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Review Article

Ion exchange mechanism of bile acid sequestrants in preventing reabsorption of bile salts in hypercholesterolemia

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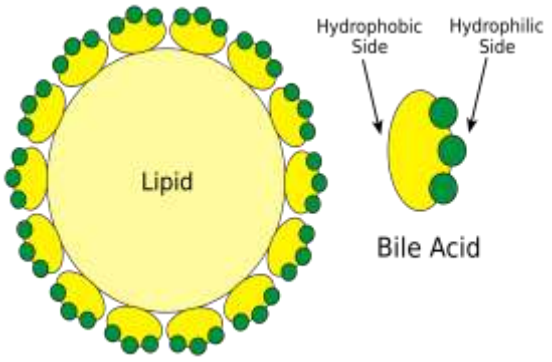
ABSTRACT

Hypercholesterolemia is the presence of high levels of cholesterol in the blood. It is a form of "hyperlipidemia" (elevated levels of lipids in the blood) and "hyperlipoproteinemia" (elevated levels of lipoproteins in the blood). Cholesterol is a sterol. It is one of three major classes of lipids which all animal cells utilize to construct their membranes and is thus manufactured by all animal cells. Plant cells do not manufacture cholesterol. It is also the precursor of the steroid hormones, bile acids and vitamin D. Since cholesterol is insoluble in water, it is transported in the blood plasma within protein particles (lipoproteins). Lipoproteins are classified by their density: very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). All the lipoproteins carry cholesterol, but elevated levels of the lipoproteins other than HDL (termed non-HDL cholesterol), particularly LDL-cholesterol are associated with an increased risk of atherosclerosis and coronary heart disease. In contrast, higher levels of HDL cholesterol are protective. Elevated levels of non-HDL cholesterol and LDL in the blood may be a consequence of diet, obesity, inherited (genetic) diseases (such as LDL receptor mutations in familial hypercholesterolemia), or the presence of other diseases such as diabetes and an underactive thyroid. Reducing saturated dietary fat is recommended to reduce total blood cholesterol and LDL in adults. In people with very high cholesterol (e.g. familial hypercholesterolemia), diet is often insufficient to achieve the desired lowering of LDL and lipid lowering medications which reduce cholesterol production or absorption are usually required. If necessary, other treatments such as LDL aphaeresis or even surgery (for particularly severe subtypes of familial hypercholesterolemia) are performed.

Keywords: Lipid, VLDL, IDL, LDL, HDL, Cholesterol, Lipoprotein, Bile & Bile acid, Bile acid sequestering agent, Ion exchange resin

INTRODUCTION

Bile or **gall** is a bitter-tasting, dark green to yellowish brown fluid, produced by the liver of most vertebrates that aids the digestion of lipids in the small intestine. In humans, bile is produced continuously by the liver (liver bile), stored and concentrated in the gallbladder (gallbladder bile) and when the organism eats, is discharged into the duodenum. The composition of gallbladder bile is 92% water, 6% bile salts, 0.3% bilirubin, 0.9-2.4% fats (Cholesterol, fatty acids and lecithin), and 200 mEq/L inorganic salts.[1]



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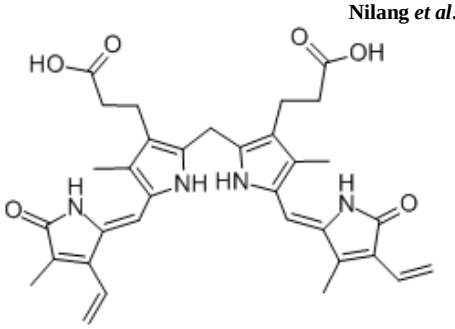

Figure-1: Lipid structure and Bilirubin

Physiology: Bile acts to some extent as a surfactant, helping to emulsify the lipids in food. Bile salt anions are hydrophilic on one side and hydrophobic on the other side; consequently, they tend to aggregate around droplets of lipids (triglycerides and phospholipids) to form micelles, with the hydrophobic sides towards the fat and hydrophilic sides facing outwards. The hydrophilic sides are negatively charged and this charge prevents fat droplets coated with bile from re-aggregating into larger fat particles. Ordinarily, the micelles in the duodenum have a diameter of around 14–33 μm. The dispersion of food fat into micelles thus provides a greatly increased surface area for the action of the enzyme pancreatic lipase, which actually digests the triglycerides and is able to reach the fatty core through gaps between the bile salts. A triglyceride is broken down into two fatty acids and a monoglyceride, which are absorbed by the *villi* on the intestine walls. After being transferred across the intestinal membrane, the fatty acids reform into triglycerides, before being absorbed into the lymphatic system through lacteals. Without bile salts, most of the lipids in food would be excreted in feces, undigested.

