St Peter's Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Medicinal chemistry I

Subject Code: BP402T

Drug Metabolism

Metabolism is the body's mechanism for processing, using, inactivating, and eventually eliminating foreign substances, including drugs. Drug exerts its influence upon the body, it is gradually metabolized, or neutralized. The liver, the blood, the lymph fluid, or any body tissue that recognizes the drug as a foreign substance can break down or alter the chemical structure of drugs, making them less active, or inert. Drugs also can be neutralized by diverting them to body fat or proteins, which hold the substances to prevent them from acting on body organs. Once a drug is metabolized, it is the kidneys that normally filter the neutralized particles, called metabolites, as well as other waste and water, from the blood. Drugs can also be excreted out of the body by the lungs, in sweat, or in feces. Drug metabolism is basically a process that introduces hydrophilic functionalities onto the drug molecule to facilitate excretion. Metabolism is defined as the process of polarization of a drug. This results in the formation of a metabolite that is more polar and, thus, less able to move into tissues and more able to be excreted from the body. Drug metabolism is a detoxification function the human body possesses to defend itself from environment hostility. Metabolism is a major mechanism of drug elimination. The first human metabolism study was performed in 1841 by Alexander Ure, who observed the conversion of benzoic acid to hippuric acid and proposed the use of benzoic acid for the treatment of gout.

PHASE I : REACTIONS

Phase I metabolism is likely to be the predominant pathway of biotransformation. The enzymes involved in Phase I reactions are primarily located in the endoplasmic reticulum of the liver cell, they are called microsomal enzymes. Phase I reactions are non-synthetic in nature, and generally produce more water soluble and less active metabolite. The most common phase I reactions are oxidative processes (aromatic hydroxylation; aliphatic hydroxylation; N—, O—, and S-dealkylation; N-hydroxylation; N-oxidation; sulfoxidation; deamination; and dehalogenation), reductive (azodye-reduction, nitroreduction) and hydrolytic reactions

Oxidation: Oxidation is normally the first step of drug metabolism. Mixed-function oxidases or monooxygenases is an important complex enzyme catalyses metabolic oxidation ofa large variety of endogeneous substances (steroidal hormones) and exogeneous substances(drugs). Some important metabolic oxidations are represented here:

Oxidation of carbon-heteroatom systems. Carbon-heteroatom systems (N, O, S) are commonly present in many drugs. They are metabolized by any of the following oxidation processes :

(a) Oxidation or hydroxylation of heteroatom: Ex: N-oxidation, N-hydroxylation, S-oxidation.

(b) Hydroxylation of carbon atom attached to the heteroatom followed by cleavage of carbon-heteroatom bond. Ex: N-dealkylation, S-dealkylation, O-dealkylation.

1. Oxidation and hydroxylation of heteroatom

N-Hydroxylation: Drugs containing non-basic nitrogen atom (amides), non-basic aromatic amines and basicamines are metabolized by N-hydroxylation.
Ex:

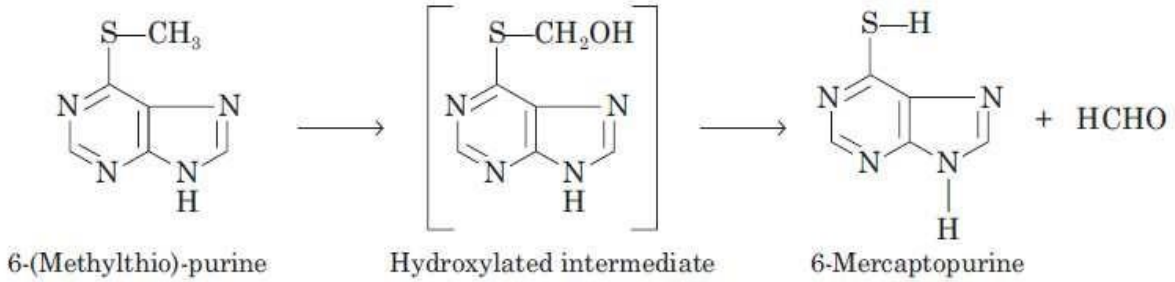
N-Oxidation: Compoun s possessing of basic nitrogen are metabolized by N-oxidation process.

