1.4. METABOLISM OF DRUGS

The liver is the major site of metabolism for many drugs. The other organs involved are lungs and kidneys. Many factors affect drug metabolism. Chemical properties such as molecular weight and degree of ionization, together with the route of administration play an important part in drug metabolism. For example by the oral route of administration extensive hepatic metabolism (first pass effect) can result with many drugs.

The other factors can be dosage, diet, age, genetic and disease state like renal failure, liver dysfunction and cardiac failure. In renal failure there is slower removal of a drug and therefore administration of the usual dose produces accumulation of the drug which can give rise to toxicity. In kidney failure the renal clearance of drugs excreted through kidney is predictable but it is not possible to predict hepatic metabolism of drugs in liver dysfunction. Therefore, in hepatitis changes may range from impaired to increased drug clearance. In cardiac failure the perfusion of the kidney and liver may also be impaired and can affect drug clearance by these organs directly or indirectly. So in congestive heart failure or hemorrhagic shock the response to the usual dose of many drugs may be excessive and may require modification.

Biochemical reactions involved in drug metabolism are:

I Oxidation
II Reduction
III Hydrolysis
IV Conjugation.

I **Oxidation :** can be microsomal or non-microsomal.

Microsomal oxidation takes place in a collection of membrane associated enzymes located in the smooth endoplasmic reticulum of many cells, especially in the liver. The enzymes involved are cytochrome P450 mixed function oxygenase and P 450 reductase.

Drugs can inhibit or activate these enzymes.

Non microsomal oxidation : Oxidative enzymes are found in the cytosol or mitochondrial cells such as alcohol dehydrogenase and aldehyde dehydrogenase which are responsible for the metabolism of ethyl alcohol. Similarly, xanthine oxidase, tyrosine hydroxylase and monoamine

dizziness headache, fatigue, cough, lassitude, rash, and renal failure. It is contraindicated in pregnancy.

Lisinopril

This is a synthetic peptide derivative, orally acting ACE inhibitor with longer duration of action. Supression of the renin-angiotensin-aldosterone axis lowers the blood pressure.

Peak serum concentration occurs in 7 hours after oral administration. It is not bound to the plasma proteins. It is not metabolised and excreted entirely in the urine in the unchanged form. Multiple dosing exhibits half life to be about 12 hours. Impaired renal function decreases its excretion. Onset of action is after one hour of administration and anti-hypertensive effect is observed for 24 hours. The dose of the drug is 2.5 mg once a day. Maximum dose can be upto 20mg a day.

Drug interactions and adverse effects : Concomitant administration of hydrochlorthiazide produces further reduction of blood pressure. Indomethacin reduces the anti-hypertensive effects. Abrupt withdrawal can cause rebound hypertension. Adverse effects are dizziness, diarrhoea and respiratory symptoms with cough.

3.12. CATECHOLAMINE DEPLETERS FROM THE ADRENERGIC NERVE TERMINALS

Rauwolfia alkaloids can be used in the treatment of hypertension, however they are not used commonly because of their large number of adverse effects. Reserpine the rauwoifia alkaloid is used in combination with other drugs in a dose of 0.1 mg two to three times a day. Reserpine produces its effect through depletion of the stores of catechol-amines from the adrenergic neurones. It also inhibits the uptake of noradrenaline into the vesicles of the nerve terminal. Intraneuronal degradation of noradrenaline also occurs both centrally and peripherally. Oral administration of reserpine takes a long time to produce antihypertensive effect because of the time factor involved in the depletion of the catecholamine stores.

Drug interactions and adverse effects : Hypotensive effects are enhanced by the thiazide diuretics and beta blockers. Reserpine increases cardiac glycoside toxicity. Tricyclic antidepressants antagonise the effect of reserpine. Reserpine has a number of

4.1.1. The classification of Barbiturates

Barbiturates can be classified according to their onset and duration of action. These properties are dependent on their rate of metabolic degradation, lipid solubility and extent of protein binding since this reduces its renal excretion.

I. Long acting barbiturates, e.g. phenobarbital and barbital. They are effective for more than 6 hours as sedative and hypnotic.

At a low dose they are used as antiepileptic. The antieplleptic dose of phenobarbital is 30 mg three times a day.

The drug is long acting because of slow oxidation in liver. Phenobarbital is also capable of inducing the liver microsomal drug metabolizing enzyme system with increased degradation of the barbiturates leading to barbiturate tolerance. There is also increased inactivation of many drugs such as anticoagulants, phenytoin, digitoxin, theophyllin and glucocorticoids which lead to drug interactions when prescribed together.

II. Ultra short acting e.g. Thiopental acts within seconds of its administration with the duration of action of about 30 minutes. It is used as an intravenous anesthetic agent.

