DRUGS USED IN HYPERLIPIDEMIA

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OVERVIEW OF LIPIDEMIA

- Lipids are necessary molecules for human life
- Cholesterol is the essential component of cell membranes is the precursor to the sterol and steroid s that are synthesized in the body
- Triglycerides which are composed of three fatty acids and glycerol are the main storage form of fuel used to generate high energy for muscle contractions and metabolic reactions
- Examples of such generated high energy compounds such is adenosine triphosphates (ATP)

HYPERLIPIDEMIA

- While these lipids play a vital function, elevated blood or serum concentration of cholesterol and triglycerides have been shown to be detrimental (harmful effects)

- **Hyperlipidemia** and **hyperproteinemia** are general terms used for the elevated concentrations of **lipids** and **lipoproteins** in the blood

- On the other hand, **hypercholesterolemia** and **hypertriglycerdemia** refer specifically refer to the respective high concentration of **cholesterol** and **triglycerides**

- **Hypercholesterolemia** contributes to the pathogenesis of atherosclerosis and has been causally associated to coronary artery diseases and other atherosclerotic vascular diseases

- **Hypertriglyceridemia** is a risk factor of **pancreatitis** but its role in the development atherosclerosis and heart disease remains uncertain

(Drugs used to control triglycerides have not shown reduction in cardiovascular diseases nor mortality)

CORONARY HEART DISEASE (CHD) AS A TARGETED DISEASE TO BE PREVENTED

- Coronary heart disease (CHD) is the main cause premature death in many countries
- It is therefore, important to detect and eliminate modifiable risk factors associated to CHD

RISK FACTORS OF CHD

i. Hyperlipidemia
ii. Low high density lipoprotein (HDL) cholsterol level
iii. Hypertension
iv. Cigarette smoking
v. Male gender
vi. Family history of CHD (First degree male relative under 55 years of age and first degree female relative
vii. Diabetes mellitus
viii. Clinical manifestations of non coronary forms of atherosclerotic diseases (e.g. aortic aneurysms, carotid artery diseases)

LIPOPROTEINS AND LIPID TRANSPORT

- Lipids are insoluble in plasma water and thus usually transported in the blood in the form lipoproteins
- There are numerous types of lipoproteins which include, chylomicrons, very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), Intermediate-density lipoproteins, high density lipoproteins (HDLs)
- These types of lipoproteins are distinguished in terms of their bouyant density, lipid and protein composition and role in lipid transport
- Each type of lipoproteins is associated with a unique group of apoprotiens some of which are exchanged between different lipoproteins as they transport lipids to various tissues

Lipoproteins and lipid Transport Cont'd

- Chylomicrons are involved primarily in the transport of dietary lipids from the gut to the adipose tissue and liver
- When cholesterol and triglycerides are ingested, they are emulsified in the intestines by the bile acids and other bile secretions and form chylomicrons in the gut wall
- After chylomicrons are secreted in the circulation, they deliver triglycerides to adipose tissues via the action of lipoprotein lipase located in the vascular endothelial cells
- Through this process, chylomicrons are converted to a cholesterol rich chylomicron which transports cholesterol to the liver

Lipoproteins and lipid Transport Cont'd

- The golgi bodies in the liver form VLDLS from triglycerides, cholesterol and protein and then secrete this formed VLDLs into circulation
- VLDLs are converted to intermediate low density lipoprotein and LDLs which contain the a high percentage of cholesterol
- LDLs transport cholesterol to the nascent atheromas and contribute to the formation of atherosclerosis
- HDLs are small lipoprotein with high density which comes about due to high ratio of protein to lipid
- HDLs transport cholesterol from atheromas and peripheral tissues to the liver

Goals of treatment

- The clinically important lipoproteins are starting from the most to the least atherogenic:
- LDL, very–low density lipoprotein (VLDL) and chylomicrons and HDL
- The occurrence of CHD is positively associated with high total cholesterol and more strongly with elevated LDL-C
- Total cholesterol is the sum of LDL-C, VLDL-C, and HDL-C
- In contrast to LDL-C, high levels of HDL-C have been associated with a decreased risk for heart disease

The primary goal is therefore;