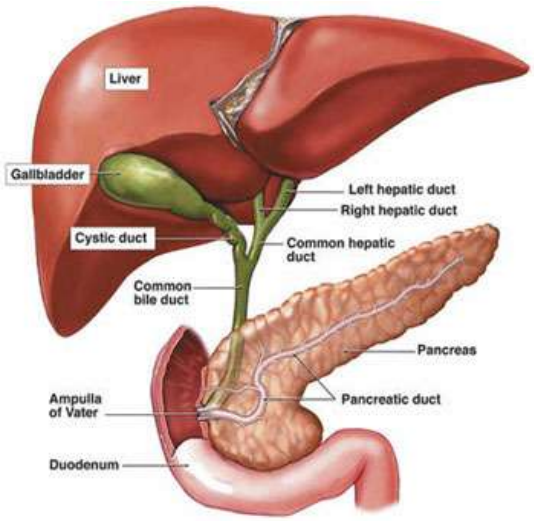

Figure-2: Liver anatomy

Since bile increases the absorption of fats, it is an important part of the absorption of the fat-soluble substances, such as the vitamins A, D, E and K. Besides its digestive function, bile serves also as the route of excretion for bilirubin, a byproduct of red blood cells recycled by the liver. Bilirubin derives from hemoglobin by glucuronidation. Bile is alkaline and also has the function of neutralizing any excess stomach acid before it enters the duodenum, the first section of the small intestine. Bile salts also act as bactericides, destroying many of the microbes that may be present in the food.[2]

Abnormality: The cholesterol contained in bile will occasionally accrete into lumps in the gallbladder, forming gallstones. Cholesterol gallstones are generally treated through surgical removal of the gallbladder. However, they can sometimes be dissolved by increasing the concentration of certain naturally occurring bile acids, such as chenodeoxycholic acid and ursodeoxycholic acid. On an empty stomach – after repeated vomiting, for example – a person's vomit may be green or dark yellow and very bitter. The bitter and greenish component may be bile or normal digestive juices originating in the stomach. The color of bile is often likened to "fresh-cut grass", unlike components in the stomach that look greenish yellow or dark yellow. Bile may be forced into the stomach secondary to a weakened valve, the presence of certain drugs including alcohol, or powerful muscular contractions and duodenal spasms. In the absence of bile, fats become indigestible and are instead excreted in feces, a condition called steatorrhea. Feces lack their characteristic brown color and instead are white or gray and greasy. Steatorrhea can lead to deficiencies in essential fatty acids and fat-soluble vitamins. In addition, past the small intestine the gastrointestinal tract and gut flora are not adapted to processing fats, leading to problems in the large intestine.

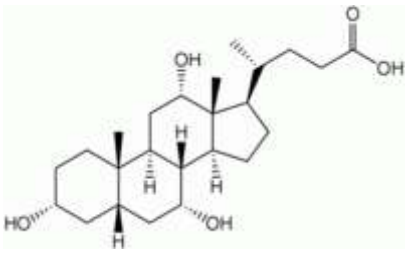

Figure-3: Cholic Acid

Cholic acid: Cholic acid is a bile acid that is insoluble in water (soluble in alcohol and acetic acid), it is a white crystalline substance. Salts of cholic acid are called cholates. Cholic acid, along with chenodeoxycholic acid, is one of two major bile acids produced by the liver where it is synthesized from cholesterol. Of the two major bile acids, cholate derivatives represent approximately

