PRODUCT MONOGRAPH

PrCHOLESTYRAMINE

Light Powder
(Cholestyramine Resin for Oral Suspension, USP)
4g / 5g Dose

Regular Powder
(Cholestyramine Resin for Oral Suspension, USP)
4g / 9g Dose

Antihypercholesterolemic and Antidiarrheal

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THERAPEUTIC CLASSIFICATION

Antihypercholesterolemic and Antidiarrheal

ACTION AND CLINICAL PHARMACOLOGY

Cholestyramine resin is a bile-acid sequestrant and cholesterol lowering agent. Following oral administration, cholestyramine resin releases chloride ions and absorbs bile acid in the intestine, forming a non-absorbable complex which is excreted along with unchanged resin in the feces. This results in partial removal of bile acid from the enterohepatic circulation. The increased fecal loss of bile acids following administration leads to an increased oxidation of cholesterol to bile acids, a decrease in beta-lipoprotein or low density lipoprotein plasma levels and a decrease in serum cholesterol levels. Although cholestyramine resin produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

INDICATIONS AND CLINICAL USE

CHOLESTYRAMINE (cholestyramine resin) is indicated as adjunctive therapy to diet and exercise for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins). Such reduction of serum cholesterol may reduce the risks of atherosclerotic coronary artery disease and myocardial infarction. Patients should be placed on a standard cholesterol-lowering diet at least equivalent to the American Heart Association (AHA) Step 1 Diet, which should be continued during treatment. If appropriate, a programme of weight control and physical exercise should be implemented. CHOLESTYRAMINE may be useful in lowering elevated cholesterol in patients with combined hypercholesterolemia and hypertriglyceridemia but it is not indicated where hypertriglyceridemia is the abnormality of most concern. CHOLESTYRAMINE is indicated as a symptomatic control of bile acid induced diarrhea due to short bowel syndrome.

CHOLESTYRAMINE is indicated for the relief of pruritus associated with partial biliary obstruction.

CONTRAINDICATIONS

CHOLESTYRAMINE (cholestyramine resin) is contraindicated in patients with complete biliary obstruction in which no bile products reach the intestine. It is also contraindicated in patients who are hypersensitive to the drug or to any ingredient in its formulation. In addition, CHOLESTYRAMINE Light Powder is contraindicated in phenylketonurics as each 5 grams of CHOLESTYRAMINE Light Powder contains 50 mg phenylalanine.

WARNINGS

Cholestyramine resin should not be taken in its dry form. Always mix cholestyramine resin with water or other fluids before ingestion.

Since cholestyramine resin may bind other drugs given concurrently, patients should take other medications at least 1 hour before or 4 to 6 hours after cholestyramine resin (or at as great an interval as possible) to avoid impeding the absorption of the other drugs.

Caution is also recommended when cholestyramine resin is withdrawn because of the risk of toxicity when suddenly increased absorption of the other medications leads to higher serum concentrations.

Pregnancy

Since cholestyramine resin is not absorbed systemically, it is not expected to cause fetal harm when administered during pregnancy in recommended dosages. There are, however, no adequate and well controlled studies in pregnant women and the known interference with absorption of fat soluble vitamins may be detrimental even in the presence of supplementation.

Nursing Mothers

Caution should be exercised when cholestyramine resin is administered to a nursing mother. The possible lack of proper vitamin absorption described in the "Pregnancy" section may have an effect on nursing infants.

Use in Children

The National Cholesterol Education Program Expert Panel recommends considering drug therapy in children ages 10 years and older under certain conditions. These circumstances include the following: if, after an adequate trial of diet therapy (6 months to 1 year) the child's Low Density Lipoprotein (LDL) cholesterol remains greater than or equal to 190 mg/dL; or if the child's LDL-cholesterol remains greater than or equal to 160 mg/dL and there is either a positive family history of premature cardiovascular disease (CVD) (before 55 years of age) or two or more other CVD risk factors are present in the child after vigorous attempts have been made to control them. Under these circumstances, the bile acid sequestrant - cholestyramine is used for the treatment of hypercholesterolemia and high LDL-cholesterol levels in children. Cholestyramine resin has proven efficacy, relative freedom from side effects and apparent safety when used in children. However, there is insufficient evidence concerning the long-term safety and the efficacy of drug therapy in children to reduce coronary heart disease morbidity and mortality in adulthood.

