

The drug metabolism



**ASSIGN
BUSTER**

Introduction:

If an exogenous microorganism enters the human body, this invokes the immune system to produce antibodies to come into contact with the foreign potentially pathogenic species and lead to its destruction. Although when drug molecules enter the human body this does not result in the synthesis of antibodies, due to their relatively small molecular weight. This is why the endogenous metabolism of drugs is vital in ensuring no or the minimum toxicity from a very broad spectrum of xenobiotics i. e.

molecules/compounds which are found in a given organism, but are not synthesized naturally by it and or normally found within it. We can define drug metabolism as the enzymatically catalysed conversion of exogenous drug molecules into generally less active metabolites, which have a faster rate of clearance from the body. (While this is true for the majority of metabolites it is important to acknowledge that some metabolites actually are of higher toxicity than their precursors.) This occurs throughout nearly every organ (excluding ectodermal tissue) in the human body, but specifically the gastro-intestinal tract, lungs, kidneys and most importantly (and abundantly) the liver.

While drug metabolism is essential in preventing a specific toxicity being produced from the accumulation of a drug(s), there are drawbacks that need to be addressed; a given drug may be a xenobiotic, but it is taken (or administered) in order to produce some degree of a therapeutic effect for its specifically targeted disease/pathology. Thus drug metabolism can inhibit the therapeutic benefit of a given molecule that ideally needs to be retained in a particular tissue of the body for a set period of time, to bring about a

therapeutic effect. This is mainly due to the fact that a large number of drug molecules do mimic the structure of endogenous molecules close enough for the corresponding specific enzymes to target them as well as nonspecific enzymes which only identify certain molecular groups as opposed to the entire pharmacophore of a given drug. This unexpected drug metabolism could result in an undesired decrease in the bioavailability of a drug which would lead to increased doses or dosage frequencies; this would cause a decrease in patient compliance which in the current medicinal environment is vital.

Absorption and clearance:

In the case of drug absorption into the desired tissues of the body generally a lipophilic character is required. This is because regardless of the site of drug uptake, it must pass through the cell membranes of targeted cells. These cell membranes are lipophilic in nature as they consist of a phospholipid bilayer. The inside of this bilayer is made up of hydrocarbon tails which are straight chain hydrocarbons which interact with each other via Van der Waal interactions and London forces. Thus drug molecules are designed to have sufficient lipophilic character that they can form these interactions with the lipid bilayers and pass into cells. Unfortunately this means that they are of limited hydrophilicity and either do not go into dissolution in an aqueous environment at all or do so at a very slow rate. As previously mentioned as this is unacceptable due to the accumulation of a given drug that would occur and produce toxicity, the drug must undergo a series of transformations that serve to increase the hydrophilic nature of the

drug molecules. This predominately occurs in liver cells (hepatocytes) in processes known as phase I and phase II metabolism.

Phase I and Phase II:

Phase I metabolism is constituted of oxidative, reductive and hydrolytic reactions. These serve to produce primary metabolites that are susceptible to other reactions, which consist of the following conjugations; glucuronic acid, sulphate, amino acid, glutathione, water, acetyl, fatty acid and methyl. These occur via the corresponding conjugating agents and are known as phase II reactions. They aim to produce secondary metabolites that are far more hydrophilic nature than their precursor drug counterparts. This is with the addition of e. g. amine, carboxylic acid, hydroxyl groups as well as others, simply to increase the number of very electronegative atoms (with lone pairs of electrons) in a given species. Thus these metabolites can form a greater number of hydrogen bonds with the aqueous medium of the nephronal filtrate of the kidneys and be excreted at a faster rate via the passing of urine.

