Hypo lipidemic drugs

- Learning objectives
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- **Statins**
- **Cholestyramine**
- **Nicotinic acid**
- **Gemfibrozil .**
- **Mechanisms of action**
- **Side effects**

Hypo lipidemic drugs

- Plasma lipids consist mostly of lipoproteins- spherical macromolecular complexes of lipid and specific protein called (apolipoproteins)

- Clinically important lipoproteins in decreasing order of atherogenisity are LDL, VLDL, chylomicrons, and HDL

- The occurrence of IHD, is positively associated with elevate LDL cholesterol in the blood in contrast high level of HDL cholesterol have been associated with decrease risk of heart diseases

- Cholesterol levels may be elevated because of an individual's life style e.g. lack of exercise and consumption of diet containing excess saturated fatty acids
- Hyperlipidemias can also result from inherited a single gene defect in lipoprotein metabolism or more commonly by a combination of genetic and life style factors

The genetic types of hyperlipidemias

1-Type one (familial hyper chylomiconemia)

where massive hyperchylomicronemia following normal dietary fat intake due to deficiency of lipoprotein lipase or deficiency of apolipoprotein C 2 ; this type not associated with increased risk of IHD

2- Type two a (familial hypercholesterolemia)

elevated LDL with normal VLDL level due to block in LDL degradation, result in increased serum cholesterol while triacylglycerol (TG) level is normal ,occur due to defect in synthesis or processing of LDL receptors and this type associated greatly with increased risk of IHD

3-Type two b (familial combined –mixed- hyperlipidemia)

similar to type 2a, but VLDL is also increased result in elevated serum TG as well as cholesterol levels caused by overproduction of VLDL by the liver.

Type three (familial dysbeta lipoproteinemia)

associated with increased level of IDL and this lead to increase serum cholesterol and TG due to overproduction by liver for IDL or underutilization

Type four (familial hypertriglyceridemia)

result from increase VLDL with normal LDL lead to increase serum TG with normal or slightly increase serum cholesterol

Type 5(familial mixed hypertriglyceridemia)

serum VLDL and chylomicron are elevated

LDL is normal or decreased lead to greatly elevated TG level ,due to over production of VLDL and chylomicron or decrease clearance

Groups of anti hyperlipidemic drugs

1-HMG-COA reductase inhibitors (Statins)

2-Niacin (nicotinic acid) (vitamin B3)

3-Fibrate e.g. Fenofibrate, Gemfibrozil, Ciprofibrate and Bezafibrate

4-Bile acid sequestrants or bile acid –binding resins e.g. Cholestyramine, Colestipol, and Colesevelam

5- Cholesterol absorption inhibitors e.g. Ezetimibe

1- HMG-COA reductase inhibitors

- Also known as a statins, lower elevated LDL cholesterol level this group of drugs inhibits the first step oh cholesterol synthesis ;
- these drugs are analog of 3-hydroxy -3-methyl glutarate, the precursor of cholesterol ;all compete effectively to inhibit HMG – COA reductase (the rate limiting step in cholesterol synthesis)
- Atorvastatin is the most potent LDL cholesterol –lowing statin drug, followed by pravastatin and Fluvastatin and then Lovastatin and Simvastatin
- This group can increase plasma HDL level in some patients and decrease in triacylglycerol also occur
- Depletion of intracellular cholesterol cause the cell to increase the number of specific cell surface LDL receptors ,thus the end result is a reduction in plasma cholesterol both by inhibit cholesterol synthesis and by increase catabolism of LDL

Clinical uses and Pharmacokinetic

- These drugs are effective in lowing plasma cholesterol levels in all types of hyperlipidemias especially type2a and type 2b

- Given orally, well absorbed from intestine, exposed for extensive first pass metabolism in the liver, excretion take place through the bile with some urinary excretion half-life range from 1.5-2 hrs.

Side effects and drug interaction

❖ Side effects

1-mild GIT upset

2- Abnormal liver functions

3- Myopathy with skin rash

❖ Drug interaction

Statin drugs increase Warfarin level thus it is important to evaluate prothrombin time frequently

❖ Contraindication

In pregnant women, breast feeding and should not use in children and teenagers

2- Niacin (Nicotinic acid)

- Can decrease level of LDL by 10-20 % and it is the most effective agent for increasing HDL; Niacin can be sue in combination with statin

Mechanism of action

- Niacin inhibits lipolysis in adipose tissue (the primary producer of circulating free fatty acids) as a major precursor for triacylglycerol synthesis , thus it decreases triacylglycerol synthesis in the liver(which is required for VLDL production),LDL(the cholesterol- rich lipoprotein)is derived from VLDL in the plasma ,therefore, reduction in the VLDL concentration also result in a decrease in the plasma LDL concentration, thus both plasma TG and cholesterol are lowered