A pediatric dosage schedule has not yet been established.

Geriatrics

Caution is required in the elderly (over 60 years of age) who may be more likely to experience gastro-intestinal side effects, as well as adverse nutritional effects with this medication.

Carcinogenesis and Mutagenesis

In studies, in rats in which cholestyramine resin was used as a tool to investigate the role of various gastro-intestinal factors (e.g. fat, bile salts, GI flora) in the development of intestinal tumors induced by potent carcinogens, the incidence of these tumors was greater in cholestyramine resin treated rats than in the control group. This observation was not evident in all studies conducted in rats, as results

from one rat study indicated a statistically insignificant increase in tumor incidence whereas a more recent study did not demonstrate any presence of tumors following ingestion of cholestyramine. The relevance of this laboratory observation from studies in rats to the clinical use of cholestyramine resin is not known.

PRECAUTIONS

Prior to instituting therapy with cholestyramine resin, patients should be placed on a standard cholesterol-lowering diet at least equivalent to the American Heart Association (AHA) Step 1 Diet. If appropriate, a programme of weight control and physical exercise should be implemented.

Serum cholesterol and triglyceride concentrations should be determined prior to and regularly during cholestyramine therapy. Serum cholesterol concentration usually decreases during the first month of cholestyramine administration. Therapy should be continued to maintain cholesterol reduction.

Prolonged use of cholestyramine resin may be associated with an increased bleeding tendency due to hypoprothrombinemia associated with vitamin K deficiency. If bleeding occurs in patients receiving cholestyramine, parenteral administration of vitamin K1 is usually valuable in restoring normal clotting time, and oral administration of vitamin K1 can be used to prevent recurrent bleeding.

Because cholestyramine is a chloride- containing anion-exchange resin, the possibility that prolonged use of the drug may produce hyperchloremic acidosis should be considered, particularly in children and smaller patients where the relative dosage may be higher.

Reduction of serum or red cell folate has been reported over long term administration of cholestyramine resin. Supplementation with folic acid should be considered in these cases. Cholestyramine resin may produce or worsen pre-existing constipation. Dosage should be reduced

or discontinued in such cases. Fecal impaction and-or hemorrhoids with or without bleeding may occur in association with constipation most often when high doses of cholestyramine have been used. Particular effort should be made to avoid severe constipation and its inherent problems in patients with clinically symptomatic coronary artery disease.

Laboratory Tests

Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

Drug interactions

Since cholestyramine resin is an anion-exchange resin, it is capable of binding to a number of drugs in the GI tract and may delay or reduce their absorption. Acidic drugs are strongly adsorbed to cholestyramine, and neutral and basic drugs may be non specifically bound.

Patients should be instructed to allow as long a time interval as possible between ingestion of other drugs and cholestyramine resin, however separation of doses may not prevent interaction with drugs that undergo enterohepatic circulation. (See WARNINGS).

Cholestyramine resin binds and may delay or reduce the absorption of thyroid hormones, digitoxin, digoxin, warfarin sodium, iron salts, chenodiol, phenylbutazone, thiazides, diuretics, phenobarbital, tetracycline, loperamide and penicillin G.
The possibility that discontinuance of cholestyramine resin in patients stabilized on potentially toxic drugs that bind to the resin may lead to toxicity, and that administration of cholestyramine to patients stabilized on other drugs may reduce the effect of these drugs should be kept in mind.

Vitamins - In patients receiving long-term high dose cholestyramine resin therapy, absorption of fat-soluble vitamins from the intestine may be impaired. Vitamin D deficiencies, bleeding deficiencies due to hypoprothrombinemia associated with vitamin K deficiency, and night blindness secondary to vitamin A deficiency have been reported. Only rarely vitamin A and vitamin D deficiencies should be considered in patients receiving prolonged high dose cholestyramine resin therapy or when malabsorption is suspected. Vitamin K deficiency and hypoprothrombinemia can be treated or prevented with phytonadione.

Hyperchloremic Metabolic Acidosis - Several cases of hyperchloremic metabolic acidosis have been reported following cholestyramine resin administration. In such an event the cholestyramine therapy should be discontinued. Patients who have concomitant renal insufficiency or volume depletion, or who are taking spironolactone are at particular risk and should be monitored carefully (See SELECTED BIBLIOGRAPHY).