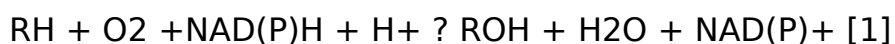
The main constituent of phase I transformations are oxidative reactions, as they activate the selected species in generally one of two ways; hydroxylation and epoxidation. We can define oxidation as the gain of oxygen in a molecule or more precisely the loss of at least one electron from a species reacting with molecular oxygen. This is true for the two general mechanisms mentioned above as adding either a hydroxyl group or an epoxide ring to a molecule increases the number of oxygen atoms that the molecule contains. Firstly this increases the ability of the newly formed metabolite to act as a nucleophile due to the lone pair of electrons available

for covalent bond formation (from the oxygen atom added to the molecule). Secondly it increases the chances of attack by an electrophilic species, because of the high electron density of the lone pair of electrons on the oxygen atom.

Oxidation

Properties and mechanisms of the Cytochrome P450 isoenzyme superfamily:

The majority of these oxidative metabolic reactions are carried out by a superfamily of enzymes known as cytochrome P450, this can be displayed as:



The P450 enzymes catalyse the biodegradation of other exogenous species that are not drugs such as; organic solvents, ethanol (or consumed alcohol), anaesthetics, pesticides and carcinogens [1]; While endogenous molecules such as organic acids, steroids and prostaglandins are also biodegraded [1].

These enzymes are intracellular hemoproteins that function as external monooxygenases (mixed function oxidases) enzymes that serve to incorporate a single atom of molecular oxygen into a lipophilic xenobiotic substrate (i. e. a drug molecule), with the concomitant reduction of the other atom to water [1]. While internal monooxygenases take two reductive equivalents from the substrate in order to reduce one atom of molecular oxygen to water, this is normally done with an external reductant for external monooxygenases [1].

In eukaryotic cells the P450 enzymes consist of around half a thousand amino acid that compose their quaternary structure, these hemoproteins are membrane bound and have a heme prosthetic group at their centres. It is thought that the reason the enzymes can be bound to the cell membranes is the N-terminus of the enzymes tertiary structure has numerous hydrophobic amino acids (i. e. ones which contain aromatic/cyclic groups and have few very electronegative atoms such as oxygen and sulphur) that can interact with the lipid bilayer of the cells. Most hemoproteins in mammalian cells have nitrogen atom from the histidine residues imidazole group to form a ligand with the iron-heme prosthetic group. While for P450 enzymes this ligand is formed between the prosthetic group and the thiol group of a cysteine residue which is located near the C-terminus of the protein. This ligand activates the porphyrin ring (four conjugated pyrrole rings) to nucleophilic substitution by an oxygen atom. This is because the thiol group has an electron inductive effect due to its high electronegativity and so makes the carbon atom it is directly bonded to very electropositive and thus of greater electrophilicity/susceptibility of nucleophilic attack by the lone pair of electrons from the oxygen atom, so allowing oxidation to take place.

The general process of the catalytic oxidative cycle of the cytochrome P450 enzyme superfamily:

1. The substrate binds to a specific P450 enzyme and is followed by the first electron of the coenzyme NADPH via the electron transport chain. This is then followed by the binding of an oxygen atom that accepts the second electron from the coenzyme to produce a ferric peroxy anion [1].

2. The anion forms a ferric hydroperoxy complex via protonation, which in turn is heterolytically cleaved to form a Fe(V)=O species [1].
3. The newly formed highly electrophilic iron-oxo intermediate then attacks the substrate to form a hydroxylated metabolite. This product disassociates to allow another substrate to bind and the oxidation cycle to continue [1].

“ Schematic organisation of different cytochrome P450 systems. Upper row, left: bacterial system, right: mitochondrial system. Lower row, left: microsomal system, right: self-sufficient CYP102 (P450-BM3).”[1]

Aromatic hydroxylation:

This leads on to the first major constituent of oxidative reactions; aromatic hydroxylation. This is simply the addition of at least one hydroxyl group to a given substrate although depending on the chemical environment that the product is formed in (e. g. pH) the hydrogen atom may be lost from the hydroxyl group. Aromatic compounds are first metabolized to the corresponding arene oxides; this is by electrophilic addition of the aromatic ring (of the previously mentioned iron-oxo intermediate) to produce either a carbocation species. This carbocation would be formed via the movement of an electron to the Fe(IV) species, giving a Fe(III) species bound to the mentioned carbocation; or by formation of a radical which serves as a tetrahedral intermediate.