80% of all bile acids. These derivatives are made from cholyl-CoA, which exchanges its CoA with either glycine or taurine, yielding glycocholic and taurocholic acid respectively. Cholic acid down regulates cholesterol-7-α-hydroxylase (rate-limiting step in bile acid synthesis) and cholesterol does the opposite. This is why chenodeoxycholic acid and not cholic acid, can be used to treat gallstones (because decreasing bile acid synthesis would supersaturate the stones even more). Cholic acid and chenodeoxycholic acid are the most important human bile acids. Some other mammals synthesize predominantly deoxycholic acid.[3]

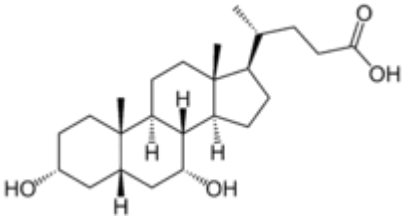

Figure-4: Chenodeoxycholic acid

Chenodeoxycholic acid: Chenodeoxycholic acid (also known as chenodesoxycholic acid and chenocholic acid) is a bile acid. It occurs as a white crystalline substance insoluble in water but soluble in alcohol and acetic acid, with melting point at 165-167°C. Salts of this carboxylic acid are called chenodeoxycholates. Chenodeoxycholic acid is one of the main bile acids produced by the liver. It was first isolated from the bile of the domestic goose, which gives it the "cheno" portion of its name. Chenodeoxycholic acid and cholic acid are the two primary bile acids in humans. Some other mammals have muricholic acid or deoxycholic acid rather than chenodeoxycholic acid. Chenodeoxycholic acid is synthesized in the liver from cholesterol by a process which involves several enzymatic steps. Like other bile acids, it can be conjugated in the liver with taurine or glycine, forming taurochenodeoxycholate or glycochenodeoxycholate. Conjugation results in a lower pKa.

This means the conjugated bile acids are ionized at the usual pH in the intestine and will stay in the gastrointestinal tract until reaching the ileum where most will be reabsorbed. Bile acids form micelles which facilitate lipid digestion. After absorption, they are taken up by the liver and re-secreted, so undergoing an enterohepatic circulation. Unabsorbed chenodeoxycholic acid can be metabolized by bacteria in the colon to form the secondary bile acid known as lithocholic acid. Choendeoxycholic acid is the most potent natural bile acid at stimulating the nuclear bile acid receptor, farnesoid X receptor (FXR). The transcription of many genes is activated by FXR.[4]

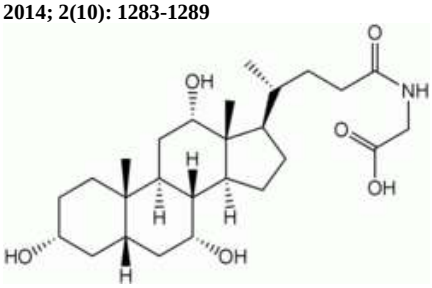

Figure-5: Glycocholic acid

Glycocholic acid, or **cholylglycine**, is a crystalline bile acid involved in the emulsification of fats. It occurs as a sodium salt in the bile of mammals. It is a conjugate of cholic acid with glycine. Its anion is called **glycocholate**.[5]

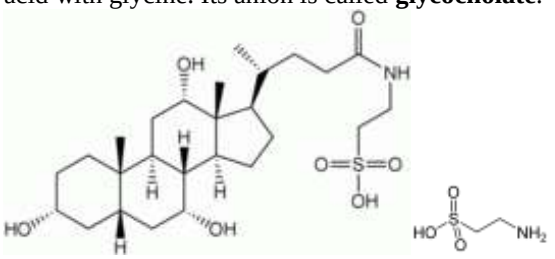

Figure-6: Taurocholic acid & Taurine

Taurocholic acid, known also as cholaic acid, cholyltaurine, or *acidum cholatauricum*, is a deliquescent yellowish crystalline bile acid involved in the emulsification of fats. It occurs as a sodium salt in the bile of mammals. It is a conjugate of cholic acid with taurine. In medical use, it is administered as a cholagogue and choleretic. Hydrolysis of taurocholic acid yields taurine. For commercial use, taurocholic acid is manufactured from cattle bile, a byproduct of the meat-processing industry. This acid is also one of the many molecules in the body that has cholesterol as its precursor.[6]