ADVERSE EFFECTS

The most common adverse effects of cholestyramine resin involve the GI tract, especially after high doses and in patients over 60 years of age. The most frequent adverse effect of cholestyramine resin is constipation. Cholestyramine resin may also increase the severity of pre-existing constipation. Fecal impaction and/or hemorrhoids with or without bleeding have rarely been reported in association with constipation, most often when high doses of cholestyramine have been used in children and in the elderly. Although constipation is usually mild, transient, and controllable with standard treatment, some patients may require a temporary decrease in dosage or discontinuation of therapy.

Other less common adverse GI effects of cholestyramine resin are abdominal pain and distention, bloating, flatulence, nausea, vomiting, diarrhea, anorexia, heartburn, biliary colic, and indigestion. Bloating and flatulence often disappear with continued therapy.

Other reported adverse GI effects include dysphagia, hiccups, ulcer attack, rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from known duodenal ulcers, sour taste, pancreatitis, rectal pain, and diverticulitis: however, a direct relationship of these effects to drug therapy with cholestyramine has not been clearly established.

Metabolic and Electrolyte Effects:

Hyperchoremic acidosis and increased urinary calcium excretion have been seen with high doses or usual doses in small patients or children. Increased urinary excretion of calcium may lead to osteoporosis.

Calcification of the biliary tree including the gall bladder has been reported in patients with biliary cirrhosis who were given cholestyramine resin, but this has not been attributed directly to the drug.

Other Adverse Effects:

Adverse dermatologic effects of cholestyramine resin including rash, irritation of skin, tongue and perianal area have been observed in some patients.

The following adverse reactions have been reported, however, a direct relationship to the drug has not been established:

Hematological: Prolonged prothrombin time, ecchymosis, anemia and dental bleeding.

Musculoskeletal: backache, muscle and joint pains and arthritis.

Neurological: headache, anxiety, vertigo, dizziness, fatigue, tinnitus, syncope, drowsiness, femoral nerve pain and paresthesia.

Renal: hematuria, dysuria, burnt odor of urine and diuresis.

Eye: uveitis.

Hypersensitivity: urticaria, asthma, wheezing and shortness of breath have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has been no experience to date with overdoses of cholestyramine resin. The principal risk of overdoses of the drug is obstruction of the gastrointestinal tract. Specific measures for treatment would depend on the degree and location of obstruction and the presence or absence of normal gut motility.

DOSAGE AND ADMINISTRATION

CHOLESTYRAMINE Light and Regular Powders (cholestyramine resin) are administered orally. To avoid esophageal irritation or blockage or intestinal blockage, the drug should not be taken in its dry form. (See WARNINGS).

CHOLESTYRAMINE Light and Regular Powders should always be mixed with an appropriate fluid prior to ingestion (see Preparation).

To minimize gastrointestinal side effects and to familiarize the patient with CHOLESTYRAMINE Light and Regular Powders, it is desirable to begin with one dose daily. After one to two days the dosage can be increased to meet the patient's needs.

The recommended adult dose is 4 grams of cholestyramine resin, one to six times daily. Dosages may be adjusted as required to meet the patient's needs.

A pediatric dosage schedule has not been established.

Preparation

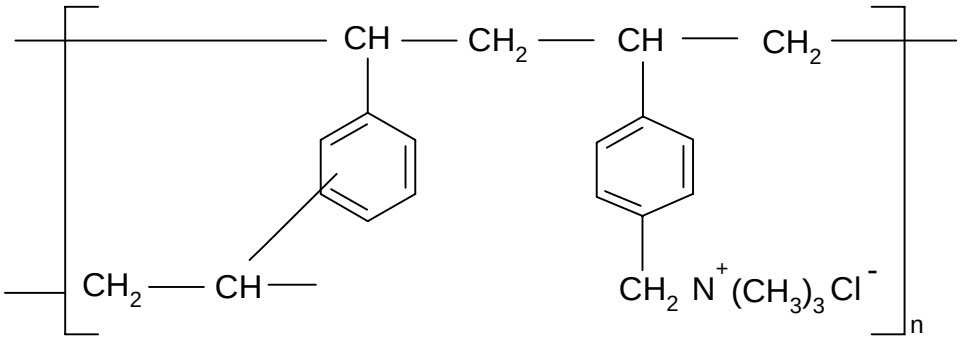
Place the contents of one pouch or one level scoop of CHOLESTYRAMINE Light or Regular Powder on the surface of 120 mL - 180 mL of water, or non-carbonated beverage such as milk or fruit juice. After 1-2 minutes mix thoroughly by stirring.

