**ANTIHYPERLIPIDAEMIC AGENTS**

**Learning objectives**

* Upon completion of this chapter, students should be able to understand basic concepts in Hyperlipidaemia, classification, mechanism of action, adverse effects and therapeutic uses of anti-hyperlipidaemic drugs.

**Basic concepts in Hyperlipidaemia**

* ***What is Hyperlipidaemia?***

Hyperlipidaemia is a broad term, also called hyperlipoproteinaemia, is a common disorder in developed countries and is a major cause of coronary heart disease. It results in abnormalities in lipid metabolism or plasma lipid transport or disorder in the synthesis and degradation of plasma proteins.

* ***Causes of Hyperlipidaemia***

Hyperlipidaemia is caused by lifestyle habits or treatable medical conditions. Obecity, not exercising, smoking, diabetes, obstructive jaundice and an underactive thyroid gland inherit Hyperlipidaemia.

* ***What are Lipids?***

Lipids are heterogeneous mixtures of fatty acids and alcohols in the body. The major lipids in the blood stream are cholesterol and its esters, triglycerides and phospholipids.

* ***What are Lipoproteins?***

Since blood and other body fluids are watery, fat needs a special transport system to travel around the body. They are carried from one place to another mixing with protein particles, called lipoproteins. There are 4 or 5 different types of lipoproteins each having distinct jobs- chylomicrons, LDL, VLDL, IDL, HDL

* ***Types of Hyperlipidaemia***
1. Primary Hyperlipidaemia- it is due to genetic causes such as mutation in receptor protein, while secondary Hyperlipidaemia arises due to other underlying causes such as diabetes.
2. Secondary Hyperlipidaemia- it is an abnormal rise in blood lipids (fats), including cholesterol and triglycerides. It does not cause discernible symptoms but can increase the risk of heart attack and stroke.

**Classification of Antihyperlipidaemics:**

1. HMG- CoA reductase inhibitors- e.g. Atorovastatin
2. Fibrates – Fenofibrate, Clofibrate
3. Bile acid Sequestrants – Cholestyramine, Colestipol
4. Nicotinic acid – Niacin
5. Cholesterol absorption Inhibitors- Ezetimibe
6. Antioxidant drugs- Probucol
7. Herbal drug- Guggulipids
8. **HMG- CoA REDUCTASE INHIBITORS:-**

Introduced in the 1980s, these classes of compounds are the most efficacious and best tolerated hypolipidaemic drugs. They competitively inhibit conversion of 3- Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 20–50%. This results in compensatory increase in LDL receptor expression on liver cells → increased receptor mediated uptake and catabolism of IDL and LDL. Different statins differ in their potency and maximal efficacy in reducing LDL-CH. The daily dose for lowering LDL-CH by 30–35% is lovastatin 40 mg, pravastatin 40 mg, simvastatin20 mg, atorvastatin 10 mg, rosuvastatin 5 mg and pitavastatin 2 mg. All statins produce peak LDL-CH lowering after 1–2 weeks therapy. Hepatic synthesis of VLDL is concurrently reduced and its removal from plasma is enhanced. Because HMG-CoA reductase activity is maximum at midnight, all statins are administered at bed time to obtain maximum effectiveness. All statins, except rosuvastatin are metabolized primarily by CYP3A4.

**Lovastatin:** It is the first clinically used statin; is lipophilic and given orally in the precursor lactone form. Absorption is incomplete and first pass metabolism is extensive. Metabolites are excreted mainly in bile. The t½ is short (1–4 hours).

**Simvastatin:** It is twice as potent as lovastatin; also more efficacious. A greater rise in HDLCH (when low) has been noted with simvastatin than lovastatin or pravastatin. Like lovastatin, it is lipophilic and given in the lactone precursor form. Oral absorption is better and first pass metabolism extensive; t½ is 2–3 hr.

**Atorvastatin:** This newer and most popular statin is more potent and appears to have the highest LDL-CH lowering efficacy at maximal daily dose of 80 mg. Atorvastatin has a much longer plasma t½ of 18– 24 hr than other statins, and has additional antioxidant property.

**Adverse effects:** All statins are remarkably well tolerated;. Notable side effects are: Gastrointestinal complaints and headache are usually mild. Rashes and sleep disturbances are uncommon. Rise in serum transaminase can occur, but liver damage is rare. Monitoring of liver function is recommended.

**Uses:** Statins are the first choice drugs for primary hyperlipidaemias with raised LDL and total CH levels, with or without raised TG levels, as well as for secondary (diabetes, nephrotic syndrome) hypercholesterolaemia.

1. **BILE ACID SEQUESTRANTS (Resins):** Cholestyramine and Colestipol: These are basic ion exchange resins supplied in the chloride form. They are neither digested nor absorbed in the gut: bind bile acids in the intestine interrupting their enterohepatic circulation. Faecal excretion of bile salts and CH is increased. This indirectly leads to enhanced hepatic metabolism of CH to bile acids. More LDL receptors are expressed on liver cells: clearance of plasma IDL, LDL and indirectly that of VLDL is increased. Resins have been shown to retard atherosclerosis, but are not popular clinically because they are unpalatable, inconvenient, have to be taken in large doses, cause flatulence and other g.i. symptoms, interfere with absorption of many drugs and have poor patient acceptability.
2. **LIPOPROTEIN-LIPASE ACTIVATORS (Fibrates):** The fibrates (isobutyric acid derivatives) primarily activate lipoprotein lipase which is a key enzyme in the degradation of VLDL resulting in lowering of circulating TGs. This effect is exerted through peroxisome proliferator-activated receptor α (PPARα) that is a gene transcription regulating receptor expressed in liver, fat and muscles. Activation of PPARα enhances lipoprotein lipase synthesis and fatty acid oxidation. PPARα may also mediate enhanced LDL receptor expression in liver seen particularly with second generation fibrates like bezafibrate, fenofibrate. Fibrates decrease hepatic TG synthesis as well. A peripheral effect reducing circulating free fatty acids has also been shown. Gemfibrozil: This fibric acid derivative effectively lowers plasma TG level by enhancing breakdown and suppressing hepatic synthesis of TGs. Besides high efficacy in type III hyperlipoproteinemia, gemfibrozil has shown action in subjects with raised blood CH in addition. In the ‘Helsinki Heart Study’ men without known CAD treated with gemfibrozil had a 34% reduction in fatal and nonfatal MI, though overall mortality was not affected. That these benefits extend to secondary prevention of coronary events in men with existing CAD and low HDLCH, has been demonstrated in another trial. Additional actions to decrease the level of clotting factor VII-phospholipid complex and promotion of fibrinolysis have been observed, which may contribute to the antiatherosclerotic effect. Pharmacokinetics: Gemfibrozil is completely absorbed orally, metabolized by glucuronidation and undergoes some enterohepatic circulation. It is excreted in urine; elimination t½ is 1–2 hr. Adverse effects: Common side effects are epigastric distress, loose motions. Skin rashes, body ache, eosinophilia, impotence, headache and blurred vision have been reported. Myopathy is uncommon. Gemfibrozil + statin increases risk of myopathy. Incidence of gallstone is not increased as was seen with clofibrate. It is contraindicated during pregnancy.