The produced arene oxides then take on further transformations, which involve removal of the epoxide group that was added and introduction of a hydroxyl group and potentially another nucleophilic substitute. The simplest transformation is simply intramolecular rearrangement to form a para-arenol.

Also hydration can take place in the presence of water and using the enzyme epoxide hydrolase. This causes opening of the epoxide ring and formation of a trans-3, 4 arenediol. These primary metabolites can also undergo attack by large macromolecules which serve as nucleophiles. This is because the oxygen in the epoxide ring serves to make both the meta and para carbon positions electropositive and electrophilic in nature. Although any nucleophilic substitution that does go on to occur is at the para position, due to greater resonance stability of the formed secondary metabolite.

Another example of aromatic hydroxylation would be the metabolism of isoliquiritigenin. It is a chalcone found in licorice roots and other plants [3] which has shown potent antitumor, phytoestrogenic activity and antioxidant properties. [3] Schematics for its metabolism can be shown below. [3]

The metabolism of aromatic compounds that get hydroxylated can be slowed by using para-substituted aromatic compounds with either chlorine or a fluorine atom in the para position. While electron withdrawing groups deactivate the ring towards electrophilic substitution and activate it towards nucleophilic substitution; electron donating groups activate the ring towards electrophilic substitution and deactivate it towards nucleophilic substitution. While most ring deactivators go in the meta position, halogens direct ortho-para, i. e. the same as ring activators. This is because the halogens, especially fluorine and chlorine are very electronegative and thus have an electron inductive effect and decrease the electron density of the ring. This inductivity is far greater than the resonance stability that the halogen can give the ring thus deactivating it. Thus the addition of these halogen atoms decreases the nucleophilic nature of the ring and decreases the rate of

metabolism. This can be shown with the metabolism of the drug Diclofenac (shown below [4]) which is an anti-inflammatory drug as it has a half-life of around one hour. While its derivative fenclofenac which has a para-substituted chlorine atom has a half-life twenty times longer.

Alkene epoxidation:

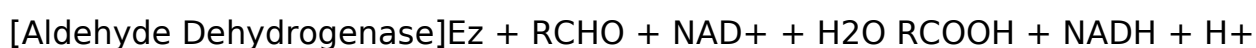
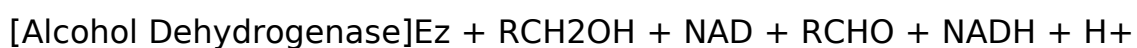
Epoxidation of alkenes occurs readily, because they are more volatile than the π bonds of aromatic compounds, this simply involves the addition of an epoxide ring to a molecule in order for it to then undergo further transformations. " For example the drug Coumarin has been used clinically at high dosages in humans in the treatment of high-protein lymphedemas (Jamal and Casley-Smith, 1989) and as an antineoplastic agent in the treatment of renal cell carcinoma (Marshall et al., 1994) and malignant melanoma (Marshall et al., 1989)." [5] It and its 3/7-hydroxy isomers undergo epoxidation and then either glutathione conjugation or non-enzymatic intramolecular rearrangement [5] to secondary metabolites. This is shown schematically below. [5]