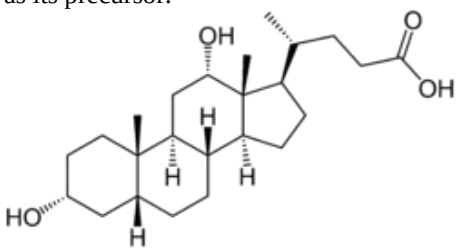

Figure-7: Deoxycholic acid

Deoxycholic acid, also known as **deoxycholate**, **cholanoic acid**, and **3*α*,12*α*-dihydroxy-5β-cholanate**, is a bile acid. Deoxycholic acid is one of the secondary bile acids, which are metabolic byproducts of intestinal bacteria. The two primary bile acids secreted by the liver are cholic acid and chenodeoxycholic acid. Bacteria metabolize chenodeoxycholic acid into the secondary bile acid lithocholic acid and they metabolize cholic acid into deoxycholic acid. There are additional secondary bile acids, such as

ursodeoxycholic acid. Deoxycholic acid is soluble in alcohol and acetic acid. When pure, it comes in a white to off-white crystalline powder form.[7]

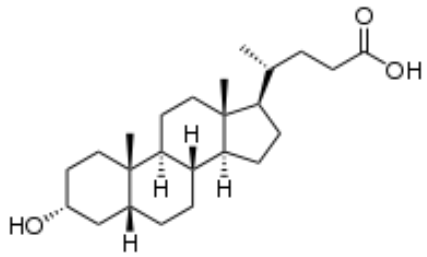

Figure-8: Lithocholic acid

Lithocholic acid (LCA) is a bile acid that acts as a detergent to solubilize fats for absorption. Bacterial action in the colon produces LCA from chenodeoxycholic acid by reduction of the hydroxyl functional group at carbon-7 in the "B" ring of the steroid framework. It has been implicated in human and experimental animal carcinogenesis. Preliminary *in-vitro* research suggests that LCA selectively kills neuroblastoma cells, while sparing normal neuronal cells and is cytotoxic to numerous other malignant cell types at physiologically relevant concentrations. Dietary fiber can bind to lithocholic acid and aid in its excretion in stool; as such, fiber can protect against colon cancer. LCA (and LCA acetate and LCA propionate) can activate the vitamin D receptor without raising calcium levels as much as vitamin D itself.

Bile acid sequestrants: The bile acid sequestrants are a group of resins used to bind certain components of bile in the gastrointestinal tract. They disrupt the enterohepatic circulation of bile acids by combining with bile constituents and preventing their re-absorption from the gut. In general, they are classified as hypolipidemic agents, although they may be used for purposes other than lowering cholesterol. They are used in the treatment of chronic diarrhea due to bile acid mal-absorption. Bile acid sequestrants are polymeric compounds that serve as ion-exchange resins. Bile acid sequestrants exchange anions such as chloride ions for bile acids. By doing so, they bind bile acids and sequester them from enterohepatic circulation. Bile acid sequestrants are large polymeric structures and they are not significantly absorbed from the gut into the bloodstream. Thus, bile acid sequestrants, along with any bile acids bound to the drug, are excreted via the feces after passage through the gastrointestinal tract.[8]

