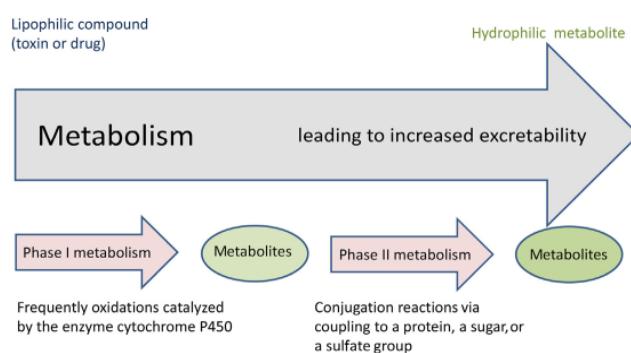


METABOLISM OF DRUGS

- Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid-soluble) compounds polar (lipid-insoluble) so that they are not reabsorbed in the renal tubules and are excreted.
- Most hydrophilic drugs, e.g. streptomycin, neostigmine, pancuronium, etc. are little biotransformed and are largely excreted unchanged. Mechanisms which metabolize drugs (essentially foreign substances) have developed to protect the body from ingested toxins.
- The primary site for drug metabolism is liver; others are—kidney, intestine, lungs and plasma.



RESULTS OF BIOTRANSFORMATION/ METABOLISM-

- Biotransformation of drugs may lead to the following.
 - (i) **Inactivation**- Most drugs and their active metabolites are rendered inactive or less active, e.g. ibuprofen, paracetamol, lidocaine,
 - (ii) **Active metabolite from an active drug**- Many drugs have been found to be partially converted to one or more active metabolites; the effects observed are the sum total of that due to the parent drug and its active metabolite(s). eg codeine to morphine.
 - (iii) **Activation of inactive drugs**- Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called a prodrug. The prodrug may offer advantages over the active form in being more stable, having better bioavailability or other desirable pharmacokinetic properties or less side effects and toxicity. Some prodrugs are activated selectively at the site of action. For example- levodopa.

ENZYMES INVOLVED IN METABOLISM-

- **Microsomal Enzymes**- Microsomal enzymes are typically found in the endoplasmic reticulum of hepatocytes. They are also found in intestinal mucosa, kidneys and lungs. Microsomes are fragments of endoplasmic reticulum and attached ribosomes that are isolated together when homogenized cells are centrifuged. There are several microsomal enzymes, including flavin monooxygenases, cytochrome P450, NADPH cytochrome c reductase, UDP Glucuronosyltransferases (UGT), glutathione-S-transferases, epoxide hydrolases, etc. Microsomal enzymes are inducible by drugs, diet and other agencies.
- **Non-microsomal Enzymes**- These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma. The esterases,

amidases, some flavoprotein oxidases and most conjugates are non microsomal. The non microsomal enzymes are not inducible but many show genetic polymorphism.

Both microsomal and non microsomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids. The amount and kind of drug metabolizing enzymes is controlled genetically and is also altered by environmental factors. Thus, marked interspecies and interindividual differences are

seen, e.g. cats are deficient in UGTs while dogs are deficient in NATs. Up to 6-fold difference in the rate of metabolism of a drug among normal human adults may be observed. This is one of the major causes of individual variation in drug response.

TYPES OF BIOTRANSFORMATION REACTIONS-

Biotransformation reactions can be classified into:

- (a) **Nonsynthetic/Phase I/Functionalization reactions:** a functional group is generated or exposed- metabolites may be active or inactive. This phase reaction includes oxidation, reduction, hydrolysis, cyclization and decyclization.
- (b) **Synthetic/Conjugation/ Phase II reactions:** Phase II reactions consist of adding hydrophilic groups to the original molecule, a toxic intermediate or a nontoxic metabolite formed in phase I, that requires further transformation to increase its polarity. These involve conjugation of the drug or its phase I metabolite with an endogenous substrate, usually derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile. Conjugation reactions have high energy requirements.

NONSYNTHETIC OR PHASE I REACTIONS

- **Oxidation-** This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are: hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation, oxidative deamination, etc. In many cases the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone/epoxide/superoxide intermediates which then convert to stable compounds. Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involves a cytochrome P-450 hemoprotein, NADPH, cytochrome P-450 reductase and molecular O₂. More than 100 cytochrome P-450 isoenzymes differing in their affinity for various substrates (drugs), have been identified. Barbiturates, ibuprofen, paracetamol, steroids, and many other drugs are oxidized in this way. Few drugs like ranitidine, clozapine are oxidized at their N, P or S atoms by a group of flavin-monooxygenases that are also located at hepatic endoplasmic reticulum, but are distinct from CYP enzymes.
- **Reduction-** This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction. Drugs primarily reduced are chloral hydrate, halothane, warfarin.
- **Hydrolysis-** Hydrolysis is any chemical reaction in which a molecule of water breaks one or more chemical bonds. amides and polypeptides are hydrolysed by amidases and peptidases. In addition, there are epoxide hydrolases which detoxify epoxide metabolites of some drugs generated by CYP oxygenases. Hydrolysis occurs in the

liver, intestines, plasma and other tissues. Examples of hydrolysed drugs are choline esters, procaine, lidocaine etc.

- **Cyclization-** This is formation of ring structure from a straight chain compound, e.g. proguanil.
- **Decyclization-** This is the opening up of the ring structure of the cyclic drug molecule, e.g. barbiturates, phenytoin. This is generally a minor pathway.