Drug Metabolism and elimination pharmacology

Biotransformation or metabolism is a chemical alteration of the drug in the body. It makes non-polar (lipid-soluble) drugs; water-soluble (polar); so that they are not reabsorbed in the renal tubules and are excreted.

Most hydrophilic drugs e.g. streptomycin, neostigmine etc. are little biotransformed and largely excreted unchanged.

The primary site for drug metabolism is the liver; others are the kidney, intestine, lungs and plasma.

Biotransformation of drugs may lead to:

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).

Active drug with its active metabolite

1. Codeine - Morphine
2. Digitoxin - Digoxin
3. Imipramine - Desipramine
4. Amitriptyline - Nortriptylline

iii. Activation of inactive drug

Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called prodrug.

Prodrug and its active form
1. Enalapril - Enalaprilat
2. Prednisone - Prednisolone
3. Bacampicillin - Ampicillin

4. Acyclovir - Acyclovir triphosphate

Biotransformation reactions can be classified into:

1. Nonsynthetic / Phase I / Functionalization reactions -
2. Synthetic / conjugation / Phase II reactions

1. Phase I reactions

A functional group is generated and a metabolite may be active or inactive.

Non-synthetic reactions include

a. Oxidation

Involves addition of oxygen / negatively charged radical or removal of hydrogen / positively charged radical. Oxidation is one of the most important drug-metabolizing reactions.

Barbiturates, phenothiazines, imipramine, paracetamol, ibuprofen, steroids and many other drugs are oxidized and they involve a cytochrome P-450 enzyme.

b. Reduction

The reaction is the converse of oxidation and involves a cytochrome P-450 enzyme working in the opposite direction. Alcohol, quinolones are reduced. Examples of drugs primarily reduced include chloramphenicol, halothane, warfarin.

c. Hydrolysis

Involves removal of a water molecule. Hydrolysis occurs in the liver, intestines, plasma and other tissues.

Examples, lidocaine, procainamide, procaine.

d. Cyclization

Formation of a ring structure from a straight-chain compound e.g. proguanil.

e Decyclization

Opening of a ring structure of the cyclic drug molecule e.g. a barbiturate, phenytoin. This is a minor pathway.

Cytochrome P450 enzymes

Cytochrome p450 is a family of heme-containing enzymes that catalyze the conversion of lipophilic substances into hydrophilic molecules which can then be excreted by kidneys into the urine. It represents a major part of the body's powerful detoxification systems.

The cytochrome p450 system metabolizes endogenous and exogenous substrates through a variety of reactions including epoxidation, N-dealkylation, O-dealkylation,

S-oxidation, and hydroxylation. Exogenous substances (products ingested or absorbed) include not only pharmaceutical compounds given as therapeutic drugs, but also foodstuffs and dietary components, and occupational pollutants and industrial chemicals.

The cytochrome p450 mixed-function mono-oxygenase system is probably the most important element of phase I metabolism in mammals. More than half of all drugs are primarily cleared by the cytochrome p450 system.

As a group, these enzymes are often referred to as drug-metabolizing enzymes (DME). The activity of these enzymes is modulated by a variety of factors including age, diet, concomitant medications as well as genetic variability.

The cytochrome p450 system has evolved into a gene family and expanded into multiple chromosome loci, each with tandem arrays of genes, and each gene with substantial polymorphism. This system is an illustration of gene expansion, multi-gene families, and allelic functional variation. Genomics has supplied a rich resource of gene mapping data as well as the individual variants in each gene at the single nucleotide polymorphism (SNP) and chromosome locus levels.

The 57 cytochrome p450 isoforms now known in humans, along with the hundreds of genetic variations, have produced a large set of biomarkers predictive of susceptibility to specific toxins.

The fact that the pharmaceutical industry routinely includes an assessment of the main metabolic pathways of a candidate drug to derive clinical pharmacological correlations is indicative of the importance of this knowledge. In addition, certain cytochrome p450 alleles can also be disease susceptibility markers. For example, some are known to be implicated in detoxification or activation of environmental toxins and variants associated with cancer risk.

The nomenclature used to categorize the variant alleles of the cytochrome p450 enzyme system has been defined by various organizations. In general, the descriptors rely on the hierarchy of the genetic structures involved in the construction of the enzymes.

Of the cytochrome P450 enzymes described to date and most closely related to clinical applications through pharmacogenetic testing are the CYP2D6, CYP2C9, and CYP2C19 enzymes. Factors such as the high prevalence of variants, and in the case of CYP2D6 full-length gene duplications, in human populations and a wide range of therapeutics metabolized by these enzymes render them among the most relevant drug metabolizing enzyme for PGx diagnostics.

Phase II reactions

Involves conjugation of the drug or its phase I metabolite with the endogenous substrate, derived from carbohydrate or amino acid.

Inhibition of drug metabolism

One drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or cofactors.
Microsomal enzyme induction

Many drugs may increase the synthesis of microsomal enzymes and thus induce drug metabolism, especially cytochrome P-450 enzymes.

Examples of drugs that induce drug metabolism of other drugs; phenobarbitone, rifampicin, isoniazid etc.

Some drugs can induce their own metabolism (autoinduction), e.g. Carbamazepine, rifampicin.

Enzyme induction may lead to decreased intensity/duration of action for drugs that are inactivated by metabolism.

Drug elimination / excretion

Drugs / their metabolites are passed out from the body.

1. Urine – It is the most important channel of excretion for the majority of drugs. The kidney is responsible for excreting all water-soluble substances.

2. Faeces – apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Drugs that attain high concentration in bile are erythromycin, ampicillin, rifampicin, tetracycline, oral contraceptives etc.

3. Exhaled air – Gases and volatile liquids (general anaesthetics, paraldehyde and alcohol) are eliminated by lungs, irrespective of their lipid solubility.

4. Saliva and Sweat – These are of minor importance for drug excretion. Lithium, potassium iodide, rifampicin and heavy metals are present in these secretions in significant amounts.

5. Milk – The excretion of drugs in milk is not of importance for the mother, but the suckling infant inadvertently receives the drug. Generally, the total amount of drugs reaching infant through breastfeeding is small and the majority of drugs can be given without ill effect on the infant.

Plasma half-life (t1/2)

It is the time a drug takes for its plasma concentration to be reduced to half of its original value