It is also vitally important that environmental carcinogens are broken down via drug metabolism, in particular by the P450 enzymes. For example acrylonitrile (AN2) " is widely used in the production of acrylic and modacrylic fibres, plastics, rubbers, resins, and as a chemical intermediate in the synthesis of many other industrial products (IARC, 1999). Early epidemiological studies have suggested that AN may increase the incidence of lung, colon, and stomach cancers among exposed workers (Thiess and Fleig, 1978; Blair et al., 1998)." [6] As a result P450 epoxidation is vital for preventing carcinogenic action of AN. While the " metabolic basis of the

acute toxicity of AN has not been fully elucidated, it is generally attributed to its metabolism to CEO (cyanoethylene oxide) and cyanide, and glutathione depletion. The primary target of acute toxicity of AN is the central nervous system due, at least partially, to the liberation of cyanide (Ahmed and Patel, 1981; Benz et al., 1997).” [6] The below diagram illustrates how AN is metabolised by the P450 enzymes, specifically the CYP2E1 isoform.[6]

Alcohol and aldehyde metabolism:

Alcohols and aldehydes can be metabolized by cytochrome P450 enzymes to aldehydes and carboxylic acids respectively, but the majority of these transformations are catalysed by alcohol dehydrogenase and aldehyde dehydrogenase. These enzymes are predominantly in the liver and require the coenzyme NAD⁺ or NADP⁺. General equations for these reactions are shown below.



Reduction:

Cytochrome P450 enzymes are used along with reductases to metabolise drugs that have a carbon atom that is able to be reduced such as a carbonyl or an unsaturated carbon, a nitro group or a compound with an azo group. In addition upon reaction usually a specific stereoisomer is formed. The structure of the rest of the compounds often attribute to which stereoisomer is formed. Some stereoisomers can prove to be toxic.

Carbonyl compounds:

Carbonyl compounds are reduced by cytochrome P450 into alcohols and are NADP or NADPH dependent. The enzymes involved in the reduction of carbonyls are classified based upon their gene sequence, 3-D structure and cofactor dependence into superfamilies of; medium-chain dehydrogenases/reductases, aldo-keto reductases, short-chain dehydrogenases/reductases which include carbonyl reductases. The majority of these enzymes are present in the cytosol however there are some that are found in the microsomes and mitochondria. Short-chain dehydrogenases/reductases (SDRs) and aldo-keto reductases (AKR) are the most common enzymes used in drug metabolism. These enzymes also exhibit high specificity for the drugs that they reduce.

Saturated ketones reduced to alcohols whilst in an unsaturated ketone both the ketone group and the double bonds are both reduced. Steroidal drugs undergo oxidoreduction of the hydroxy/keto group at C17[7]. This makes the compound more water soluble and hence easier to be excreted.

Some metabolising enzymes behave differently and undergo different types of reactions when in different cells. An example is carbonyl reductases within tumour cells and normal cells. These have become a target of new drugs such as oracin in the treatment of breast cancer [9]. The enzymes within the cancer cells metabolise oracin and doxorubin more effectively than in normal cells hence reducing the efficacy of the cytostatic effect of the drugs.

Some carbonyl compounds however do not undergo reduction via the cytochrome P450 pathway but are rather reduced by other pathways

including the aldo-keto reductases (AKR). An example is a drug containing a 1, 3-diketone derivative S-1360 which upon reduction produces a key metabolite HP1 which constitutes a major clearance pathway[9].

Nitrogen compounds:

The reduction of nitrogen containing compounds are reduced to amines in order to aid excretion as amines are more water soluble than their nitro groups. Azo compounds on the other hand may be metabolised within the body to produce the active drug as opposed to the precursor which may be formulated to get pass the first pass effect or the hydrophilic barrier in order to enter their target cells. The azo group provides 2 compounds with amine groups which can be further metabolised like any other amine. Both of these functional groups are both reduced by cytochrome P450 enzymes and are NADPH dependent.

