# Drug mechanisms and reactions

## Phase 1: Drug Metabolism

The whole range of biochemical processes that occur within an organism, Metabolism consists both of anabolism and catabolism (the buildup and breakdown of substances, respectively). The biochemical reactions are known as metabolic pathways and involve enzymes that transform one substance into another substance, either breaking down a substance or building a new chemical substance. The term is commonly used to refer specifically to the breakdown of food and its transformation into energy.

The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active sometimes even more than the parent compound. An inactive or weakly active substance that has an active metabolite is called a pro-drug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization, whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver.

Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached, in others, metabolism may be so slow that usual doses have toxic effects. Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

For many drugs, metabolism occurs in two phases:

Phase I reactions: Which involve formation of a new or modified functional group or cleavage, these reactions are nonsynthetic.

## Phase II reactions

Which involve conjugation with an endogenous substance, these reactions are synthetic. Metabolites formed in synthetic reactions are more polar and more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. Some drugs undergo only phase I or phase II reactions, thus, phase numbers reflect functional rather than sequential classification.

## Phase I Drug Metabolism

Phase I metabolism includes oxidation, reduction, hydrolysis and hydration reactions, as well as other rarer miscellaneous reactions. Oxidations performed by the microsomal, mixed-function oxidase system (cytochrome P450-dependent) is considered separately because of its importance and the diversity of reactions performed by this enzyme system.

## Classification of Phase I Reactions:

- Oxidation
- Reduction
- Hydrolysis
- Hydration
- Dethioacetylation
- Isomerization

## Oxidations involving cytochrome P450 (the microsomal mixed-function oxidase)

The mixed-function oxidase system found in microsomes (endoplasmic reticulum) of many cells (notably those of liver, kidney, lung and intestine) performs many different functionalisation reactions.

CYP 450: The cytochrome P450(CYP) enzyme system consists of a superfamily of hemoproteins that catalyse the oxidative metabolism of a wide variety of exogenous chemicals including drugs, carcinogens, toxins and endogenous compounds such as steroids, fatty acids and prostaglandins. The CYP enzyme family plays an important role in phase-I metabolism of many drugs. The broad range of drugs that undergo CYP mediated oxidative biotransformation is responsible for the large number of clinically significant drug interactions during multiple drug therapy.

All of these reactions require the presence of molecular oxygen and NADPH as well as the

complete mixed-function oxidase system (cytochrome P450, NADPH-cytochrome

P450 reductase and lipid).

All reactions involve the initial insertion of a single oxygen atom into the drug molecule. A subsequent rearrangement and/or decomposition of this product may occur, leading to the final products formation.

(i) Aromatic hydroxylation: This is a very common reaction for drugs and xenobiotics containing an aromatic ring. In this example the local

anaesthetic and antidysrhythmic drug, lignocaine, is converted to its 3-hydroxy derivative.

(ii) Aliphatic hydroxylation: Another very common reaction, e. g. pentobarbitone hydroxylated in the pentyl side chain.

(iii) Epoxidation: Epoxides are normally unstable intermediates but may be stable enough to be isolated from polycyclic compounds (e. g. the precarcinogenic polycyclic hydrocarbons). Epoxides are substrates of epoxide hydrolase (discussed later), forming dihydrodiols, but they may also spontaneously decompose to form hydroxylated products or quinones. It has been suggested that epoxide formation is the first step in aromatic hydroxylation.

(iv) Dealkylation: This reaction occurs very readily with drugs containing a secondary or tertiary amine, an alkoxy group or an alkyl substituted thiol. The alkyl group is lost as the corresponding aldehyde. The reactions are often referred to as N-, O- or S-dealkylations, depending on the type of atom the alkyl group is attached to.

(v) Oxidative deamination: Amines containing the structure -CH(CH3)-NH2 are metabolised by the microsomal mixed-function oxidase system to release ammonium ions and leave the corresponding ketone. As with dealkylation, oxidative deamination involves an intermediate hydroxylation step with subsequent decomposition to yield the final products.

The product of the oxidative deamination of EPI or NE is 3, 4-didydroxyphenylclycoaldehyde (DOPGAL). DOPGAL is subject to reduction to

the corresponding alcohol (3, 4-dihydroxyphenylethylene glycol, DOPEG) or oxidation to the corresponding carboxylic acid (3, 4-dihydroxymandelic acid, DOMA), the latter being the major pathway.

(vi) N-oxidation: Hepatic microsomes in the presence of oxygen and NADPH can form N-oxides. These oxidation products may be formed by the mixedfunction oxidase system or by separate flavoprotein N-oxidases. The enzyme involved in N-oxidation depends on the substrate under study. Many different chemical groups can be N-oxidised including amines, amides, imines, hydrazines and heterocyclic compounds.

(vii) S-oxidation: Phenothiazines can be converted to their S-oxides (sulfoxides (S¼O) and sulfones (¼S¼O)) by the microsomal mixed-function oxidase system.