Ex: Tertiary amines yield N-oxides.

S-Oxidation: Compounds possessing of carbon-sulfur bonds are metabolized to sulfoxides by S-oxidation.The sulfoxides may be excreted as urinary metabolites or oxidized to sulfones (—SO2—).

2. Dealkylations. The second type of oxidative biotransformation comprises dealkylations.

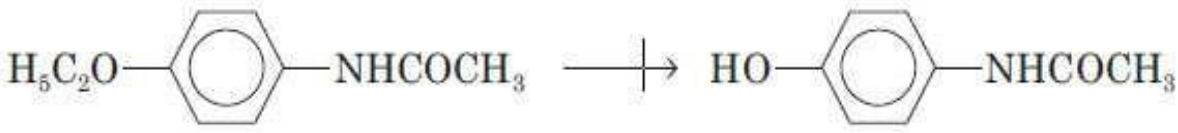
S-Dealkylation. S-Dealkylation involves oxidative cleavage of alkyl carbon-sulfur bonds



6-(Methylthio)-purine Hydroxylated intermediate 6-Mercaptopurine

N-Dealkylation. In the case of primary or secondary amines, dealkylation of an alkyl group starts at the carbon adjacent to the nitrogen; in the case of tertiary amines, with hydroxylation of the nitrogen (ex: Lidocaine).

O-Dealkylation. O-Dealkylation of drugs possessing C—O bond involves hydroxylation of α-carbon to form an unstable hemiacetal or hemiketal intermediates. These intermediates spontaneously cleave to form alcohol and carbonyl compound.



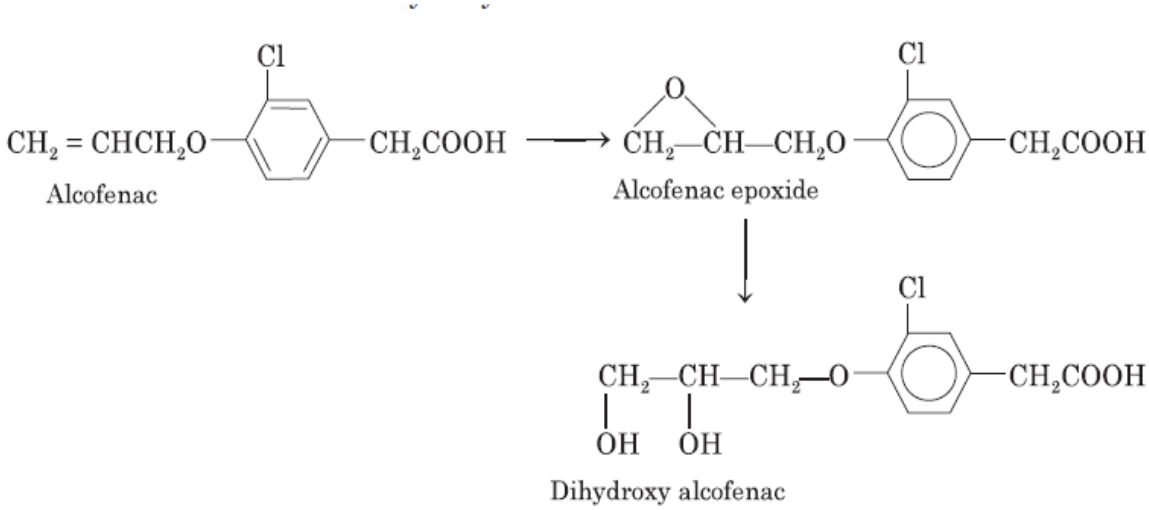
Phenacetin Paracetamol

Aromatic Hydroxylation: Aromatic hydroxylation is oxidation of aromatic compounds into phenols through the intermediate formation of highly reactive immediate i.e. arene oxide