Hydrolysis:

This is part of the Phase I metabolism pathway. The metabolites produced are all susceptible to Phase II conjugation and thus being excreted after the conjugation. The functional groups of the drugs that are metabolised by hydrolysis include esters and amides, which produce carboxylic acids, alcohols and amines. Esters are hydrolysed quicker than amides in vivo. Unlike oxidation and reduction the reactions are typically not carried out by the cytochrome P450 system. The most significant enzymes involved in the hydrolysis of the esters and amides are carboxylesterases and arylesterases, cholinesterases and serine endopeptidases. The active site of the enzymes involved may be stereospecific as to which enantiomer of the drug is

metabolised and in addition which enantiomer of the drug is generated.

Some of these products are toxic and dangerous to the body.

Amino acid reactions

Several phase I reactions produce a carboxylic acid metabolite. Xenobiotic carboxylic acids can be metabolised before elimination by amino acid conjugation. Glycine; the most common conjugating amino acid forms ionic conjugates that are water soluble with aromatic, arylaliphatic and heterocyclic carboxylic acids. In these reactions, first the xenobiotic carboxylic acid is activated by ATP to form the AMP ester by the enzyme acyl synthetase. Then the AMP ester is converted to a Coenzyme-A thioester. Next, an amide or peptide bond is formed between the thioester and the amino group of glycine. The latter reaction is mediated by the enzyme acyl transferase. These reactions are shown in figure 1.

The amino acid conjugate produced is ionic and therefore water soluble, hence it is easily eliminated in the urine and bile. (1)

Glutathione conjugation

Glutathione is a protective compound in the body that removes potentially toxic electrophilic compounds and xenobiotics. Drugs are metabolised by phase I reactions to form strong electrophiles that can react with glutathione to form conjugates that are not toxic. This phase II reaction differs from others since electrophiles are subject to conjugations rather than nucleophiles. The nucleophilic thiol group on the glutathione compound (figure 2) attacks electrophiles (electrophilic carbons with leaving groups).

Compounds that can be conjugated to give thioether conjugates of glutathione:

- Epoxides
- Haloalkanes
- Nitroalkanes
- Alkenes
- Aromatic halo- and nitro- compounds

Glutathione-S-transferases (GST) are enzymes which catalyse the reactions above. There are thirteen different human GST subunits which have been identified and they belong to five different classes. They are located in the cytosol of the liver, kidney and gut. The enzyme GST is thought to increase the ionisation of the thiol group of glutathione, leading to an increase in its nucleophilicity towards electrophiles. (1)(2)

Once formed, GSH conjugates may be excreted directly or more often they are further metabolised to N-acetylcysteine conjugates which can then be excreted via ' phase III metabolism'.

Phase III Metabolism – further modification and excretion

Before being excreted in the urine, most xenobiotics are made less toxic and more water soluble as polarity increases by metabolising enzymes in phase II reactions. In phase III metabolism water soluble compounds are excreted in the urine. However, some drug compounds are not metabolised and therefore are not excreted. These non-metabolised compounds are readily reabsorbed from the urine through the renal tubular membranes and into the plasma to be recirculated. (3)

Some xenobiotic conjugates from phase II reactions are further metabolised during phase III metabolism reactions. Glutathione-S conjugates may be metabolised further by hydrolysis of the glutathione conjugate (GSR) at the γ -glutamyl bond of the glutamate residues by γ -glutamyl transferase (γ -GT) followed by hydrolysis of glycine residues resulting in a cysteine conjugate containing a free amino group of the cysteine residue. This then undergoes N-acetylation to form mercapturic acid. The final products; mercapturic acids are S-derivatives of N-acetylcysteine synthesised from glutathione (figure 4).
(1)(2)

First-pass Metabolism

The metabolism of many drugs is dependent on the route of administration therefore orally administered drugs are subject to first pass metabolism and consequently their bioavailability is reduced. This occurs as a result of the orally administered drugs entering the systemic circulation via the hepatic portal vein, so the drug is exposed to the intestinal wall and the liver, which is thought to be the main site of first-pass metabolism of orally administered drugs. Other possible sites are the gastrointestinal tract, blood, vascular endothelium and lungs.

