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March 2005 "Current Trends in Treating Elevated Cholesterol" 707-000-05-003-H01

THIS MONTH
"Elevated Cholesterol"

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HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.

Certain topics require regular updates Treatment of elevated cholesterol is one of these. Our goal is to discuss the therapeutic options. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-05-003-H01.

Pharmacists completing this lesson by March 31, 2008 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. List the risk factors that contribute to atherosclerotic plaques.
2. State the mechanism of atherosclerotic plaque formation.
3. Describe the characteristics & transport of blood lipids.
4. Describe current government review & guidelines for evaluating/treating hyperlipidemia.
5. Discuss the significance of therapeutic lifestyle changes in prevention/treatment of hyperlipidemia.
6. State the mechanism of action & side effects of common medications used in hyperlipidemia therapy.

INTRODUCTION

In normal levels, plasma lipids, which include cholesterol, triglycerides, and phospholipids, play an important role in producing energy, assist in the maintenance of body temperatures, and provide chemical precursors to entities required by the body such as hormones, adrenal corticoids, and vitamin D. Cholesterol is a monohydric alcohol that can be synthesized in the liver, and is a normal constituent of bile. It is widely distributed in animal tissue, and is found in abundance in egg yolk, various oils, fats, and nerve tissue of the spinal cord, brain and kidneys. Abnormally elevated lipids in the blood plasma allow cholesterol, in particular low-density lipoprotein cholesterol (LDL-C), to be deposited within the arterial wall of large and medium-sized arteries as atherosclerotic plaques. Such plaques cause obstruction of the arteries and may contribute to hypertension, reduction in the amount of oxygenated blood that reaches the heart, and increasing the risk of coronary heart disease (CHD), myocardial infarction, and cerebral arterial disease. Despite improvement in lifestyle (diet and exercise) and the use of cholesterol-lowering medications that resulted in considerable reduction in morbidity and mortality, CHD and strokes remain the principle causes of deaths in the U.S. The risk factors that contribute to atherosclerosis include: elevated serum lipids, cigarette smoking, hypertension, obesity, diabetes mellitus, physical inactivity, aging, excessive alcohol consumption and family history of the disease.

The major components of an atherosclerotic plaque, also known as atheroma, are cholesterol, cholesterol esters, and other lipids. The initial plaque is deposited in the smooth cells of the inner coat of large and medium-sized arteries. Lipoprotein, especially LDL-C, adheres to the smooth muscle cells, causing them to proliferate. The smooth muscle cells also produce collagen, elastin, and other proteins that become components of the plaque. The presence of collagen results in the accumulation of fibrotic tissue. The plaque will not only reduce the flow of oxygenated blood to the heart muscle, but it may break away to produce a nonocclusive or occlusive blood clot, that may lead to myocardial infarction or death. The higher the cholesterol blood level, the higher the risk of CHD, a disease responsible for over 500,000 deaths annually in the U.S.

All lipids in the blood stream do not exist in the free form, but rather as complexes (lipoproteins). To facilitate their transport, lipids bind to plasma protein (i.e., albumin, globulin) to form complexes. These complexes, which are lipoproteins, are composed of spheres that are smaller than red blood cells. Each sphere is composed of an inner core of hydrophilic lipid (cholesterol, cholesteryl esters and triglycerides) surrounded by an outer core made of protein that acts as the interface between the plasma and the lipid core. Because the protein portion of the outer core is hydrophilic in nature, the entire sphere becomes dispersible or soluble in the aqueous blood plasma.

Lipids consist of a number of different chemicals: free fatty acids (FFA), triglycerides (glycerol esters of FFA), sterols (cholesterol and cholesterol esters), and phospholipids (phosphoric acid esters of lipid substances). Following absorption, fats contribute a great deal of energy. Triglycerides exist in nature as solids (fats) or liquids (oils). This depends on room temperature, the length of the fatty acid chain, and the extent of their hydrogen bond saturation. Triglycerides with short fatty acid and/or unsaturated fatty acid exist as liquid at room temperature (i.e., plant oils such as olive oil, corn oil, etc.). Triglycerides with long fatty acid chains and/or saturated fatty acids, exist in the solid form at room temperature (i.e., animal fat such as butter, fat of meat, etc.).

