Dr. Iman Naji **lec 6.**

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 cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver to favor its elimination in urine.

2. Altering biological activity :-

Leads to abolision of biological activity through various steps:-

1) Conversion of pharmacologically active substance to an inactive substance (common pathway).

2) Conversion of one pharmacologically active substance to another active substance (prolongation of drug action).

3) Conversion of pharmacologically inactive substance to an active 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 polar molecules by introducing or unmasking a polar functional group such as –OH or –NH2.
-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_3A→ most important in drug biotransformation.
-Considerable amounts of **CYP_3A4** are found in intestinal mucosa, accounting for first-pass metabolism of drugs suchas chlorpromazine and clonazepam

- **Also others : CYP_2D_6, CYP_2C_9, CYP_2E** …….

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 alarge 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 (eg, ethanol oxidation), **esterases** (eg, metabolism of aspirin in the liver), and **hydrolysis** (eg, 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 CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions

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**, **carbamazepine.**

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.D metabolizing 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(IFinduced)) 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

Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity.

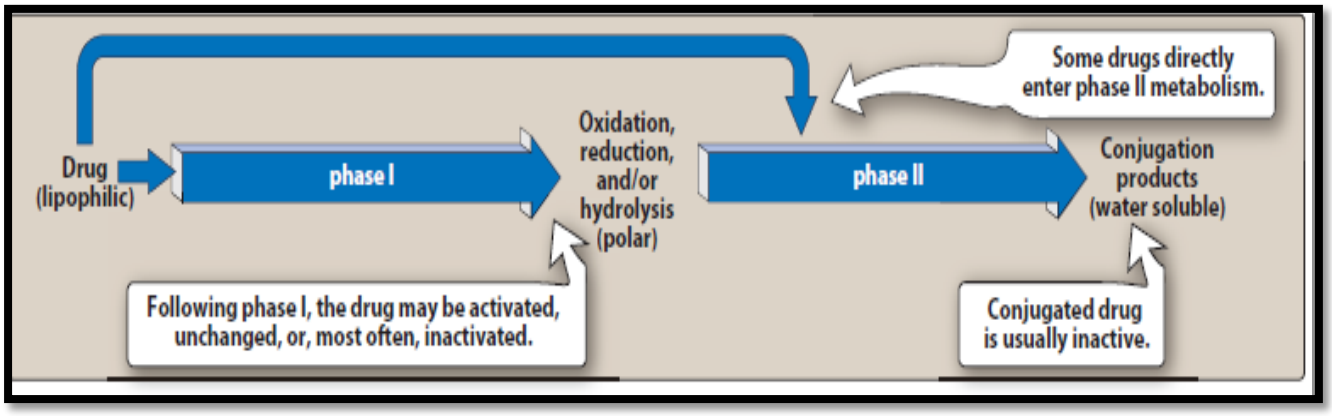
- Basis of a number of drug interactions e.g. **cimitidine** inhibits a number of P450 enzymes.

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 inhibits 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.Ofisoniazide,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); glucose 6-phosphate dehydrogenase (G6PD); deficiency of this enzyme confers partial resistance to malaria
-(X linked recessive)
- 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 primaquine , Sulfonamides , aspirin, nalidixic acid, nitrofurantoin, isoniazid, dapsone, and furazolidone

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

Similarpolymorphisms have beencharacterized for the **CYP2C** subfamily of isozymes. Forinstance**, clopidogrel**(a prodrug}carries a warning that patients

whoare poor **CYP2C19** metabolizers have a higher incidenceof cardiovascular events (for example, stroke or myocardialinfarction) when taking this drug.

Malignant hyperthermia

- is autosomal dominant is due to a mutation of the ryanodine receptor (type 1), located on the sarcoplasmic reticulum, the organelle within skeletal muscle cells that stores calcium

-RYR1 opens in response to increases in intracellular Ca^{2+} level mediated by L-type calcium channels, thereby resulting in a drastic increase in intracellular calcium levels and muscle contraction, massive metabolic reaction ,increased carbon dioxide production, metabolic and respiratory acidosis, accelerated oxygen consumption, heat production, activation of the sympathetic nervous system, hyperkalemia, disseminated intravascular coagulation (DIC), and multiple organ dysfunction and failure, tachycardia, muscle rigidity, tachypnea, and hyperkalemia

- It is triggered in susceptible individuals primarily by the volatile inhalational anesthetic agents(halothane) and the muscle relaxant succinylcholine

Treatment is with dantrolene and rapid cooling along with other supportive measures

Albinism

Is the "congenital absence of any pigmentation or coloration in a person, animal or plant, resulting in white hair and pink eyes in mammals

-albinism" can occur for a number of reasons aside from inheritance including genetic mutations, diet, living conditions, age, disease, or injury

-The production of melanin occurs in melanocytes in a complex process involving the enzyme tyrosinase. Mammals have a gene that codes for the presence of tyrosinase in cells. If this gene is altered or damaged, melanin cannot be reliably produced and the mammal becomes an albino.

-Besides the TYR gene, several other genes can cause albinism. This is because other hormones and proteins are involved in melanin production, the presence of which is genetically determined.

-All the genetic traits for albinism are recessive traits