Drug metabolism

Is the method by which drugs are inactivated or biotransformed by the body in two ways :-

1. **Reducing lipid solubility :-**

Most drugs are lipid soluble, however, the kidney – can excrete only water soluble substances, therefore, one function of metabolism is to convert lipid – soluble drugs into more water soluble metabolites to <u>favor</u> its elimination in urine.

2. **Altering biological activity :-**

Leads to abolision of biological activity through various steps:-

1) Conversion of pharmacologically <u>active</u> substance to an <u>inactive</u> substance (common pathway).

2) Conversion of one pharmacologically <u>active</u> substance to another <u>active</u> substance (prolongation of drug action).

3) Conversion of pharmacologically <u>inactive</u> substance to an <u>active</u> substance (pro-drug).

e.g. Zidovudine (inactive)→ Zidovudine triphosphate(active)

Reaction of drug metabolism

The liver is the most important drug metabolizing organ, as well as the kidney, lung, gut mucosa, skin and plasma.

1. **Phase I :-(catabolic reaction)**

-Phase I reactions convert lipophilic drugs into more polarmolecules by introducing or unmasking a polar functional group
-Metabolism brings about a change in the drug molecule by **oxidation, reduction or hydrolysis.**Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity

Oxidation is the most common, undertaken by microsomal mixed – function oxidases, The P450 system is important for the metabolism of many endogenous compounds (such as steroids,lipids) and for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP,is a super family of heme -containing isozymes that are located in most cells, but primarily in the liver and GI tract which incorporates molecular Oxygen into a drug molecule forming new hydroxyl group.

➢ Cytochrome P450 isoenzymes are grouped into families called **CYP** followed by numeral.

➢ **CYP$_1$, CYP$_2$, CYP$_3$** are concerned with human metabolism.

CYP$_3$A→ most important in drug biotransformation. Considerable amounts of **CYP3A4** are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam*

➢ **Also others : CYP$_2$D$_6$, CYP$_2$C$_9$, CYP$_2$E** …….

Each enzyme is encoded by separate gene, and gene variation can lead to differences between individuals and ethnic groups in drug metabolism.These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme.

❖ Phase I oxidation of some drugs results in formation of **epoxides** which are short – lived but highly reactive and cause cell toxicity

➢ **Glutathione** from the liver, combines with epoxides rendering them inactive, this is a defense mechanism against liver damage by some drugs e.g. paracetamol.

➢ **Phase I reactions not involving P450 system -** e.g. These include amine oxidation eg;, oxidation of catechol- amines or histamine, alcohol dehydrogenation (e.g, ethanol oxidation), esterases (e.g, metabolism of aspirin in the liver), and hydrolysis (e.g, of procaine).

2. **Phase II (conjugation):-**

Metabolism involves union of drug with water soluble – polar – endogenous molecules forming water soluble conjugate eliminated by the kidney or bile. Conjugation of drugs may occur with glucuronic acid, sulfuric acid, acetic acid, amino acid, usually more water-soluble compounds that are often therapeutically inactive. A notable exception is morphine-6-glucuronide, which is more potent than morphine**..**

3) **Reversal of order of the phases** : not all drugs undergo phase I and phase II reactions in that order e.g. isoniazid is first acetylated (phase II) and then hydrolyzed to iso nicotinic acid which is phase I reaction.

Enzyme induction

The capacity of the body to metabolize drugs can be altered by certain drugs or substances, especially when used for long time, leading to ↑ the amount and activity of

metabolizing enzyme. i.e. **enzyme induction, e.g. of enzyme inducer : chronic ethanol, tobacco smoke and rifampicin, phenytoin, phenobarbiton.**

Consequences of increased drug metabolism include:

1-decreased plasma drug concentration

2-decreased drug activity if metabolites are inactive

3-decreased therapeutic effect

4-increased therapeutic activity &toxicity if metabolites are active

Effect of enzyme induction on drug therapy

1) Drug interactions : e.g. failure of oral contraceptives.

   2)Disease : e.g. anti – epileptics – phenytoin – can induce vit.Dmetabolizing Enzyme → ↑ in break down of dietary and endogenous vit.D → osteomalacia.

3) Tolerance to drug therapy → suboptimal treatment, e.g. with anti epileptics.

4) Variability in response to drugs, e.g. with smoking or alcohol intake.

5) Increase liability to drug toxicity, e.g. **paracetamol poisoning due to enzyme induction by rifampicin → epoxide formation.**

6) -**Certain polycyclic hydrocarbons (air pollutants)can induce CYP1A** which has implication for certain drugs eg: warfarin metabolized by this enzyme(IF induced)) will lead to decrease warfarin activity
7) rifampin, an antituberculosis drug significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) **protease inhibitors,** thereby diminishing their ability to suppress HIV replication.

Enzyme inhibition

➢ More selective than enzyme induction.

➢ Consequence may be more profound than enzyme induction.

➢ Basis of a number of drug interactions e.g. **cimitidine** inhibits a number of P450 enzymes.

Also allopurinol, selegiline, enalapril, sodium –valproate, erythromycin, quinolone, MAO inhibitors

-Omeprazole inhibits 3 of CYP isozymes responsible for warfarin metabolism leading to greater inhibition of coagulation & risk of hemorrhage.