Sterols differ than triglycerides in structure. Instead of hydrocarbon chains, sterols possess hydrocarbon rings. The most valuable sterol for body function is cholesterol which is fat-soluble and contains a limited

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number of oxygen.

TYPES OF LIPOPROTEINS

There are three distinct types of lipoproteins: 1.) very low-density lipoproteins (VLDL) have an inner core that consists mainly of triglycerides; 2) low-density lipoproteins (LDL) consist of a predominantly cholesterol inner core; and, 3) high-density lipoproteins (HDL) that have a total lipid content slightly less than the weight of protein in the outer membrane and, consequently, its density is high. The inner core of HDL is made of cholesterol.

Chylomicrons: The chylomicrons are the largest lipoproteins and possess the lowest density. They consist of 85% - 95% triglycerides and 3% - 7% cholesterol. Their main function is to transport digested triglycerides in food from the intestines via the thoracic duct to the bloodstream. The majority of chylomicrons are cleared from the blood by the enzyme lipoprotein lipase (LDL) after 12 to 14 hours. The glycerol produced as a result of the breakdown of chylomicrons penetrates the cells for providing energy or storage.

Very-Low Density Lipoproteins (VLDL): This lipoprotein is produced endogenously in the liver and consists of 50% - 65% glycerols, and 20% - 30% cholesterol. Its main function is to transport triglycerides synthesized in the liver to adipose and muscular tissues. After the transport process has been completed, the residue of the VLDLs are converted to LDL. Elevated levels of VLDL may contribute to the development of atherosclerosis.

Low-Density Lipoproteins (LDL): Production of LDLs occurs as a result of the breakdown or metabolism of VLDL. They consist of 51% - 58% of cholesterol and 4% - 8%. triglyceride. This lipoprotein accounts for 60% - 75% of all plasma cholesterol. LDLs are considered the most harmful of the lipoproteins. The main function of LDL is to deliver cholesterol to the liver and peripheral tissues. Absorption of LDL by tissue cells is accomplished by means of endocytosis (engulfment), and requires the presence of LDL receptors on the cell surface. As the cell demands for cholesterol increase, the cell begins to synthesize more LDL receptors, thereby absorbing more LDL. However, if the cell fails to increase the formation of LDL receptors, then LDL absorption will be impaired. LDL has been associated with the development of atherosclerosis and coronary heart disease (CHD). Reduction of LDL can result in a decrease in the development of CHD and regression of coronary atherosclerosis. The risk of CHD in men over 45 years of age increases when total plasma cholesterol is over 200 mg/dl. Conversely, a 25% reduction in plasma LDL level may reduce the level of CHD by 50%.

High-Density Lipoprotein (HDL): HDL is the smallest and densest of lipoproteins. It consists of 18% - 25% cholesterol and 2% - 7% triglycerides. Normally, HDL contributes approximately 20% - 30% of the total cholesterol in plasma. While LDL is responsible for delivery of cholesterol to tissues including the liver, the function of HDL is to transport cholesterol (about 25% of blood cholesterol) from tissues to the liver, where it is broken down and excreted in the bile. This transport process prevents the accumulation of cholesterol and lipids in the arterial wall. Physical exercise has been shown to increase the HDL level. In contrast to LDL and VLDL, a high level of HDL is beneficial and has been shown to reduce the incidence of CHD and provides protection from such diseases.

CHOLESTEROL METABOLISM & REGULATION OF ITS PLASMA LEVELS

Cholesterol is provided to the body by the intake of food. It is also synthesized from acetyl CoA by the liver. Each day, synthesized cholesterol contributes about 900 – 1000 mg of the total cholesterol pool, while the amount of cholesterol contributed by diet is 300 – 500 mg daily.

The enzyme lipoprotein lipase (LPL) is synthesized in fatty and muscular tissues. Its main function is to mediate the triglycerides of both chylomicrons and VLDL to release fatty acids that are deposited into the adjacent tissues where they are utilized for energy or stored as fat. Insulin plays a role in the synthesis and secretion of LDL. Thus, impaired synthesis of LDL caused by low levels of insulin, as in diabetes, can cause impaired triglyceride clearance.