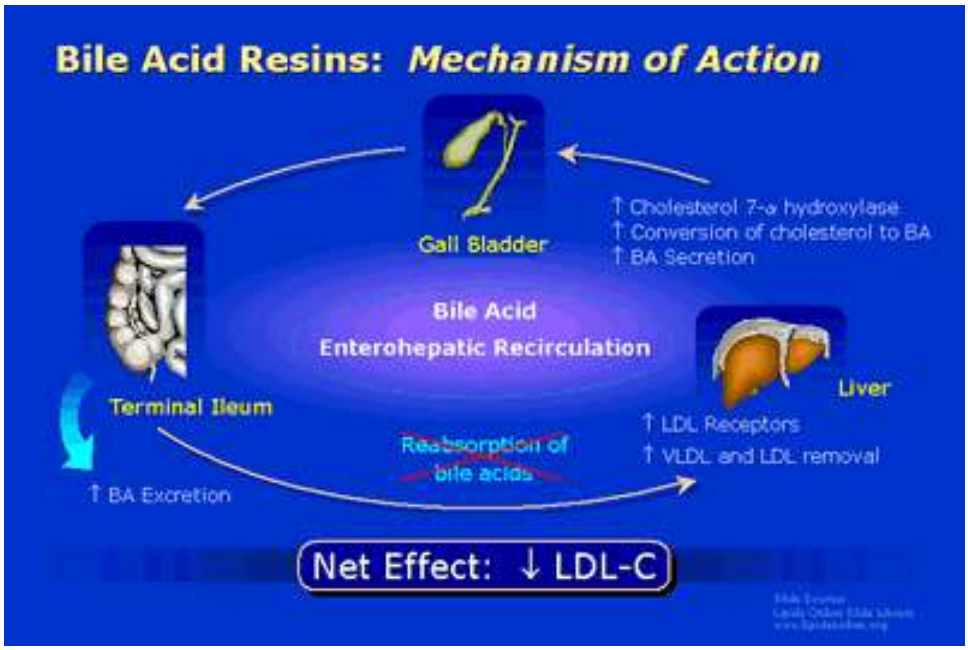

Figure-9: Mode of action

Hyperlipidemia: As bile acids are biosynthesized from cholesterol, disruption of bile acid re-absorption will decrease cholesterol levels, in particular, low-density lipoprotein (commonly known as "bad cholesterol") in blood. Consequently, these drugs have been used for the treatment of hypercholesterolemia and dyslipidemia. Use of these agents as hypolipidemic agents has decreased markedly since the introduction of the statins, which are more efficacious than bile acid sequestrants at lowering LDL. They are occasionally used as an adjunct to the statins (as an alternative to the fibrates (another major group of cholesterol-lowering drugs), which

are thought to increase the risk of rhabdomyolysis when used with statins.

Bile Acid Malabsorption: Chronic diarrhea may be caused by excess bile salts entering the colon rather than being absorbed at the end of the small intestine (the ileum). This condition of bile acid mal-absorption occurs after surgery to the ileum, in Crohn's disease, with a number of other gastrointestinal causes, or is commonly a primary, idiopathic condition. The SeHCAT test can be used for diagnosis. Bile salt diarrhea can also be a side-effect of gallbladder removal. Bile acid sequestrants are the principal therapy for bile acid-induced diarrhea. Cholestyramine, colestipol and colesevelam have all been used. Doses may not need to be as high as those previously used for hyperlipidemia. Many patients find them hard to tolerate, as although the diarrhea may improve, bloating and abdominal pain can worsen.

Use in other conditions: In chronic liver diseases such as cirrhosis, bile acids may deposit in the skin, causing pruritus (itching). Hence, bile acid sequestrants may be used for the prevention of pruritus in patients with chronic liver disease. Bile acid sequestrants may also be used to treat hyperthyroidism as an adjunct therapy. By inhibiting the enterohepatic circulation, more L-thyroxine will be lost through defecation, thus lowering body thyroxine levels.[9]Cholestyramine has been used in the treatment of *Clostridium difficile* infections, in order to absorb toxins A and B.

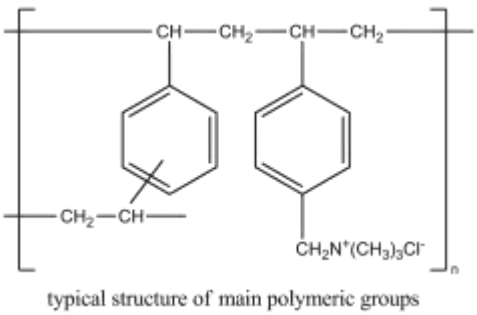

Figure-10: Cholestyramine

Cholestyramine or colestyramine (Questran, Questran Light, Cholybar, Olestyr) is a bile acid sequestrant, which binds bile in the gastrointestinal tract to prevent its re-absorption. It is a strong ion exchange resin, which means it can exchange its chloride anions with anionic bile acids in the gastrointestinal tract and bind them strongly in the resin matrix. The functional group of the anion exchange resin is a quaternary ammonium group attached to an inert styrene-divinylbenzene copolymer. Cholestyramine removes bile acids from the body by forming insoluble complexes with bile acids in the intestine, which are then excreted in the feces. As a result of this loss of bile acids, more plasma cholesterol is converted to bile acids in the liver to normalize levels. This conversion of cholesterol into bile acids lowers plasma cholesterol levels.[10]

