Drugs in hyperlipidemia

Lipids are carried in special macromolecular complexes termed as **LIPOPROTEINS**

There are 3 types of plasma lipoprotein fractions:

1. LDL-beta-lipoprotein
2. VLDL-pre beta-lipoprotein
3. HDL-alpha-lipoprotein

Pathophysiology

The normal function of lipoproteins is to distribute and recycle cholesterol.

*Cholesterol within cells, is needed for membrane growth and repair.

*Cholesterol in liver, is needed to form bile acids.

*HDL takes cholesterol from peripheral cells to the liver, so it is protective against ischemic heart diseases (IHD).

Note: HDL levels are increased by:

-exercise

-weight loss

-in those living on fish diet

Hyperlipidemia

Can be:

1. Primary- due to diet and genetics
2. Secondary-is a consequence of other conditions like DM, alcoholism, nephrotic syndrome, chronic renal failure, hypothyroidism, liver disease, administration of drugs (tamoxifen, ciclosporin, thiazide diuretics, contraceptive pills, glucocorticoids, β-blockers).

Management of hyperlipidemia

*Long term decisions on management should be initiated only on the basis at least two fasting blood samples.

Management may proceed as follows:

1. *Any medical disorder* that may be, causing hyperlipidemia should be treated first.

2. Dietary adjustment

* Overweight patients should reduce their total caloric intake
* Decrease alcohol intake
* Decrease total fat intake especially of animal origin

* Decrease carbohydrate intake, sucrose and other simple sugar intake which increases VLDL
* Excess egg yolk should be avoided
* Supplementation of fat soluble vitamins can be given

3. *Drugs*

*Diet is necessary adjunct to drug therapy and should be continued for achievement of the full potential of drug regimen.
*The decision to use lipid-lowering drugs is made on the basis of the overall absolute coronary heart disease (CHD) risk e.g. evidence of existing CHD, hypertension, diabetes mellitus, positive family history.

I. STATINS

e.g simvastatin (zocor), fluvastatin (lescol), pravastatin (lipostat) are short acting
atorvastatin (Lipitor) and rosuvastatin (crestor) are long lasting inhibitors

Mechanism of action

1. These agents block the rate limiting enzyme for endogenous hepatic cholesterol synthesis, hydroxymethylglutaryl coenzyme A (HMGCoA) reductase, this results in increased synthesis of LDL receptors (up-regultion) in the liver and increased clearance of LDL from circulation, plasma total cholesterol and LDL cholesterol fall, with a maximum effect after 1 month of therapy.
2. They also elevate HDL cholesterol
3. They have actions on the inflammatory components of atheroma progression.

All these will reduce the risk of cardiovascular events in patients with coronary artery disease.
Statins are well absorbed after oral administration, and they are metabolized in the liver.
*Short acting statins are given by mouth at night to decrease peak cholesterol synthesis in early morning.

Adverse effects are well tolerated
Headache, rash, dyspepsia, flatulence, constipation, abdominal pain, minor abnormality of liver function tests, asymptomatic elevation of muscle enzymes and myositis occurs rarely.

II. FIBRIC ACID DERIVATIVES (Fibrates)

e.g. gembfibrozil (lopid), fenofibrate, bezafibrate (bezalip), ciprofibrate

These drugs increase oxidation of fatty acids in liver and muscles. In liver, secretion of TG-rich lipoproteins falls, and in muscle the activity of lipoprotein lipase and fatty acid uptake from plasma are both increased. So plasma TG declines by 20-30% and cholesterol by 10-15%.

*There is also rise in protective HDL-cholesterol, which may contribute to the reduction in non-fatal myocardial infarction.

These drugs are well absorbed from GIT, extensively bound to plasma proteins, and are excreted mainly by kidney as unchanged drug or metabolites.

*They are drugs of choice for **mixed hyperlipidemia** (elevated cholesterol and TG), but may be used in hypercholesterolemia, alone or with anion exchange resins or statins (with care)

Adverse effects

1. GIT disturbances (nausea, abdominal pain, diarrhea)
2. Gall stone formation
3. Hepatotoxicity
4. Rarely myositis

III. ANION EXCHANGE RESINS (Bile acid sequestrants)

Cholestyramine (Questran)

Acts by binding bile acids in intestine, so inhibits the re-absorption of bile salts into their enterohepatic cycle, so bile acids are lost in feces. The depletion of bile acid pool will stimulate conversion of cholesterol to bile acids, so plasma LDL-cholesterol falls by 20-25%.

It is used in hypercholesterolemia but not hypertriglyceridemia

Adverse effects

GIT side effects including constipation, abdominal fullness, anorexia and occasionally diarrhea.

IV. Ezetimibe (Ezetrol)

Selectively blocks intestinal absorption of cholesterol, leading to decrease in delivery of intestinal cholesterol to the liver. This causes reduction of hepatic cholesterol stores and increase in clearance of cholesterol from blood.

*It deceases LDL, TG and increases HDL

***Simvastatin and Ezetimibe** in one formulation is more effective than

simvastatin alone

V. NICOTINIC ACID & DERIVATIVES (Niacin or vitaminB3)

Acts as antilipolytic agent in adipose tissue, reducing the supply of free fatty acids and hence the availability of substrate for hepatic TG synthesis and the secretion of VLDL. So it lowers plasma TG and cholesterol concentrations and raises HDL-cholesterol.

*is used in **all types of hyperlipidemia**

*oral dose is 100 times more than normal human nutritional needs.

Adverse effects

1. GIT upset (nausea, dyspepsia, abdominal pain, diarrhea)
2. pruritis and flushing of face, neck and ears
3. hepatotoxicity
4. gouty arthritis and hyperglycemia

*Its use is limited because of unpleasant side effects

VI. OTHER DRUGS

1. Omega-3 marine triglycerides (Maxepa)

Is derived from fish oil, taken for coronary heart disease prevention (benefit may be due to antithrombotic effect).

2. Alpha-tocopherol acetate (vitamin E)

Has no effect on lipid levels but is a powerful antioxidant and may have a role in prevention of atheroma (oxidation of LDL is an essential step in development of atheroma)