- Reduction of LDL-C is the primary goal of cholesterol-lowering therapy.
- Previously, cholesterol guidelines recommended treating to specific targets for LDLC guidelines do not recommend targets but instead emphasize high-intensity or moderate-intensity statin therapy in defined populations with risk for atherosclerotic cardiovascular disease (ASCVD)
- Higher-intensity therapy is recommended in those with established ASCVD or in those with a higher overall risk of heart disease

Therapeutic lifestyle changes (TLC)

- TLC s are an essential modality in the management of high cholesterol and triglyceride levels and may be affective by themselves in patients with mildly elevated cholesterol or triglycerides levels
- TLC modalities include recommendations for diet, weight management and physical activity
- The diet should be low in cholesterol, saturated fat and calories to help the patient achieve ideal weight
- Studies show that diets low in saturated and trans fatty acids and high in omega 3 fatty acids (Linoleic acid and those in fish oils) improve the ration LDL-C to HDL-C
- Lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL-C and increases in HDL-C. However,

DRUG USED FOR HYPERLIPIDEMIA

1. HMG COA REDUCTASE INHIBITORS

Examples include;

- Lovastatin
- Simvastatin
- Pravastatin
- Atorvastatin
- Fluvastatin
- Pitavastatin
- Rosuvastatin

Benefit from HMG CoA reductase inhibitors

- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower elevated LDL-C
- This results in a substantial reduction in coronary events and death from CHD
- They are considered first-line treatment for patients with elevated risk of ASCVD
- Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity
- The value of lowering LDL-C with statins has been demonstrated in patients with and without established CHD

Mechanism of action HMG CoA inhibitors

- Statins are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis
- By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol
- Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs
- Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism
- Pitavastatin, rosuvastatin, and atorvastatin are the most potent LDL cholesterol–lowering statins, followed by simvastatin, pravastatin, and then lovastatin and fluvastatin
- The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients

NB: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ

Indications of HMG CoA inhibitors

- These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias

- However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and thus benefit much less from treatment with these drugs

Pharmacokinetics

- Lovastatin and simvastatin are lactones that are hydrolyzed to the active drug
- The remaining statins are all administered in their active form Absorption of the statins is variable (30% to 85%) following oral administration
- All statins are metabolized in the liver, with some metabolites retaining activity
- Excretion takes place principally through bile and feces, but some urinary elimination also occurs
- Their half-lives are variable

Side effects

- Elevated liver enzymes may occur with statin therapy
- Therefore, liver function should be evaluated prior to starting
- Myopathy and rhabdomyolysis (disintegration of skeletal muscle have been reported though rare)
- In most of these cases, patients usually had renal insufficiency or were taking drugs such as erythromycin, gemfibrozil or niacin
- Simvastatin is metabolized by cytochrome P450 3A4 and inhibitors of this enzyme may increase the risk of rhabdomyolysis

2. NIACIN (NICOTINIC ACID)

- Niacin can reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C
- It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 grams/day
- Niacin can be used in combination with statins, and a fixed-dose combination of lovastatin and long-acting niacin is available

Mechanism of action

- At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids
- The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis
- Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations

Indications of Niacin

- Niacin being effective at lowering plasma levels of both cholesterol and triglycerides
- It is useful in the treatment of familial hyperlipidemias
- It is also used to treat other severe hypercholesterolemias often in combination with other agents

Pharmacokinetics

- Niacin is administered orally
- It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD+)
- Niacin, its nicotinamide derivative and other metabolites are excreted in the urine
- Note: Nicotinamide alone does not decrease plasma lipid levels

Side effects

- Intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus
- Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated
- Some patients also experience nausea and abdominal pain
- Slow titration of the dosage or usage of the sustained-release formulation of niacin reduces bothersome initial adverse effects
- Niacin inhibits tubular secretion of uric acid and thus, predisposes to hyperuricemia and gout
- Impaired glucose tolerance and hepatotoxicity have also been reported
- The drug should be avoided in hepatic disease

3. FIBRATES

Examples;

- Fenofibrate and gemfibrozil

- These are derivatives of fibric acid that lower serum triglycerides and increase HDL levels

Mechanism of action of Fibrates

- The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism
- PPARs function as ligand-activated transcription factors whose ligands are fatty acids, eicosanoids or anti-hyperlipidemic drugs
- Fibrates then bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase
- They further decrease apolipoprotein (apo) concentration
- Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels
- Fibrates also increase the level of HDL cholesterol by increasing