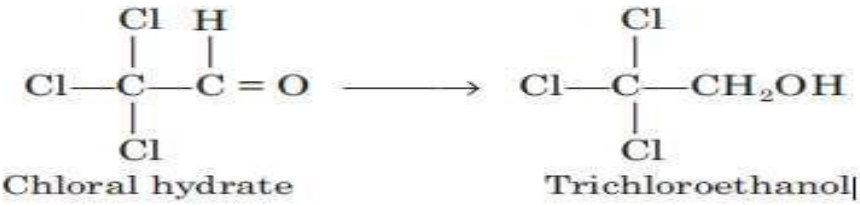
Ex: Many drugs containing phenyl groups (phenylbutazone, phenytoin, amphetamine, phenformin etc.) are metabolized by aromatic hydroxylation.

Oxidation of benzylic carbons: The carbons directly attached to aromatic rings are oxidized to aldehydes and carboxylicacids via alcohols.

Oxidation of olefins: Alcofenac is oxidized to dihydroxyalcofenac.



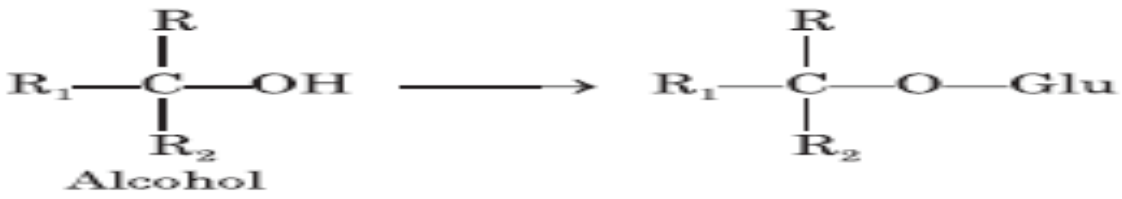
2. Reductive reactions: Drugs containing carbonyl, nitro, and azo groups are metabolized by reduction to alcohols and amines respectively. The reduced compounds are conjugated and eliminated from the body. Ex :

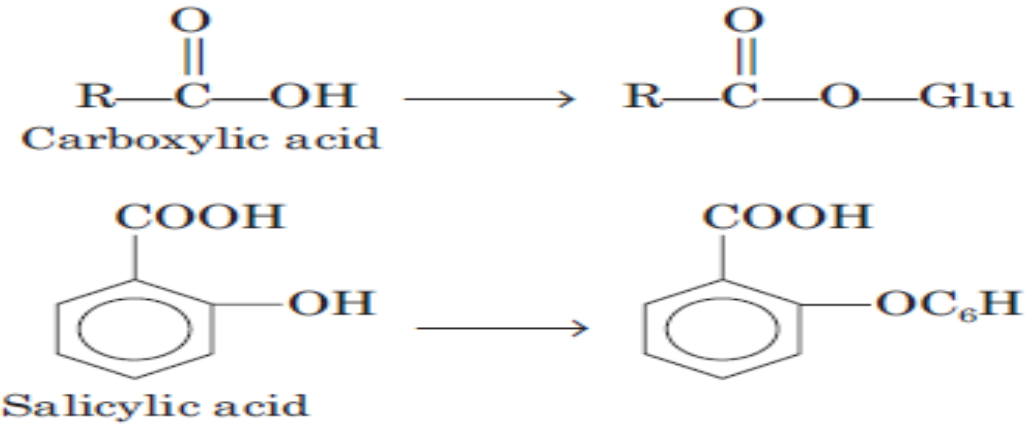


PHASE II : REACTIONS: Conjugation reactions are also known as phase-II reactions. Phase II pathways are synthetic reactions where the product or the metabolite from Phase I gets conjugated. This always produces a large, polar, metabolite that is readily excreted from the body. Some drugs are mainly conjugated and undergo very little oxidative metabolism.