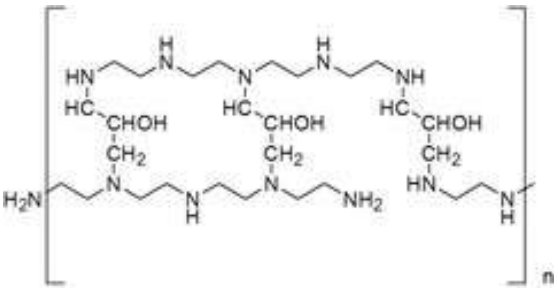

Figure-11: Colestipol

Colestipol (trade names Colestid, Cholestabyl) is a bile acid sequestrant used to lower blood cholesterol, specifically low-density lipoprotein (LDL). Like cholestyramine, colestipol works in the gut by trapping bile acids and preventing them from being reabsorbed. This leads to decreased enterohepatic recirculation of bile acids, increased synthesis of new bile acids by the liver from cholesterol, decreased liver cholesterol, increased LDL receptor expression and decreasing LDL in blood.[11]

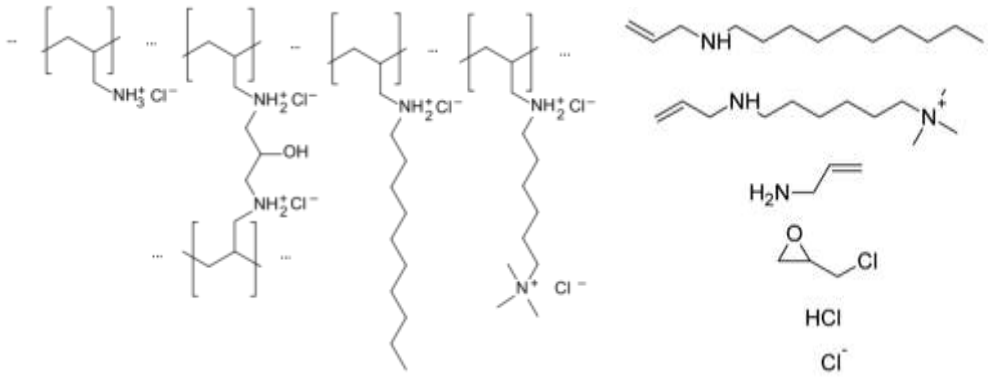

Figure-12: Colesevelam & Polyallylamine

Colesevelam is a bile acid sequestrant administered orally. It was developed by Gel Tex Pharmaceuticals and later acquired by Genzyme. It is marketed in the US by Daiichi Sankyo under the brand name **Welchol** and elsewhere by Genzyme as **Cholestagel**. In Canada it is marketed by Valeant as **Lodalis**. Colesevelam is a modified polyallylamine. It is made by cross-linking polyallylamine with epichlorohydrin and then modifying it with bromodecane and (6-bromohexyl) trimethylammonium bromide. The bromide ions are then replaced with chloride ions when the material is washed. The constituents of the polymer colesevelam shown as subunits that do not exist per se in the final product are: *N-prop-2-enyldecan-1-amine; trimethyl-[6-(prop-2-enylamino)hexyl] azanium; prop-2-en-1-amine; 2-(chloromethyl) oxirane; hydrogen chloride; chloride.* Colesevelam is part of a class of drugs known as bile acid sequestrants. Colesevelam hydrochloride, the active pharmaceutical ingredient in Welchol, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their re-absorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is up-regulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. Serum TG levels may increase or remain unchanged. It is not yet known how Colesevelam works to help control blood sugar in people with type 2 diabetes. However, it is clear that the drug works within the digestive tract, since it is not absorbed into the rest of the body.[12]

