- Both drugs act at same target site exerting synergism(addition , potentiation) or antagonism
- Drugs may act at same or different receptors or process.

Side effects: many unwanted effects, are medically minor and need not to stop the drug, called side effects.

- **Adverse reactions:** harmful or seriously unpleasant effects occurring at therapeutic doses and which call for reduction of dose or withdrawal of the drug and /or forecast hazards from future administration.
- **Toxicity:** Direct action of the drug, often at high dose, damaging cell.

  e.g. liver damage from paracetamol over dose,

  8^{th} cranial nerve damage from gentamicin .

All the drugs are said to be toxic in over dose

However, Some times drugs in ordinary dose may become toxic due to under lying abnormality in patient .

e.g. in renal impairments- drugs will remain in the body and not excreted so they may have an exaggerated effects on the patient.

Classification of adverse effects:

Type "A" OR Type "1"

- 75% of all adverse reactions.
- unwanted effects related to the main pharmacological
- actions of the drug that occur when the drug produces greater therapeutic effect than is necessary.
  - warfarin → anticoagulant → bleeding.
  - Insulin → normoglycemia → hypoglycemia.
- they can occur in every one
- they are common
- they are predictable
- they are dose dependent
- skill management can reduce their incidence
- They are mostly part of normal pharmacology of drug.

Type "B"

- are bizarre reactions. (Bizarre= strange, weird, or unexpected)
- they are less than 25% of adverse effects
- only occur in some people
- not a part of normal pharmacology of drug
- Non dose related
- Cannot be predicted.
- Types:

a. Hypersensitivity (allergic) reaction:

- allergic or other immuonologic responsivness to drugs.
- Antigen-antibody reactions (anaphylactic reaction) (anaphylactic means: It is an immediate hypersensitivity reaction on exposure to specific antigen leading to life threatening respiratory distress followed by vascular collapse)
- Unpredictable.
- Require prior exposure to the drug.
- Rashes, hypotension, bronchospasm.

b. Idiosyncrasy: -MCQ-

- is abnormal response to the drug due to genetic disorder.
- unrelated to pharmacological reaction
- Occurs in small proportion of patient. E.g.
- Succinyl choline apnea.
- Malignant hyperthermia.
- Favism.

- Porphyria.

Type "C" (continuous)

due to long term use of drugs

- ❖ e.g. analgesic nephropathy
- ❖ tardive dyskinesia with neuroleptics

Type"D" (delayed)

a. Teratogenesis:

- usually occur at 1st trimester.
- Is a congenital malformations occurring in the fetus due to exposure to drugs during pregnancy.

b. Carcinogenesis:

- is ability of some substances to induce cancer.

E.g. stilbesterol → adenocarcinoma of vagina in female offspring

Type "E" (ending of use) where discontinuous is too abrupt.

e.g. This is due to the receptors down-regulation that is caused by the agonist drug and their up-regulation by the antagonist drug. So when an agonist is administered the receptors are decreased while when an antagonist is administered, the receptors are increased. So when propanlol (B-blocker or an antagonist drug for epinephrine) is administered, the number of receptors will increase but most of them will be blocked by the drug and little remaining will be the available ones for epinephrine binding so the binding of epineohrine will decrease and the HR will decrease as well. NOW, if propanlol was stopped abruptly, the receptors will remain very many and the inhibition will stop so this may cause an even higher blood pressure than the patient had.

These adverse effects may be

irreversible

- As in paracetamol's hepatotoxicity and
- Aminoglysides' (gentamycin) damaging effect on the 8th cranial. nerve

Reversible

e.g. morphine poisoning reversed by administration of Naloxone.