The endogenous transport system of lipids is responsible for transferring the lipids from the liver to the peripheral tissues and from peripheral tissues back to the liver. Only 10% of the total cholesterol produced in the body originates from the liver. The remainder is synthesized by the peripheral tissues. Endogenous cholesterol production occurs as a result of enzymatically-mediated reactions such as the conversion of 3-

hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonic acid, which is catalyzed by HMG-CoA reductase enzyme. Once cholesterol is produced by the liver and peripheral tissues, it is released into the bloodstream in the form of VLDL, which rapidly becomes an intermediate density lipoprotein (IDL). Within 2 to 6 hours, IDL is either taken by liver receptors or remains in circulation where it breaks down and loses more glycerides and becomes LDL. Thus, the main source of LDL is VLDL.

Diet is the source of exogenous cholesterol. In industrialized societies, a normal individual consumes approximately 70 - 150 gm of fat, and 0.5 gm of cholesterol during 3 meals. Normally, the body disposes of the circulating fat within 8 hours of the last meal. However, some individuals with dyslipidemia may have fat in their bloodstream for up to 24 hours after the last meal. Triglycerides are absorbed from the intestinal lumen where they are engulfed by chylomicron particles. The chylomicron carries the triglycerides from the intestines to the venous system. Once it reaches adipose and muscular tissues, the vast majority of chylomicron glyceride is hydrolyzed by LPL. The fatty acids and glyceride derived from the hydrolysis enter the cells as energy sources or storage. Remnants of chylomicrons, which are mostly cholesterol-rich particles, are removed from the bloodstream by receptors located in the liver. This exogenously obtained cholesterol joins the endogenously synthesized cholesterol in the liver to be utilized in forming bile acids or incorporated into VLDL and then released into circulation where it is converted to LDL. About 60% of plasma LDL is removed by the liver and the remainder by active receptor sites located on fibroblasts and other cells that bind to the protein of LDL. A small quantity of LDL is believed to be removed by ingestion of scavenger macrophages that may reach arterial walls and form part of the atherosclerotic plaque.

CURRENT GOVERNMENT REVIEW AND GUIDELINES FOR THE EVALUATION AND TREATMENT OF HYPERLIPIDEMIA

About 25 years ago, the National Heart, Lung and Blood Institute conducted a survey, and the results revealed that the majority of physicians did not provide adequate instructions regarding diet and also failed to prescribe medications to individuals with high blood cholesterol levels, or who were at a higher risk for CHD, or stroke. It was concluded that there is a need for an educational program regarding detection, evaluation, and treatment of high blood cholesterol, to both health care professionals and the general public. The National Institute of Health (NIH) filled that void by establishing a National Cholesterol Education Program (NCEP). Guidelines were instituted in 1987, and the Adult Treatment Panel (ATP) of the NCEP periodically issues updated reports as warranted by newer advances to guide the health care professionals for the testing, evaluation, monitoring and treatment of hyperlipidemia. The most recent update was issued by ATP III in 2001. An important component of ATP guidelines is the development of treatment goals for hyperlipidemia based on patient's risk for CHD. ATP I established a criteria for prevention of CHD in individuals with high levels of LDL (³160 mg/dl) or with borderline high LDL (130-159 mg/dl) and multiple (2+) risk factors. ATP II added criteria concerning the management of LDL in individuals with established CHD. For such persons, ATP II affirmed a new lower LDL goal of £ 100 mg/dl. The main part of ATP III is based on ATP I and ATP II, but placed emphasis on primary prevention in persons with multiple risk factors, as well as on more intensive LDL-lowering treatment. Patients with high risk for CHD will gain benefits from more aggressive LDL-lowering therapy than recommended in ATP II. The primary goal of ATP III is to lower LDL, since it has been shown that this results in reduction in the risk of CHD.