First-pass Metabolism in the Liver

During first-pass metabolism, the cytochrome P450 enzymes family represent the most significant of the hepatic enzymes. It has been estimated that the endoplasmic reticulum of the liver contains approximately 25 000 nmol of cytochrome P450. Although there are several human P450 subfamilies and multiple individual isozymes within subfamilies, only five

P450 enzymes are shown to be significant for the process of first-pass metabolism:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4

Cytochrome P450 drug substrates are commonly highly extracted during first-pass metabolism. Examples of these drugs are; morphine, verapamil, propranolol, midazolam, lidocaine. Drugs that are highly extracted such as lidocaine have a low bioavailability when taken orally therefore they are not administered orally. CYP3A4 is the most commonly active isozyme against P450 drug substrates. This is possibly due to the enzyme's abundance and broad substrate specificity. Highly extracted substrates for conjugative, reductive or non-P450 oxidative enzymes are less common. These include labetalol, morphine, terbutaline, isoproterenol and pentoxifylline.

The gut is also an important organ involved in pre-systemic metabolism. Metabolism here for drugs with high first-pass metabolism leads to a reduced bioavailability. Some metabolizing enzymes such as CYP3A4 is found at a higher level in enterocytes than in the liver. Recent findings state that gut wall metabolism is the major cause of low bioavailability of certain drugs.

Intestinal First-pass Metabolism

Various drug metabolizing enzymes found in the liver are also found within the epithelium of the gastrointestinal tract. These include cytochromes P450,

glucuronosyl transferases, sulfotransferases, N-acetyl transferase, glutathione S-transferases, esterases, epoxide hydrolase and alcohol dehydrogenase. The small intestine contains high amounts of three cytochrome P450 enzymes; CYP3A, CYP2D6 and CYP2C. Unlike the liver which has a relatively uniform distribution of P450enzymes, the distribution of P450 enzymes is not uniform along the small intestine and villi. Proximal mucosal P450 content is normally higher than distal mucosa P450 content.

Therefore it has been established that protein level and catalytic activity of drug-metabolizing enzymes in the small intestine are generally lower than those in the liver. This has been demonstrated by comparison of cytochrome P450 enzymes in the liver and the small intestine. The extent of first-pass metabolism can result from interindividual variability:

1. Genetic variation
2. Induction or inhibition of metabolic enzymes
3. Food increases liver blood flow. This can increase the bioavailability of some drugs by increasing the amount of drug presented to the liver to an amount that is above the threshold for complete hepatic extraction
4. Drugs that increase liver blood flow (similar effects to food) and drugs that reduce liver blood flow
5. Non- linear first pass kinetics, i. e. dose
6. Liver disease increases the bioavailability of some drugs with extensive first-pass metabolism (4)

To avoid first pass metabolism a drug can be administered sublingual and buccal routes. These routes lead to drugs being absorbed by the oral

mucosa. During sublingual administration the drug is put under the tongue where it dissolves in salivary secretions. An example of a sublingual drug is nitroglycerine. During buccal administration the drug is positioned between the teeth and the mucous membrane of the cheek. Both of these routes avoid destruction by the GI fluids and first pass effect of the liver. Drugs may also be administered via other routes to avoid first-pass metabolism, for example; rectal, inhalation, transdermal, intravenous. (5)

Prodrugs

Many drugs require metabolic activation in order to exert their pharmacological action; these are described as pro-drugs. There are two types; type I and type II which has subtypes A and B dependent on the site of activation. Type I prodrugs are converted intracellularly at the target cells (A) or at tissues that usually metabolise compounds (B). An example of a type IA prodrug is Zidovudine and type IB prodrug is captopril. Metabolic activation of type I prodrugs is usually linked to phase I metabolic enzymes. Type II prodrugs are converted extracellularly in GI fluids (A) or in the systemic circulation (B). An example of a type IIA prodrug is sulfasalazine and type IIB prodrug is fosphenytoin. Type II prodrugs are very popular as they are involved in overcoming bioavailability problems, which are commonly experienced with many drugs, by improving permeability and reducing the first pass effect. (6)