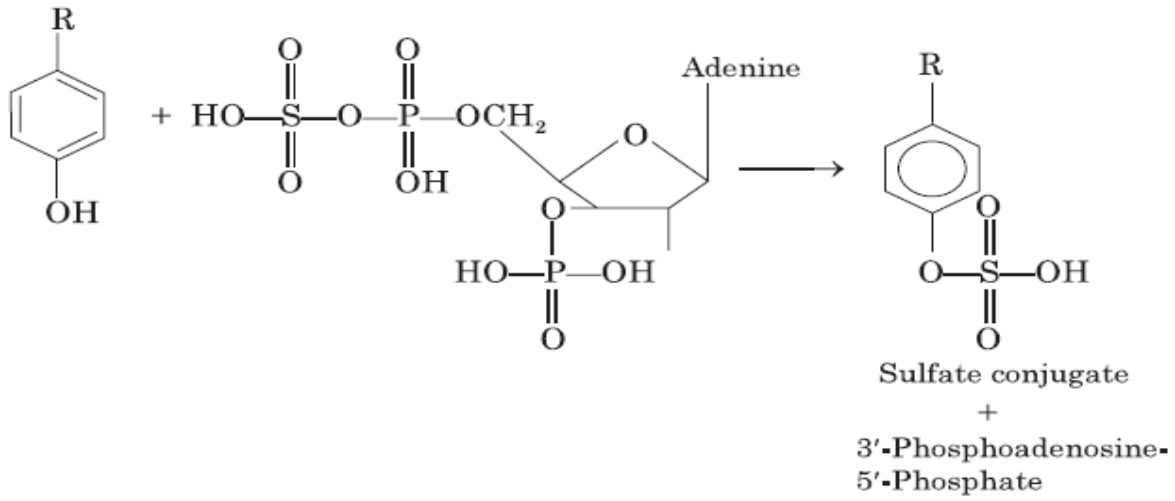
Phase II occurs by glucuronidation, sulfation, aminoacid conjugation, acetylation, methylation or glutathione conjugation to facilitate elimination. Phase II conjugation introduces hydrophilic functionalities such as glucuronic acid, sulfate, glycine, or acetyl group onto the drug or drug metabolite molecules. These reactions are catalyzed by a group of enzymes called transferases. Most trasferases are located in cytosol, except the one facilitates glucuronidation, which is a microsomal enzyme. This enzyme, calleduridine diphosphate glucuronosyl transferase (UGTs), catalyzes the most important phase II reaction, glucuronidation.

Glucuronidation. Glucuronidation involves conjugation of metabolite or drug molecule with glucuronic acid. In these reactions glucuronic acid molecule is transferred to the substrate from a cofactor (uridine-51-diphospho-α-D-glucuronic acid). Glucuronidation is catalyzed by various microsomal glucuronyl transferases. Glucuronides are generally inactive and are rapidly excreted into the urine and bile. Molecules associated with phenolic hydroxyl, alcoholic hydroxyl, and carboxylic acid groups undergo glucuronidation reaction.