(viii) Phosphothionate oxidation: The replacement of a phosphothionate sulfur atom with oxygen is a reaction common to the phosphothionate insecticides, e. g. parathion. The product paraoxon is a potent anticholinesterase and gives the potent insecticide action as well as the toxicity in humans.

## Oxidations not catalysed by cytochrome P450 (Non-Microsomal)

A number of enzymes in the body not related to cytochrome P450 can oxidize drugs.

(i) Alcohol Oxidation by Alcohol dehydrogenase: This enzyme catalyses the oxidation of many alcohols to the corresponding aldehyde and is localised in

the soluble fraction of liver, kidney and lung cells. This enzyme uses NAD+ as co-factor and is a true dehydrogenase.

(ii) Aldehyde oxidation: Aldehydes can be oxidised by a variety of enzymes involved in intermediary metabolism, e. g. aldehyde dehydrogenase, aldehyde oxidase and xanthine oxidase (the latter two being soluble metalloflavoproteins).

(iii) Oxidation by Xanthine oxidase: This enzyme will metabolise xanthine-containing drugs, e. g. caffeine, theophylline and theobromine, and the purine analogues to the corresponding uric acid derivative.

## Metabolic Reduction

(i) Azo- and nitro-reduction can be catalysed by cytochrome P450 (but can also be catalysed by NADPH-cytochrome P450 reductase).

(ii) Ring cleavage: Epoxides can be converted back to the parent hydrocarbon, e. g. benzo(a)anthracene- 8, 9-epoxide whereas some heterocyclic compounds can be ring cleaved by reduction.

(iii) Reductive defluorination: Fluorocarbons of the halothane type can be defluorinated by liver microsomes in anaerobic conditions.

## Metabolic Hydrolysis

Esters, amides, hydrazides and carbamates can readily be hydrolysed by various enzymes.

(i) Ester hydrolysis: The hydrolysis of esters can take place in the plasma (nonspecific acetylcholinesterases, pseudocholinesterases and other

esterases) or in the liver (specific esterases for particular groups of compounds). Procaine is metabolised by the plasma esterase, whereas pethidine (meperidine) is only metabolised by the liver esterase.

(ii) Amide hydrolysis: Amides may be hydrolysed by the plasma esterases (which are so non-specific that they will also hydrolyse amides, although more slowly than the corresponding esters) but are more likely to be hydrolysed by the liver amidases. Ethylglycylxylidide, the N-deethylated phase 1 product of lignocaine, is hydrolysed by the liver microsomal fraction to yield xylidine and ethylglycine.

(iii) Hydrazide and carbamate hydrolysis: Less common functional groups in drugs can also be hydrolysed, such as the hydrazide group in isoniazid or the carbamate group in the previously used hypnotic, hedonal.

## Factors Affecting Metabolism

Many factors can affect liver metabolism, such as:

In aging, the numbers of hepatocytes and enzyme activity declines.

Diseases that reduce hepatic blood flow like heart failure or shock can also reduce the metabolic potential of the liver.

Also the use of other drugs as well as dietary and environmental factors can influence liver metabolic function.

Metabolism can also be altered due to a genetic deficiency of a particular enzyme.

Differences in metabolism that result from functional genetic polymorphisms can be accommodated by knowing the frequency of different genotypes, and by modifying either the enzyme abundance (null alleles, for example, in the case of CYP2D6 ‘ poor metabolizers’) or the intrinsic enzyme activity (for example, CYP2C9 variants). Data on developmental changes in the abundance and activity of different CYPs can also be incorporated into the models to predict hepatic clearance in neonates, infants and children.

## Conclusion

Metabolism is the breakdown of Drugs inside the body, to disable their activity, forming inactive metabolites, however some drugs are either not affected by metabolism or activated by it, some even form toxic metabolites Examples:

Imipiramine not affected by metabolism:

Paracetamol produce Toxic Metabolite

Metabolism occurs in two phases, Phase I Metabolism, and Phase II Metabolism.

Phase I Metabolism converts the drug into metabolite by formation of a new functional group or modifying it, while phase II Metabolism or reactions involve conjugation with indigenous substance.

Phase I Reactions Include:

Oxidation, reduction, hydrolysis and hydration reactions, and other rare miscellaneous reactions.

Oxidation can be divided into Microsomal or non Microsomal according to whether it involves mitochondrial CYP 450 enzymes.

Oxidation involves:

## Microsomal

Aromatic Hydroxylation, Aliphatic Hydroxylation, Epoxidation, Dealkylation, oxidative deamination, N- oxidation, S-oxidation and Phosphothionate oxidation.

## Non-Microsomal

Alcohol Oxidation by Alcohol dehydrogenase, Aldehyde Oxidation and Oxidation by Xanthine oxidase.

Reduction involves: Azo- and nitro-reduction, Ring cleavage, Reductive defluorination

Hydrolysis involves: Ester hydrolysis, Amide hydrolysis, Hydrazide and carbamate hydrolysis