The ability of any agent to affect the CNS is dependent on its ability to cross blood brain barrier. Blood brain barrier is constituted by the lining of the brain capillaries and the foot processes of astrocytes. These capillaries unlike those in other tissues have some pinocytic vesicles. Lipid soluble substances remain unionized at physiological pH and are poorly bound to plasma proteins and therefore are able to diffuse across the blood-brain barrier. The ultra short acting barbiturates due to their high lipid solubility reach the brain tissue and get redistributed to the other tissues e.g. the muscle, in a very short time. So they have a very short duration of action since they remain in the CNS for a very short time.

III. Short acting barbiturates are represented by Pentobarbital, Hexobarbital and Secobarbital. They have about 2 hours duration of action and their chief use is in sleep induction.

IV. Intermediate acting barbiturates are those which have effect for about 3 to 5 hours. The examples are Amobarbital

repulse the termini of the other fibrinogen molecules there by preventing aggregation. Thrombin breaks the peptide linkage. Consequently the repulsive forces between the termini of the fibrinogen vanish and which aggregation takes place to form fibrin polymer clot which traps the red cells, platelets and other components of blood to form the thrombus.

8.2. ANTICOAGULANTS

Chemicals and drugs can act at different points of coagulation to act as anticoagulants and thrombolytics. Chemicals like calcium oxalate, citrate and EDTA prevent blood clotting in vitro. All of them produce their action by virtue of their effect on ionized calcium. However these chemicals are not effective in vivo because ionized levels are sufficiently low to obtain an anticoagulant effect and all the above mentioned chemicals are incompatible with living organism.

8.2.1. Heparin

Heparin is a sterile preparation containing the sodium salt of a complex organic acid present in mammalian tissues having the characteristic property of delaying the clotting of shed blood. It contains not less than 100 Units per mg, calculated with reference to the substance dried to constant weight at 60°C. The potency of a sample of heparin is determined by comparing the concentration necessary to prevent clotting of shed blood, with the concentration of the standard preparation necessary to give the same effect. The standard preparation is a quantity of the dried sodium salt of heparin prepared from the crystallised barium salt of ox heparin. The unit is the specific activity contained in such an amount of the standard preparation as stated in pharmacopoeia. Heparin is a charged molecule that can block clotting both *in vitro* and *in vivo*. The anticoagulant effect of heparin is because of inhibition of several activated clotting factors. In low concentrations heparin increases the activity of antithrombion against activated stuartprower factor and thrombin. So low doses of heparin are used. It is not absorbed from the oral route so it is administered as intravenous injection. The half life of heparin varies from 1 to 2 hours. Heparin is available as injections having 1000 to 40000 units per ml.

of the precursor of prostaglandins. It is contraindicated in persons sensitive to aspirin and peptic ulcer and in platelet disorder.

8.3. DRUGS USED IN HYPERLIPIDEMIA

Antihyperlipidemic agents are indicated for the modification of abnormal serum lipid profile. Abnormal blood lipids have been associated with diseases that arise out of arteriosclerosis, with an increase of blood cholesterol. Alteration in lipid metabolism leads to hyperlipidemic state. A normal blood sample has the following lipid profile.

Total cholesterol lies in the range of 150 to 240mg per 100ml of the blood. High level of serum cholesterol usually shows an increase in concentration of low density lipoprotein cholesterol (LDLC) which accounts for 60 to 70% of the total blood cholesterol.

The normal value of LDLC is 150mg per 100ml of blood.

The other factor which is important in the determination of hyperlipidemia is the concentration of high density lipoprotein cholesterol (HDLC). This is present in blood in a range of 38 to 64mg per 100 ml of the blood.

The ratio of LDLC to HDLC should be less than 3 in normal individuals. Any value above this warrants attention.

Most of the hypercholesterolemic conditions are due to the defect in receptor mediated catabolism of LDL cholesterol. Secondary lipoprotein cholesterol abnormalities are due to the defect in receptor mediated catabolism of LDL cholesterol.

Secondary lipoprotain cholesterol abnormilities are associated with endocrine disorders such as diabetes mellitus, hyperthyroidism, obesity and kidney diseases. Drugs can also induce change in the lipid profile, such as thiazide diuretics may lower HDLC and may raise triglycerides and LDLC levels in blood. There are a number of different types of drugs used in lowering blood cholesterol.

Nicotinic acid (Nicin) : This drug depresses the synthesis of very low density lipoproteins. Nicin is used in the dose of 1gm daily in combination with fish oil. 300 to 600mg capsules produce lowering of triglycerides and LDLC. It is used in the therapy of hyperlipidemia.