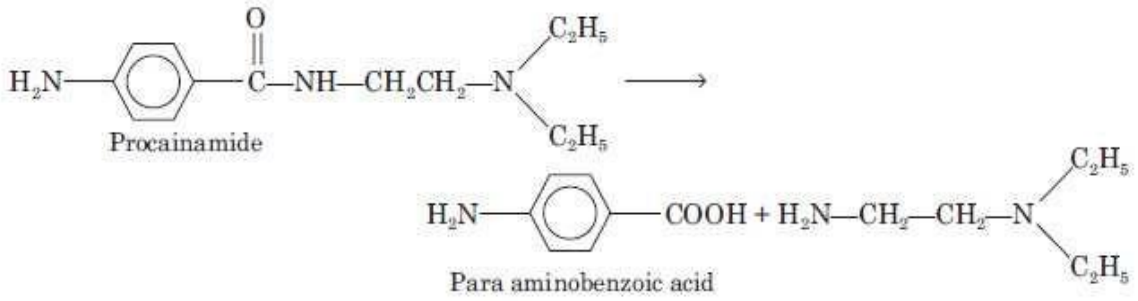




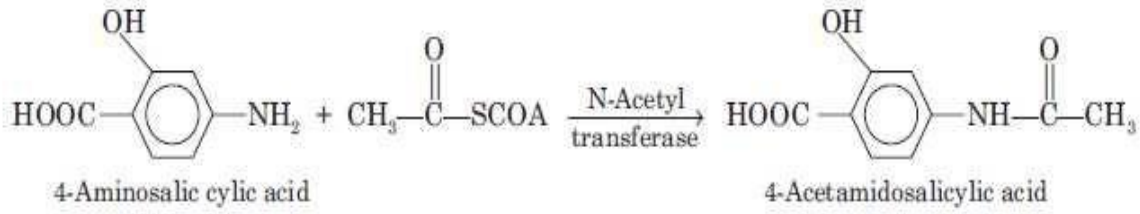
Sulfate Conjugation: Sulfate conjugation involves transfer of a sulphate molecule from the cofactor (31- phosphoadenosine-51-phosphosulfate) to the substrate (metabolite or drug moiety) by the enzymes (sulfotransferases). Sulphate conjugation is the common conjugation reactions of substrate molecules possessing of alcoholic hydroxyl, phenolic hydroxyl and aromatic amine groups. Ex:



Hydrolysis: Hydrolysis is also observed for a wide variety of drugs. The enzymes involved in hydrolysis are esterases, amidases, and proteases. These reactions generate hydroxyl or amine groups, which are suitable for phase II conjugation.



Acetylation: Acetylation is an important metabolic pathway for drugs containing primary amino groups. The acetylated conjugates are generally non-toxic and inactive. Ex: histamine, procainamide, para aminosalicylic acid (PAS), hydralazine, isoniazid.



Cytochrome p450: The cytochromes P450s [CYPs] are membrane bound proteins with an approximate molecular weight of 50 kD, and contain a heme moiety. There are about 30 human cytochrome P450enzymes out of which only six, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4are the metabolising enzymes.

Factors affecting the drug metabolism

A number of factors may influence the rate of drug metabolism. They are ;

1. **Physicochemical properties of drugs**. Molecular size, shape, acidity or basicity, lipophilicity, pKa, and steric and electronic characteristics of drugs influence its interaction with the active sites of enzymes.

2. **Chemical factors**. A large number of chemical substances such as drugs, insecticides etc. can increase the rate of drug metabolism due to increased rate of formation of newer enzymes or decreased rate of degradation of drug metabolising enzymes. Ex. Alcohol enhances metabolism of phenobarbitone, phenytoin etc.

3. **Diet.** The enzyme content and activity is altered by a number of dietary compounds. Fat free diet depresses cytochrome P450 levels since phospholipids, which are important components of microsomes become deficient.

4. **Genetic or hereditary factors.** Genetic and hereditary factors are the most significant factors in drug metabolism. Genetic differences among individuals or ethnic groups can lead to an excessive or prolonged therapeutic effect or toxic overdose.Ex: The enzyme CYP2D6 metabolises a large number of drugs. The activity of this enzymevaries widely among ethnic groups. About 1% of Arabies, 30% Chinese and 7-10% caucasionsare poor metabolizers of CYP2D6 drugs.

5. **Environmental factors:** Environmental factors such as smoking, alcohol consumption and concomitant drug therapy also influence the outcome of drug metabolism. Ex: Cigarette smoke produces polynuclear aromatic hydrocarbons. CYP1A2 metabolises the polynuclear aromatic hydrocarbons to carcinogens responsible for lung and colon cancer.

References:

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2. Foye's Principles of Medicinal Chemistry.
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4. Introduction to principles of drug design- Smith and Williams.
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6. Martindale's extra pharmacopoeia