Type I Prodrugs are used to target a drug to its specific site of action; an example of this is the drug used in Parkinson's disease levodopa; the inactive form of the drug which is metabolised in the neurone by the enzyme dopa decarboxylase to the active form; dopamine. Dopamine does not cross

the blood-brain barrier so it is given as the levodopa precursor which is lipophilic so it can cross the barrier and then metabolized in vivo to dopamine. (7)

Another example of the use of prodrugs is the pharmacological activation of a type II prodrug Azathioprine to mercaptopurine which is a chemotherapeutic agent used in the treatment of leukaemia. When mercaptopurine is administered, its clinical usefulness is restricted because of its rapid biotransformation by xanthine oxidase to an inactive metabolite 6-thiouric acid. Therefore larger doses have to be given as it has a low bioavailability, this leads to toxicity. By administering mercaptopurine as its cysteine conjugate, the limitations can be overcome. This ionic form of the pro-drug conjugate is selectively taken up by the renal organic anion transport system. The kidney B-lyase enzyme system then cleaves the prodrug conjugate to give the active mercaptopurine in the kidney (figure 5). (8)(9)

To conclude, prodrugs can be metabolised in different ways to form the active drug. They can be used to target specific sites, improve absorption and improve oral delivery of poorly water-soluble drugs. They can also be used to avoid first pass metabolism in drugs with high first pass extraction and reduce toxicity. (6)

Factors affecting metabolism

There are several factors that can affect drug metabolism. Age, sex, inducers and inhibitors are some of which can effect drug metabolism which are mentioned below.

How does age affect drug metabolism:

There are many physiological changes that occur with ageing. The changes have the potential to affect both drug disposition and metabolism. Drug metabolism is mainly functioned by the liver, its size, blood perfusion and synthetic capacity for proteins which all determine the rate of hepatic drug elimination[5].

Paediatric population

Phase one and phase two metabolic pathways may not be active at birth due to maturational changes. The paediatric population and elderly population have differences in their capacity to metabolise a drug which can therefore produce a lower or higher plasma concentration of active substances compared with adults depending on the enzyme system used. There are examples of metabolites produced by therapeutic agents in children that are not usually seen in adults. The metabolites produced maybe the reason for some of the efficacy and or toxicity visible with drug administration in children. An example is: caffeine production in a neonate receiving Theophylline. Other therapeutic agents which show changes in metabolite production in children are;

- Valproic acid,
- paracetamol,
- Chloramphenicol,
- Cimetidine
- Salicylamide.

In most cases the differences that occur between children and adults are in the ratios of the metabolites relative to the parent drug rather than in new

metabolites individual to the paediatric population with some exceptions. The paediatric population shows the same set of enzymes as the adult population. (1)

In general age related changes in drug metabolism have been shown to occur due to a consequence of diminished enzyme activities within the elderly human liver due to the size of the liver decreasing and hepatic blood flow decreasing. With age the liver blood flow is generally reduced by about 20-30% and there is a decrease in liver size by about (17-36%).

Currently there is no clear pattern; however there are two general trends that influence the rate of metabolism. One trend is that drugs that are undergoing hepatic microsomal oxidation are more likely to be metabolised slowly in the elderly and those which are conjugated are not likely to be influenced by the age factor. Secondly, drugs that have high hepatic clearance, extraction ratios example-Chlormethiazole, and Labetalol and undergo extensive first pass metabolism whilst oral absorption may show a large increase in bioavailability in the elderly.

Elderly population

In general in the elderly population hepatic blood flow decreases up to 40% and there can be a considerable reduction in the amount of drug reaching the liver per unit. Studies have shown that the effect of ageing on liver enzymes with particular drug