ATP III classification of blood LDL levels, as well as total and HDL levels is as follows:

LDL Cholesterol (mg/dl)	
≤ 100	optimal
100 –129	Near or above optimal
130 – 159	Borderline high
160 – 189	High
≥ 190	Very High
Total Cholesterol	**(mg/dl)**
< 200	Desirable
200 – 230	Borderline high
240	High
HDL Cholesterol (mg/dl)	
< 40	Low
≥ 60	High

The ATP III included new aspects such as consideration of diabetes without CHD as equivalent to the risk factors of CHD; use of Framingham projection of 10-year absolute CHD risk; consideration of persons with multiple metabolic factors as candidates for intensified therapeutic lifestyle changes; recommendation for initial tests that include total, LDL and HDL cholesterol and triglycerides rather than that for total cholesterol; recommendation for the use of plant sterols and soluble fiber in diet to enhance lowering of LDL cholesterol; adherence to therapeutic lifestyles changes; and, treatment beyond LDL lowering in the presence of triglycerides of ≥ 200 mg/dl. ATP III includes the following major risk factors for atherosclerotic vascular disease: 1) cigarette smoking; 2) blood pressure ≥ 140/90 mm Hg; 3) low HDL (< 40 mg/dl); 4) family history of premature CHD; and, 5) age (men ≥ 45 years, women ≥ 55 years).

ATP III instituted recommendations regarding LDL levels at which to initiate therapeutic lifestyle changes, as well as LDL levels at which to consider drug therapies:

1) Persons with CHD or CHD risk equivalents (10-year risk > 20%) should attain an LDL level of < 100 mg/dl. The LDL level at which to initiate therapeutic lifestyle changes (TLC) is ≥ 100 mg and the LDL levels at which to consider drug therapy is ≥ 130 mg/dl;
2) For persons with 2+ risk factors (10-year risk ≤ 20%), the LDL goal is < 130 mg/dl; the LDL level at which to initiate TLC is ≥ 130 mg/dl, and the LDL at which to consider drug therapy for 1-year risk 10% - 20% is ≥ 130 and for 10-year risk is ≥ 160 mg/dl;
3) For persons with 0 – 1 risk factor, the LDL goal is < 160 mg/dl, and the LDL level at which to initiate TLC is ≥ 160 mg/dl and the LDL level of 160 – 189 mg/dl, drug therapy is optional. It is important to realize that when LDL lowering drugs are utilized, one should maintain TLC.

TREATMENT OF HYPERLIPIDEMIA

ATP III recommends two methods of treatment: 1) therapeutic lifestyle changes (TLC); and, 2) drug therapy.

1. Therapeutic Lifestyle Changes (TLC):

Individuals without CHD or CHD risk equivalent and < 2 risk factors should utilize TLC as first-time treatment. Diet modification, regular physical activity, smoking cessation, and weight reduction play an important role in reducing LDL and CHD risk.

A healthy diet is the cornerstone of TLC. Depending on the level of LDL elevation, diet modification may lead to an acceptable level without a need for drug therapy. The main goals of dietary therapy are to: reduce plasma LDL and reduce body weight of overweight and obese individuals.

A sedentary lifestyle may lead to increased risk of CHD. Increased physical activity such as running, walking, swimming, bicycling, etc., tend to reduce LDL and elevate HDL. To achieve full benefit, an exercise program should be instituted and should be followed regularly.

Weight reduction is important for success of TLC. Cigarette smoking cessation should be encouraged.

2. Drug Therapy:

Diet, exercise and weight reduction may be inadequate to achieve the goals set by ATP III. High LDL-C, presence of risk factors and documentation of CHD should justify instituting drug therapy along with TLC. Monotherapy has been shown to be effective in treating dyslipidemia, but combination therapy may be required for a comprehensive approach. There are a number of lipid-lowering drugs that are currently used most often: 1) Statins 2) Ezetimibe, 3) Bile acid sequestrants or bile binding resins, 4) Niacin, 5) Fibric acid derivatives, and 6) Plant sterols.

THE STATINS

The statins are considered the foundation for treatment, as they are well tolerated and possess a predominant effect on lowering LDL-C. In addition, they have the highest level of patient compliance among all the lipid-lowering medications. The use of statins has enhanced preventive cardiology. These medications are useful for high-risk patients such as those with CHD and diabetes. Combination therapy with a statin and one of the aforementioned lipid-lowering drugs may be beneficial in patients who do not respond to monotherapy.

The mechanism of action by which the statins reduce LDL-C concentration is to competitively inhibit HMG – CoA reductase, the enzyme that catalyzes the rate-limiting step in hepatic cholesterol biosynthesis. Statins tend to cause an alteration in the formation of LDL–C.

