Drugs used in treatment of Cardiovascular System

Antihyperlipidemic drugs

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2017

Hyperlipidemia

- Plasma lipids consist mostly of lipoproteins, a spherical macromolecular complexes of lipids and specific proteins (apolipoproteins).
- The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL.
- The occurrence of CHD is positively associated with high total cholesterol, and even more strongly with elevated LDL cholesterol in the blood.
- Reduction of the LDL level is the primary goal of cholesterol-lowering therapy

Hyperlipidemia:

elevated of serum lipids.

- Drugs used to treat hyperlipidemia generally are targeted to:

1. Decreased production of lipoproteins in plasma & tissues.
2. Increased catabolism of lipoproteins in the plasma.
3. Increased removal of cholesterol from the body.

A. Treatment options for hypercholesterolemia

- In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL levels and increases in HDL levels.
- However, most patients are unwilling to modify their lifestyle sufficiently to achieve LDL treatment goals, and drug therapy may be required.
- Patients with LDL levels higher than 160 mg/dL and with one other major risk factor, such as hypertension, diabetes, smoking, or a family history of early CHD, are candidates for drug therapy.
- Patients with two or more additional risk factors should be treated aggressively, with the aim of reducing their LDL level to less than 100 mg/dL and, in some patients, to as low as 70 mg/dL.

B. Treatment options for hypertriacylglycerolemia

- Elevated triacylglycerol (triglyceride) levels are independently associated with increased risk of CHD.
- Diet and exercise are the primary modes of treating hypertriacylglycerolemia.
- If indicated, niacin and fibric acid derivatives are the most efficacious in lowering triacylglycerol levels.
- Triacylglycerol reduction is a secondary benefit of the statin drugs (the primary benefit being LDL cholesterol reduction).

Types of Hyperlipidemias

1. I - Familial hyperchylomicronemia.
2. II - A Familial hypercholestermia.

   II - B Familial combined hyperlipidemia.
3. Type III Familial dysbetalipoproteinemia.
4. Type IV Familial hypertriglyceridemia.
5. Type V Familiar mixed hypertriglyceridemia

Drugs that Lower the Serum Lipoprotein Concentration

A. 3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (COA) reductase inhibitors (Statins)

- This group of antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis, and they are the first-line and more effective treatment for patients with elevated LDL cholesterol.

- Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.

- The value of lowering the level of cholesterol with statin drugs has now been demonstrated in 1) patients with CHD with or without hyperlipidemia, 2) men with hyperlipidemia but no known CHD, and 3) men and women with average total and LDL cholesterol levels and no known CHD.

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Mechanism of action

A. Inhibition of HMG CoA reductase

- Lovastatin, Simvastatin, Pravastatin, Atorvastatin, fluvastatin, and rosuvastatin are analogs of HMG, the precursor of cholesterol.
- Because of their strong affinity for the enzyme, all compete effectively to inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol.
- Rosuvastatin and atorvastatin are the most potent LDL cholesterol-lowering statin drugs, followed by simvastatin, pravastatin and then lovastatin and fluvastatin.

Mechanism of action

B. Increase in LDL receptors:

- Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs.
- Thus, the end result is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL.
- The HMG CoA reductase inhibitors, like the bile acid sequestrant cholestyramine, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD.
- Decreases in triglyceride also occur.

Therapeutic uses:

- Effective in lowering plasma cholesterol levels in all types of hyperlipidemias.
- However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.
- It should be noted that in spite of the protection afforded by cholesterol lowering, about one-fourth of the patients treated with these drugs still present with coronary events. Thus, additional strategies, such as diet, exercise, or additional agents, may be warranted.

Niacin (nicotinic acid)

- Mechanism of action:
- Niacin strongly inhibits lipolysis in adipose tissue (the primary producer of circulating free fatty acids). The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production. LDL (the cholesterol-rich lipoprotein) is derived from VLDL in the plasma.

- Niacin can reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

Therapeutic uses:

1. Treatment of type II-B & IV hyperlipoproteinemia in which both VLDL & LDL elevated.
2. Also used in treatment of sever hypercholesterolemias.
3. It’s the most potent antihyperlipidemic agent for raising plasma HDL levels.

Adverse effects

- Intense cutaneous flush and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated.
- Some patients also experience nausea and abdominal pain, hyperuricemia, gout and hepatotoxicity.

The Fibrates: Fenofibrate & Gemfibrozil

- Mechanism of action:
- They stimulate lipoprotein lipase activity leading to decrease the level of acylglycerol levels by hydrolyzing it into chylomicrons & VLDL.
- It increase HDL levels moderately.
- Fibrates inhibit cholesterol in liver & lower plasma fibrinogen levels.

Therapeutic uses:

1. Treatment of hyperglyceridemias.
2. Treatment of type III hyperlipidemia.
3. Patients with hypertriacylglycerolemia Type IV (elevated VLDL) or Type V (elevated VLDL plus chylomicron) disease who do not respond to diet or other drugs may also benefit from treatment with these agents.

- **Side effects:**

1. GIT disturbances, Lithiasis leads to formation of gall stone.
2. Malignancy leads to death.
3. Myositis.

Drug interactions:

Both fibrates compete with the coumarin anticoagulants and potentiate anticoagulant activity.

Contraindications:

They should not be used in patients with severe hepatic and renal dysfunction or in patients with preexisting gallbladder disease. Also in pregnant or lactating women.

Bile acid binding resins

Cholestyramine & Colestipol

- **Mechanism of action:**

  They form resin-bile complex which excreted in feces thus, preventing the bile acids from retuning to the liver by the enterohepatic circulation which result in decreasing the total plasma cholestrol concentration (fall in plasma LDL).

- **Therapeutic uses:**

1. DOC in treatment of type II A & II B hyperlipidemias.
2. Cholestrymine can treat pruritis in patients with biliary obstruction.
3. Diarrhea of excessive bile excretion.

- **Side effects:** GI disturbances, impaired absorption.

- **Drug interaction:**

  This group interact with the intestinal absorption of tetracycline, Phenobarbital, digoxine, warfarin, pravastatin, aspirin & thiazide diuretics. So should be given either before 1 hr or 4-6 hrs after the bile acid-binding resins.

Cholesterol absorption inhibitors

- *Ezetimibe* selectively inhibits intestinal absorption of dietary and biliary cholesterol in the small intestine.
- This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.
- A formulation of ezetimibe and simvastatin has been shown to lower LDL levels more effectively than the statin alone.

Combination therapy

- Type II hyperlipidemias, patients are commonly treated with a combination of niacin plus a bile acid-binding agent, such as cholestyramine.
- The combination of an HMG CoA reductase inhibitor with a bile acid-binding agent has also been shown to be very useful in lowering LDL cholesterol levels.
- A low dose statin in combination with ezetimibe achieves comparable or even greater LDL cholesterol reduction than a very-high-dose statin.
- Simvastatin and ezetimibe are currently available combined in one pill to treat elevated LDL cholesterol.

End of Antihyperlipidemia