CHOLESTYRAMINE Light and Regular Powders may also be mixed in highly fluid soups or pulpy fruits with high moisture content such as applesauce or crushed pineapple.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Cholestyramine Resin



Chemical Name: Styrene - divinylbenzene copolymer with quaternary ammonium functional groups.

Structural Formula**:**

Description: The drug is the chloride form of a basic quaternary ammonium anion-exchange resin in which the basic groups are attached to a styrene-divinylbenzene copolymer. Cholestyramine resin occurs as a white to buff-colored, fine, hygroscopic powder which may have a slight, amine-like odor and is insoluble in water and in alcohol.

Composition

CHOLESTYRAMINE (cholestyramine resin) Light Powder

Each 5 gram dose contains 4 grams of cholestyramine resin and the following non-medicinal ingredients: Aspartame (each 5 grams of CHOLESTYRAMINE Light Powder contains 50 mg phenylalanine), Citric Acid Anhydrous, Colloidal Silicon Dioxide, FD&C Yellow #6, Orange Flavor, Propylene Glycol Alginate.

CHOLESTYRAMINE Light Powder is also available in lemon-lime flavour with the following non-medicinal ingredients: Aspartame, Citric Acid Anhydrous, Colloidal Silicon Dioxide, D&C Yellow No. 10, Natural Lemon-Lime Flavour, Propylene Glycol Alginate.

CHOLESTYRAMINE Regular Powder

Each 9 gram dose contains 4 grams of cholestyramine resin and the following non-medicinal ingredients: Citric Acid Anhydrous, Colloidal Silicon Dioxide, D&C Yellow No. 10, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6, Orange Flavour, Propylene Glycol Alginate, Sucrose.

Storage recommendations

Store at room temperature (15˚-30˚C). Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

CHOLESTYRAMINE Light Powder is available in cartons of thirty pouches (each pouch contains one dose of cholestyramine resin). Each 5 gram dose of CHOLESTYRAMINE Light Powder contains 4 grams of cholestyramine resin (dried basis). Sugar free.

CHOLESTYRAMINE Regular Powder is available in cartons of 30 pouches (each pouch contains one dose of cholestyramine resin). Each 9 gram dose contains 4 grams of cholestyramine resin (dried basis).

INFORMATION FOR THE CONSUMER

This information sheet is to be used by persons taking either CHOLESTYRAMINE (cholestyramine resin) Light Powder or CHOLESTYRAMINE Regular Powder.

CHOLESTYRAMINE lowers the level of cholesterol, particularly Low Density Lipoprotein (LDL) Cholesterol, in the blood. CHOLESTYRAMINE reduces cholesterol absorbing bile acids from the intestine and forms a complex which is excreted in the feces. The loss of bile acids from the intestine causes a conversion of cholesterol to bile acids and leads to a reduction of blood cholesterol.

CHOLESTYRAMINE is available only with your physician's prescription. It is to be used as an adjunct to a medically recommended and carefully supervised diet for the long-term treatment of hypercholesterolemia and is not a substitute for such a diet. In addition, depending on your condition, your physician may recommend an appropriate regimen of exercise and weight control.

Use only as specifically directed. Do not alter the dosage unless ordered to do so by your physician. Check with your physician before discontinuing medication since this may result in an increase of your blood lipids.

Before using this medication, you should have told your physician if:

- you have already taken CHOLESTYRAMINE and have developed an allergy or intolerance to it;
- you suffer from Diabetes;
- you suffer from renal disease;
- you are pregnant, intend to become pregnant or are breast feeding, or intend to breast-feed;
- you are taking any other medication.

The elderly may be more likely to experience gastro-intestinal side (unwanted) effects.

Although CHOLESTYRAMINE is not absorbed after oral administration, adverse effects on the fetus during pregnancy or on the nursing infant during lactation may potentially occur because of interference with the absorption of vitamins and nutrients.