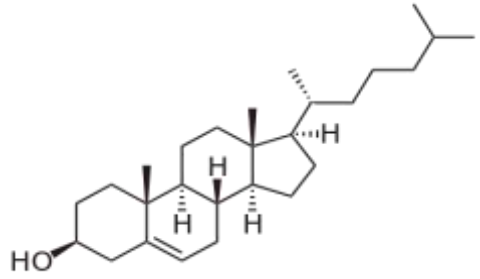

Figure-13: Cholesterol

Since Colesevelam can lower total and LDL cholesterol levels (along with raising HDL - "good" cholesterol), taking it may decrease one's risk of developing certain health problems in the future. Previous clinical research studies indicate individuals taking 3,800 mg to 4,500 mg of Colesevelam daily were able to: (a) Reduce LDL cholesterol by 15-18%. (b) Reduce total cholesterol by 7-10%. (c) Raise HDL cholesterol by 3%. The combination of Colesevelam with a HMG-CoA reductase inhibitor (known more commonly as a statin) can further lower cholesterol levels.

Bile Acid Sequestrants for High Cholesterol:

Generic Name	Brand Name
cholestyramine	Locholest, Prevalite
colesevelam	Welchol
colestipol	Colestid

Sequestrants are sometimes called bile acid resins or gels.[13]

Figure-14: Heart & Drug

CONCLUSION

Sequestrants bind to bile acids in the intestine and prevent them from being reabsorbed into the blood. The liver then produces more bile to replace the bile that has been lost. Because the body needs cholesterol to make bile, the liver uses up the cholesterol in the blood, which reduces the amount of LDL cholesterol circulating in the blood. These medicines may be prescribed, along with dietary therapy, to lower LDL cholesterol in people who have high cholesterol and known heart disease or in people who are at high risk for heart disease. For

people who have very high cholesterol levels (over 240 mg/dL or 6.21 mmol/L), these drugs also may be prescribed in combination with medicines called statins. People who have the following conditions should not take sequestrants: High triglycerides, Familial dysbetalipoproteinemia (a rare form of lipid disorder), Severe constipation (sequestrants make constipation worse)

Bile acid sequestrants: (a) Reduce LDL cholesterol by 15-30%. (b) Raise HDL cholesterol by 3-5%. May increase triglycerides, so you should not take these medicines if your triglyceride levels are above 300 mg/dL.

Side Effects: All medicines have side effects. But many people don't feel the side effects, or they are able to deal with them. Ask your pharmacist about the side effects of each medicine you take. Side effects are also listed in the information that comes with your medicine. Here are some important things to think about:

(a) Usually the benefits of the medicine are more important than any minor side effects. (b) Side effects may go away after you take the medicine for a while.

If side effects still bother you and you wonder if you should keep taking the medicine, call your doctor. He or she may be able to lower your dose or change your medicine. Do not suddenly quit taking your medicine unless your doctor tells you to. Bile acid sequestrants are insoluble polymers that trap bile acids in the intestinal lumen and promote their excretion in feces. As a consequence, they lower the hepatic cholesterol pool and promote the expression of LDL receptors in the liver. Bile acid sequestrants are the safest lipid-lowering drugs but have frequent undesirable gastrointestinal effects. In lipid-lowering trials, bile acid sequestrants, such as colesevelam, cholestyramine, colestipol and colestimide, at maximum dose, lower LDL-C by 15–21%, and raise HDL-C by 3–9% and TG by 2–16%. Bile acid sequestrants are used in the treatment of hypercholesterolemia, in monotherapy when statins are not well tolerated or in combination with statins when statins alone are not able to achieve the LDL-C target. Cholestyramine and colestipol have demonstrated to be efficient in the lowering of LDL-C and reducing coronary death. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) cholestyramine reduced CHD risk and decreased LDL-C by 12%. The second generation of bile acid sequestrants, for example colesevelam, is more specific, binds bile acids with greater affinity and is better tolerated. As monotherapy at a daily dose of 3.8g colesevelam reduces LDL-C by up to 16% in hypercholesterolemic patients. An additive effect in combination with atorvastatin and simvastatin has been observed. Moreover, an important action of the bile acid sequestrants is the lowering of plasma glucose and glycosylated hemoglobin levels in an important way (0.9%). Thus, they are useful in the treatment of hypercholesterolemia in diabetes.

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