In spite of their effectiveness and use in clinical practice, statins have a number of limitations that need to be taken into consideration. At the standard doses used, statins are capable of reducing LDL-C levels by 30% - 40%. Studies have shown that when such doses are administered, the LDL-C levels of over 40% of high-risk patients failed to reach the ATP III LDL-C goal of 100 mg/dl. Increasing the dose of statins has its disadvantages: 1) Doubling, tripling, and quadrupling the dose will result in only 6%, 12% and 18% respectively in LDL-C lowering; 2) the higher the dose of statin, the greater the potential for toxicity, the most serious of which is myopathy; and, 3) some patients have low-tolerance to higher doses due to the occurrence of adverse effects such as elevation of transaminase, weakness, fatigue and muscular pain.

Currently the following are the statins in use: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. Comparison of efficacy of these revealed that atorvastatin resulted in the highest reductions of LDL-C (42%), lovastatin and simvastatin, each (36%). Results of triglyceride reduction were atorvastatin (19%) simvastatin (13%) and lovastatin (12%). Serum HDL-C level increased by 5% - 6% with all five statins.

The most significant adverse effects of statins are those that affect the liver and skeletal muscle. Mild, transient elevations in serum transaminase occur in about 1% - 2% of individuals. When serum aminotranferase becomes more than three times the upper limit of normal, therapy should be discontinued. Myopathy, a rare side effect that occurs in about 1 in 1000 patients, is dose-related. Myopathy may lead to rhabdomyolysis and acute renal failure. These side effects rarely occur in statin monotherapy, but may be enhanced when statins are used in combination with niacin, or are given to patients with hepatic or renal impairment, acute infection, and hypothyroidism. Liver function should be assessed prior to initiation of therapy and at regular intervals thereafter. Patients should be advised to report any unexplained muscle pain.

Lovastatin (Mevacor): is partially absorbed from the GI tract and undergoes first-pass extraction. Food appears to enhance the rate of absorption after oral administration. Lovastatin is excreted in urine and feces. The main side effects involve the GI tract. They are usually transient and mild and include abdominal pain, inflammation, cramps, diarrhea, nausea, and dyspepsia. An increase in serum concentration of hepatic transaminase, as well as elevated creatine phosphokinase may occur in some patients. Headache, rash and pruritis have been experienced.

Dosage of lovastatin varies from one individual to another and should be determined in accordance with the requirements and response of the patient. The usual initial dose in adults is 20 mg daily given in the evening with dinner. The dose may be increased at an interval of 4 weeks or more until the desired lipoprotein concentration is achieved, or a maximum daily dose is reached. The usual maintenance dose is 10 – 80 mg daily given in a single or divided dose. Care must be exercised when giving lovastatin to patients with renal impairment due to its slow excretion in the urine.

Pravastatin (Pravachol®): Side effects include nausea and/or vomiting, diarrhea, abdominal cramps, heartburn, flatulence, constipation, increased serum aminotransferase, muscular pain, headache, skin rash and increased serum creatine kinase. Pravastatin can be taken with meals, as food does not appear to affect its resultant antilipidemic activity. The usual initial adult dosage is 20 mg at bedtime, while that of individuals with renal or hepatic impairment and geriatric patients is 10 mg daily. The dose should be increased at intervals of no less than 4 weeks until the targeted lipoprotein concentration is reached, or a maximum dose of 40 mg is attained. The usual maintenance dose is 10 – 40 mg daily.

Simvastatin (Zocor®): The most frequently encountered side effects include: abdominal discomfort, constipation, flatulence, nausea, dyspepsia, anorexia, heartburn, increased serum creatine kinase, rash and headache. Myalgia and/or muscle weakness are rarely reported. The usual initial dose in adults is 20 mg daily at bedtime. A dosage of 10 mg daily is initiated, and this may be increased at intervals of no less than 4 weeks until the recommended lipoprotein concentration is obtained, or a maximum dosage of 80 mg daily is reached.

Fluvastatin (Lescol®): At the recommended dosage, fluvastatin possesses a low incidence of side effects and usually is well tolerated. The most encountered adverse effects include GI disturbances, back pain, headache, upper respiratory infections, a potentially serious increase in hepatic aminotransferase, myopathy, elevated creatine kinase concentration, rash and headache. Tooth disorder, gynecomastia, loss of libido, erectile dysfunction, and thyroid abnormalities have been reported.