- The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes

-Natural substances like grape fruit juice may inhibit CYP3A4 (amlodipine , clarithromycin, indinavir metabolized by this enzyme) therefore ,increases the therapeutic &/or toxic effects of these drugs .
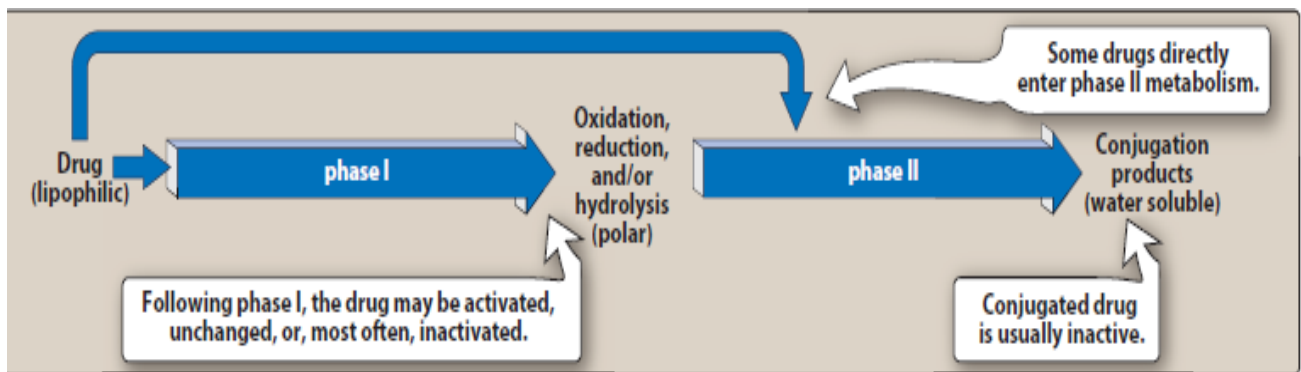
Elimination of drugs

Will be through:

1- Kidney2- Bile   3- Intestine   4- Lung   5- Milk

-Drugs are eliminated from the body after being partly or wholly converted to water soluble metabolites..

- Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

Renal elimination Involves :-

➢   **Glomerular filtaration :-**

        The rate at which a drug enters the glomerular filtrate depends on the concentration of free drug in plasma water and its molecular weight.

-Free drug passes through slits in the capillaries into Bowman's space with glomerular filtrate.

-Molecular weight **< 10000** (includes almost all drugs) pass easily through the pores of glomerular membrane.

-Lipid solubility and PH do not influence passage of drugs into the glomerular filtrate. variations in GFR and protein binding of drugs do affect
this process.

> **Renal tubular secretion :-**

Drug that is not transferred into the glomerular filtrate passes with efferent arterioles → capillary plexus surrounding the proximal tubules.

-Cells of the proximal renal tubule actively transfer strongly charged molecules form plasma → tubular fluid.

- There are two systems, one for **acids** → penicillin and probenecid, and another for **base** → amiloride.

-Competition between drugs for the carrier can occur for each system.

> **Renal tubular reabsorption**

-As the drug moves towards the distal convoluted tubules, its concentration ↑.

-If the drug is nononized (lipid soluble) it diffuses back into the systemic circulation.

-If tubular fluid becomes more alkaline, acidic drug ionized, reabsorption ↓ and alkaline drugs become unionized ↑ reabsorption.

-Manipulation of urine PH to ↑ the ionized form of the drug will ↑ clearance of an undesirable drug, e.g. **Na – bicarbonate** is given to alkalinize urine to Rx **aspirin overdose**. (Ion – trapping) i.e. make urine basic → trapping of acidic drug.

-if over dose with a weak base eg: cocaine, acidification of urin with NH_4CL ,leads to protonation of the drug and increases its clearance

❖ **Faecal elimination**

-A proportion of a drug intended for systemic effect taken by mouth remains in the bowel and excreted in faeces.

-A drug may diffuse passively into the gut lumen from the blood depending on PH and PKa.

❖ **Biliary excretion**

   Active transport system for acidic and other for basic drugs (similar to proximal renal tubules).

❖ **Pulmonary elimination**

   The lungs are the main route for elimination of volatile anesthetic drugs.

Pharmacogenetics

-●Study of genetic variation that gives rise to differing response to drugs, and refers to genetic differences in metabolic pathways which can affect individual responses to drugs ,both in terms of therapeutic &adverse effects **((genetic polymorphism)** eg:

●-One in 3500 caucasians has less efficient variant of butyrylcholinesterase that metabolizes suxamethonium ,so drug effect is prolonged with slower recovery from surgical anesthesia.

●- Variation in N-acetyltransferase gene divides people into slow &rapid acetylators with different $t_{1/2}$&blood conc. Of isoniazide , procainamide& other drugs metabolized by this enz.

●-Deficincy in thiopurin methyl transferaseenz that metabolizes 6-mercaptopurin &azathioprine, diverts the metabolism to proceed by other pathways producing toxic bone marrow metabolites causing sever bone marrow depression

●   *glucose 6-phosphate dehydrogenase* **(G6PD);**
● G6PD Deficiency is a hereditary abnormality in the activity of an erythrocyte enzyme. This enzyme (G-6-PD), is essential for assuring a normal life span for red blood cells, and with NADPH will **reduced glutathione** to get rid of free radicals that cause oxidative damage. This enzyme deficiency may provoke the sudden destruction of red blood cells and lead to hemolytic anemia with jaundice following the intake of fava beans, infection and various drugs <u>primaquine</u> , <u>Sulfonamides</u> , <u>aspirin</u>, <u>nalidixic acid</u>, <u>nitrofurantoin</u>, <u>isoniazid</u>, <u>dapsone</u>, and <u>furazolidone</u>

CYP2D6 mutations result in very low capacities to metabolize substrates. Some individuals, for example, obtain no benefit from the opioid analgesic *codeine,* because they lack the CYP2D6 enzyme that activates the drug

 Similar polymorphisms have been characterized for the **CYP2C** subfamily of isozymes. For instance**, *clopidogrel*** (a prodrug }carries a warning that patients who are poor CYP2C19 metabolizers have a higher incidence of cardiovascular events (for example, stroke or myocardial infarction) when taking this drug.