Indication for fibrates

- The fibrates are used in the treatment of hypertriglyceridemias
- They are particularly useful in treating type III hyperlipidemia
- Type III hyperlipidemia also known as dysbetalipoproteinemia
- This is the hyperlipidemia where the inter-mediate density lipoprotein particles accumulate

Pharmacokinetics of Fibrates

- Gemfibrozil and fenofibrate are completely absorbed after oral administration
- Fibrates are also widely distributed and protein bound
- Fenofibrate is a prodrug, which is converted to the active moiety fenofibric acid
- Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates

Side effects

- The most common adverse effects are mild gastrointestinal (GI) disturbances which lessen as the therapy progresses
- Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones
- Myositis (inflammation of a voluntary muscle) and hence muscle weakness or tenderness should be evaluated, patients with renal insufficiency being at high at risk
- Myopathy and rhabdomyolysis have been reported in patients taking gemfibrozil and statins together, making the use of gemfibrozil is contraindicated with simvastatin
- Both fibrates may increase the effects of warfarin and so INR should, therefore, be monitored more frequently when a patient is taking both drugs
- Fibrates should not be used in patients with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease

4. Bile acid binding resins

Examples;

- Cholestyramine, colestipol, colesevelam
- These drugs are also referred to as Bile acid sequestrants
- They have significant LDL cholesterol- lowering effects, although the benefits are less than those observed with statins

Mechanism of action of Bile resins

- These drugs are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine
- The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration
- This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile
- Consequently, intracellular cholesterol concentrations decrease
- This further activates an increased hepatic uptake of cholesterol containing LDL particles and thus a fall in plasma LDL-C through an up-regulation of cell surface LDL receptors

Indications of Bile Resins

- The bile acid-binding resins are mostly used in combination with diet or niacin for treating type IIA and type IIB hyperlipidemias
- Bile resins are less effective on LDL levels in individuals who are homozygous for type IIA and where functional LDL receptors are totally lacking
- Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis
- Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects

Pharmacokinetics of Bile resins

- Bile acid sequestrants are insoluble in water and have large molecular weights
- After oral administration, they are neither absorbed nor metabolically altered by the intestine
- Instead, they are totally excreted in feces

Side effects

- GI disturbances, such as constipation, nausea, and flatulence
- Colesevelam has fewer GI side effects than other bile acid sequestrants
- These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K)
- Also interfere with the absorption of many drugs e.g digoxin, warfarin, and thyroid hormone
- Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins.
- These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL)

5. CHOLESTEROL ABSORPTION INHIBITORS

Example;

- Ezetimibe

- This drug selectively inhibits absorption of dietary and biliary cholesterol in the small intestine

- This leads to a decrease in the delivery of intestinal cholesterol to the liver

- This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood

Cholesterol absorption inhibitors Cont'd

- Ezetimibe lowers LDL cholesterol by approximately 17% which less compared to other drugs
- Based on this modest LDL-lowering effects, ezetimibe is often used as an adjunct to statin therapy or in statin-intolerant patients
- Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion
- Therefore, patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe

6. OMEGA 3 FATTY ACIDS

- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering
- Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver
- The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon
- Marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by approximately 25% to 30%, with small increases in LDL-C and HDL-C

Omega 3 fatty acids Cont'd

- Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone
- Icosapent ethyl is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C
- Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL)
- Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality
- The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste
- Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets

COMBINATION DRUG THERAPY

- It is often necessary to use two anti-hyperlipidemic drugs to achieve treatment goals in plasma lipid levels
- The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL-C levels
- Simvastatin and ezetimibe, as well as simvastatin and niacin, are currently available combined in one pill to treat elevated LDL cholesterol
- However, more clinical information is needed to determine whether combination therapy produces better long-term benefits than the use of a high-dose statin
- Until this uncertainty is resolved, many experts recommend maximizing statin dosages and adding niacin or fibrates only in those with persistently elevated triglycerides
- It is worth noting that combination drug therapy is not without risks. Liver and muscle toxicity occurs more frequently with lipid-lowering drug combinations

END