Atorvastatin (Lipitor®): Like fluvastatin, this drug is synthetically prepared and differs structurally from

lovastatin, pravastatin, and simvastatin. Atorvastatin calcium is used to reduce elevated serum total and LDL-C and triglyceride concentrations. The drug is used orally without restriction to meal-type or time of the day. Atorvastatin is contraindicated in patients with liver diseases.

Adult dosage of atorvastatin should be personalized and should be adjusted within 2 – 4 weeks after the initial dose of 10 mg daily. The maintenance daily adult dose is 10 – 80 mg.

EZETIMIBE (Zetia®):

Ezetimibe is the first drug of a new class to be used in the management of dyslipidemia. This drug, which was approved by the FDA in October 2002, appears to be effective as monotherapy for patients with a low risk of CHD, but cannot tolerate the statins. For patients with moderate to high risk for CHD, ezetimibe has been shown to be capable of reducing LDL-C comparable to that achieved following the administration of high doses of statins, with short-term safety levels identical to placebo. Because of its safety, tolerability, and effectiveness, ezetimibe appears to lead to enhanced patient compliance.

The mechanism of action of ezetimibe differs from the currently available lipid-lowering medications. The drug is a selective cholesterol absorption inhibitor. Following a meal, approximately 50% of the total cholesterol contributed by food is absorbed by the intestines, and the remainder is excreted in the feces. In the intestines, the cholesterol is stored as triglyceride-rich chylomicrons. Ezetimibe acts by blocking the absorption of dietary and biliary cholesterol. The precise mechanism of action by which ezetimibe blocks the uptake of cholesterol into the intestines is not known, but it is believed that it interacts with a cholesterol transport protein.

BILE ACID SEQUESTRANTS

The bile acid-binding resins, cholestyramine, colestipol and colesevelam, combine with bile acids present in the intestine to form an insoluble complex. This leads to an increase in LDL-C receptors and a reduction in plasma LDL-C. The bile acid sequestrants can be used alone or in combination with statins. When used concurrently with TLC, they can produce a 15% - 30% reduction in LDL-C levels. When used along with statins, they can reduce LDL-C levels by approximately 18% beyond what is achieved by statins alone. Because the bile acid-binding resins are not absorbed from the GI tract, they do not have systemic adverse effects. However, these drugs are associated with side effects that are limited to the GI tract such as constipation, nausea, flatulence and indigestion. These adverse effects may become unpalatable enough to limit patient compliance.

Cholestyramine is taken orally as a suspension prepared from a powder. Caution should be exercised not to take the powder in the dry form as it may cause esophageal irritation or blockage. The usual initial adult dose is 3 gm, 3 times daily before meals. The usual maintenance adult dose is 4 gm, 3 to 4 times daily before meals and at bedtime. Similar results may be achieved by administering the drug twice daily.

The patient should be instructed to mix the powder with liquids such as water, fruit juices, soups, or with pulpy fruits such as applesauce or crushed pineapple. Because cholestyramine is an anion-exchange resin, it may bind certain drugs in the GI tract and retard or interfere with their absorption. Thyroid hormones, warfarin, thiazide diuretics and phosphate supplements are examples of drugs that may be affected when administered along with cholestyramine.

Colestipol hydrochloride is a high molecular weight basic anion-exchange resin. The mechanism of action, adverse effects and mode of administration are similar to those of cholestyramine. It is dispensed in the tablet and granular forms. The tablets must be taken whole with plenty of water or other liquids. The granules must be added to a glass of water, fruit juice, or milk and stirred until uniformly mixed. The usual adult dosage is 1 to 16 gm daily.

NIACIN

Niacin is capable of reducing LDL-C (15% - 25%), VLDL-C (25% - 35%) and triglyceride concentration, and at the same time results in elevation of HDL-C (15% -25%). The mechanism of action is not fully understood, but in has been postulated that niacin can partially inhibit free fatty acid release from adipose tissue and

reduce the rate of synthesis of VLDL-C. Niacin is considered safe and effective in reducing practically all forms of dyslipidemia. However, crystalline niacin has side effects that are not only unpleasant, but can be hazardous. The most frequent adverse reactions include uncomfortable and potentially dose-limiting flushing of the skin, itching, skin rash, GI disturbances, hepatoxocicity, and an increase in blood sugar and uric acid. Niacin is available in tablets, extended-release capsules, and elixirs. The usual adult maintenance dose is 1 to 2 gm, three times daily after meals. The extended release forms reduce flushing. Niacin may be used in combination with statins.

