Anti-hyperlipidemic drugs

These are drugs which lower the levels of lipids and lipoproteins in blood.

The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals.

CLASSIFICATION:

1. ***HMG-CoA reductase inhibitors (Statins)*****:** Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Pitavastatin

2. ***Bile acid sequestrants (Resins)*****:** Cholestyramine, Colestipol

3. ***Lipoprotein lipase activators (PPARα activators, Fibrates):*** Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.

4. ***Lipolysis and triglyceride synthesis inhibitor:*** Nicotinic acid.

5**.** ***Sterol absorption inhibitor:*** Ezetimibe.

HMG-CoA REDUCTASE INHIBITORS (Statins)-

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. Over long-term, feedback induction of HMG-CoA reductase tends to increase CH synthesis, but a steady-state is finally attained with a dosedependent lowering of LDL-CH levels.

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. Moreover, at their maximum recommended doses simvastatin (80 mg) causes 45–50% reduction, while atorvastatin (80 mg) and rosuvastatin (40 mg) can reduce LDL-CH by upto 55%. The ceiling effect of lovastatin and pravastatin is 30–40% LDL-CH reduction. 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. However, this is not necessary for atorvastatin and rosuvastatin, which have long plasma t½. All statins, except rosuvastatin are metabolized primarily by CYP3A4. Inhibitors and inducers of this isoenzyme respectively increase and decrease statin blood levels.

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. At this dose a greater reduction in TGs is noted if the same was raised at baseline. 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; overall incidence of side effects not differing from placebo. 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.

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 (which is absorbed with the help of bile salts) 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.

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 HDL-CH, 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.

LIPOLYSIS AND TRIGLYCERIDE SYNTHESIS INHIBITOR:

Nicotinic Acid (Niacin): It is a B group vitamin (*see* Ch. 67) which in much higher doses reduces plasma lipids. This action is unrelated to its vitamin activity

and not present in nicotinamide. When nicotinic acid is given, TGs and VLDL decrease rapidly, followed by a modest fall in LDL-CH and total CH. A20–50% reduction in plasma TGs and 15–25% reduction in CH levels has been recorded. Nicotinic acid is the most effective drug to raise HDL-CH, probably by decreasing rate of HDL destruction; a 20–35% increase is generally obtained. Relatively lower dose suffices to raise HDL–CH. It also reduces lipoprotein Lp (a), which is considered more atherogenic. Nicotinic acid reduces production of VLDL in liver by inhibiting TG synthesis. Indirectly the VLDL degradation products IDL and LDL are also reduced. No direct effect on CH and bile acid metabolism has been found. It inhibits intracellular lipolysis in adipose tissue and increases the activity of lipoprotein lipase that clears TGs.

Adverse effects: The large doses needed for hypolipidaemic action are poorly tolerated. Only about half of the patients are able to take the full doses. Nicotinic acid is a cutaneous vasodilator: marked flushing, heat and itching (especially in the blush area) occur after every dose. This is associated with release of PGD2 in the skin, and can be minimized by starting with a low dose taken with meals and gradually increasing as tolerance develops.

Dyspepsia is very common; vomiting and diarrhoea occur when full doses are given.

Peptic ulcer may be activated.

Dryness and hyperpigmentation of skin can be troublesome.

Other long-term effects are: Liver dysfunction and jaundice. Serious liver damage is the most important risk. Hyperglycemia, precipitation of diabetes (should not be used in diabetics).

It is contraindicated during pregnancy and in children.

STEROL ABSORPTION INHIBITOR:

Ezetimibe: It is a novel drug that acts by inhibiting intestinal absorption of cholesterol and phytosterols. It interferes with a specific CH transport protein NPC1L1 in the intestinal mucosa and reduces absorption of both dietary and biliary CH. There is compensatory increase in hepatic CH synthesis, but LDL-CH level is lowered by 15–20%. The enhanced CH synthesis can be blocked by statins, and the two drugs have synergistic LDL-CH lowering effect. Due to very poor aqueous solubility, ezetimibe is not absorbed as such. A fraction is absorbed after getting conjugated with glucuronic acid in the intestinal mucosa. This is secreted in bile and undergoes enterohepatic circulation to be mainly excreted in faeces. A plasma t½ of 22 hours has been calculated.