Clinical uses

- Lipid- lowering properties require much higher doses than when used as a vitamin, often used in combination with other lipid-lowing agents

1-Sever hypercholesterolemia (all types), often in combination with other lipid lowing drugs

2- It is the most potent lipid lowing agent for raising plasma HDL level

Pharmacokinetic and Side effects of Niacin

- **Pharmacokinetic**

Administered orally converted in the body to nicotinamide which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD), excretion in urine

- **Side effects**

❖ More common side effect is cutaneous flush and pruritus, intake of Aspirin prior to taking Niacin decrease the flash

❖ sometimes nausea abdominal pain

❖ hyperuricemia and hepatotoxicity have also been reported

❖ to minimize side effects start on low initial dose and gradually increase it and taken with meals

3- Fibrate group

- Fenofibrate and Gemfibrozil are derivative of fibric acid that lower serum TG and increase HDL levels ,both have the same mechanism of action ,but Fenofibrate is more effective than Gemfibrozil in lowing plasma LDL cholesterol and TG levels

Mechanism of action

- Fibrate mediated gene expression lead to decrease triacylglycerol concentration (by increase the expression of lipoprotein lipase and decrease apoC-2 concentration), and increase level of HDL cholesterol (by increase the expression of apo-A-1 and Apo- A-2) that mean

1- activation of lipase which breakdown cholesterol

2- Suppress release of free fatty acid from adipose tissue

3- Inhibit synthesis of TG in the liver

4- Increase secretion of cholesterol in the bile

Clinical uses

- The fibrate are used in the treatment of hypertriacylglycermia, causing significant decrease in plasma triacylglycerol levels
- Fenofibrate and Gemfibrozil are particularly useful in treating type 3 hyperlipidemia (dysbeta lipoproteinemia) in which IDL accumulated
- Patients with hypertriacylglycermia (type 4 elevated VLDL) or type 5 (elevated VLDL+ chylomicron) diseases who don't respond to diet or other drugs may also benefit from treated with these drugs

Pharmacokinetic and Side effects

- Both drugs are completely absorbed after oral dose, both distributed widely in body, bound to albumin, both are undergo extensive hepatic metabolism and are excrete in the urine
- **Side effects**

  1-the most common is GIT disturbances

  2- Lithiasis (gall stone formation)

  3- Myositis and myopathy

  4-Prolonged prothrombin time

- **Drug interaction**

  Both fibrates compete with the anticoagulant drugs

- **Contraindication**

  In pregnancy and lactating women, they should not be use in patients with severe hepatic and renal dysfunction or in patients with preexisting gall bladder diseases

4-Bile acid binding resins

- Have significant LDL cholesterol –lowing effect, these drugs act by binding to bile acids and bile salts in small intestine, the resin/ bile acid complex is excrete in the feces, this preventing the bile acid from returning to the liver by enterohepatic circulation
- Lowing the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, consequently the intracellular cholesterol concentration decrease which activate increase hepatic uptake of cholesterol containing LDL lead to a fall in plasma LDL ,the final outcome of this sequence of events is decrease total plasma cholesterol concentration

Clinical uses and side effects

- **Clinical uses**

  1-Drugs of choice in treatment type 2a and type two b hyperlipidemia

  2- Cholestyramine can also relive pruritus caused by accumulation of bile acids in patients with biliary obstruction

- **Pharmacokinetic**

  These drugs taken orally, because they are insoluble in water and are very large, they are neither absorbed nor metabolically altered by the intestine, but they are totally excreted in feces

- **Side effects**

  1-GIT disturbances are more common

  2- Impaired fat- soluble vitamins (A, D, E, K), especially by Cholestyramine and Colestipol, but not Colesevelam, patients on long- term therapy may need supplement fat-soluble vitamins

- **Drug interaction**

  Cholestyramine and Colestipol are interfere with the intestinal absorption of many drugs e.g. Tetracycline, Digoxin, Warfarin, Aspirin, Thiazide diuretic, therefor; drugs should be taken at least one- two hours before or 4-6 hours after the bile acid-binding resins

5- Cholesterol absorption inhibitors e.g. Ezetimibe

- Selectively inhibits intestinal absorption of dietary and biliary cholesterol in small intestine
- it is metabolized in the liver and intestine with biliary and renal excretion, half-life 22 hours
- it decreases LDL, TG, and increase HDL, Simvastatin and Ezetimibe in one formulation is more effective than Simvastatin alone