FIBRIC ACID DERIVATIVES

Gemfibrozil (Lopid) and fenofibrate (Tricorâ) have a minimal effect on lowering LDL-C serum concentration, but are effective in reducing plasma triglyceride content by increasing fatty acid oxidation in the liver, thereby reducing secretion of VLDL-C. Additionally, they can increase HDL-C levels. The drugs may be used in combination with niacin or bile acid sequestrants in order to assist in lowering of HDL-C levels. When used with bile acid sequestrants, fibric acid derivatives should be given at least two hours after the ingestion of the sequestrants. The most frequently encountered adverse effects are rashes and GI disturbances. Statin-fibrate combination therapy resulted in a 35% - 42% decrease in LDL, a 48% - 57% decrease in triglycerides and an increase of 14% - 17% in HDL.

PLANT STEROLS

Plant sterols are capable of lowering LDL-C by approximately 10%. They act by blocking cholesterol absorption from the intestines. Plant sterols are available as nonprescription drugs and should not be recommended as primary therapy, especially in high-risk patients.

CONCLUSION

Epidemiological studies show that CHD patients may benefit from lowering of LDL-C and triglycerides. Patients at high risk of CHD should be treated to target lipid levels stated in ATP III. In addition to therapeutic lifestyle changes (TLC), monotherapy with a statin, a fibrate, a bile acid sequestrant, or niacin, combination therapy of a statin and any one of the aforementioned drugs may realize lipid goals. The concurrent use of a plant sterol with a statin may be useful.

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LESSON EVALUATION

Please fill-out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Please rate each of the following from 1 to 7. Circle your choices. (1 is the lowest rating; 7 is the highest).

	Poor			Average			Excellent
1. Relevance of topic to practice.	1	2	3	4	5	6	7
2. Author's ability to communicate.	1	2	3	4	5	6	7
3. Author's knowledge of topic.	1	2	3	4	5	6	7
4. Appropriateness of topic.	1	2	3	4	5	6	7

5. Do you have any further comments about this lesson? _____

Please Select the Most Correct Answer

1. Cholesterol is synthesized in the:
   A. Adipose tissue
   B. Pancreas
   C. Liver
   D. Gastric mucosa
2. The outer core of a lipoprotein sphere is made of:
   A. Protein
   B. Lipid
   C. Water
   D. A hydrocarbon chain
3. Which of these lipoproteins has the lowest density?
   A. VLDL
   B. Chylomicrons
   C. Triglycerides
   D. HDL
4. According to ATP III, blood LDL cholesterol level is considered optimal if that level is:
   A. 130 to 159 mg/dl
   B. $\leq$ 100 md/dl
   C. $<$ 40 mg/dl
   D. 200 – 230 mg/dl
5. Which is not a risk factor for CHD?
   A. Obesity
   B. Hypertension
   C. Regular physical activity
   D. Smoking
6. Which of these acts by blocking the absorption of dietary & biliary cholesterol?
   A. Atorvastatin
   B. Pravastatin
   C. Simvastatin
   D. Ezetimibe
7. Which one of these is not an adverse reaction to statins?
   A. Myopathy
   B. Elevation of serum transaminase
   C. Muscular pain
   D. Drowsiness
8. Which of these can cause flushing of the skin?
   A. Fluvastatin
   B. Gemfibrozil
   C. Nicotinic acid
   D. Colistipol HCl
9. Which statement is correct concerning bile acid sequestrants?
   A. Not absorbed by GI tract
   B. Must be used alone & not with statins
   C. Cause severe systemic adverse reactions
   D. Contain plant sterols
10. Usual maintenance dose of Pravastatin is:
    A. 10 mg – 40 mg daily
    B. 80 mg – 150 mg daily
    C. 40 mg, 4 times daily
    D. 5 mg daily

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