You should be aware that the effects of
CHOLESTYRAMINE in prevention of heart attacks, arteriosclerosis, or heart disease are not known.

Side effects (unwanted)

Along with its intended action, any medication may cause unwanted effects in certain patients which may appear and disappear without involving any particular risk. However, if any unwanted effects persist or become bothersome you must contact your doctor without delay. The most common unwanted effect is constipation. Other less common unwanted effects consist of distention, bloating, flatulence, nausea, vomiting, diarrhea, anorexia, heartburn, indigestion, rash, irritation of skin, tongue and perianal area.

This medicine is prescribed for a particular health problem and for your personal use. Do not give it to other persons. Keep all medicines out of the reach of children.
If you want further information, ask your doctor or pharmacist.

Proper Use of This Medication

Since CHOLESTYRAMINE may bind other drugs given concurrently, patients should take other medication at least 1 hour before or 4 to 6 hours after CHOLESTYRAMINE (or at as great an interval as possible) to avoid impeding the absorption of the other drugs.

Preparation of CHOLESTYRAMINE Light Powder and CHOLESTYRAMINE Regular Powder

CHOLESTYRAMINE Light and Regular Powders should never be taken in their dry forms as they can cause you to choke. Always mix CHOLESTYRAMINE Light and Regular Powders with liquid before ingestion.

CHOLESTYRAMINE Light and Regular Powders can be prepared in fluids or in highly fluid foods.

With fluid add the contents of one level scoop of CHOLESTYRAMINE Light or Regular Powder to 120 mL - 180 mL (4-6 ounces) of water or your favorite non-carbonated beverage i.e. milk, orange juice. After 1-2 minutes mix thoroughly by stirring vigorously or using a shaker. CHOLESTYRAMINE is then ready to drink.

With highly fluid foods such as soups, applesauce, yogurt and puddings, pour the contents of one pouch or one level scoop of CHOLESTYRAMINE Light or Regular Powder in a bowl. Add up to 120-180 mL (4-6 ounces) of your chosen food and mix well before eating.

Do not take a double dose of CHOLESTYRAMINE Light or Regular Powder to make up for missed doses.

Contents of CHOLESTYRAMINE Light Powder Each 5 gram dose contains 4 grams of cholestyramine resin and the following non-medicinal ingredients: Aspartame (each 5 grams of CHOLESTYRAMINE Light Powder contains 50 mg phenylalanine), Citric Acid Anhydrous, Colloidal Silicon Dioxide, FD&C Yellow No. 6, Orange Flavor, Propylene Glycol Alginate..

CHOLESTYRAMINE Light Powder is also available in lemon-lime flavour with the following non-medicinal ingredients: Aspartame, Citric Acid Anhydrous, Colloidal Silicon Dioxide, D&C Yellow No. 10, Natural Lemon-Lime Flavour, Propylene Glycol Alginate.

Contents of CHOLESTYRAMINE Regular Powder Each 9 gram dose contains 4 grams of cholestyramine resin and the following non-medicinal ingredients: Citric Acid Anhydrous, Colloidal Silicon dioxide, D&C Yellow No. 10, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6, Orange Flavour, Propylene Glycol Alginate, Sucrose.

Storage Recommendations

Store at room temperature (15˚-30˚C). Protect from moisture

PHARMACOLOGY

Animal Pharmacology

Binding of Drugs

Cholestyramine, an anion exchange resin, has a strong affinity for acidic drugs and may also adsorb neutral materials or to a lesser extent basic materials.

The following drugs have been studied either in vitro or in vivo for the binding or absorption by cholestyramine:

(i) **Six Acidic Drugs**

Acetylsalicylic acid
Chlorothiazide

Phenobarbital

Phenylbutazone

Tetracycline

Warfarin

(ii) **Four Basic Drugs**

Chlorpheniramine maleate

Dextromethorphan

Dextrocodeinone bitartrate

Quinidine sulfate

(iii) **One Neutral Drug**

Digoxin

With both basic and neutral drugs, any drug that was bound to cholestyramine could be easily washed from the resin with buffer solutions.

In vitro studies have shown that acetylsalicylic acid, a stronger acid than cholic acid, was not bound to cholestyramine as tightly as cholic acid. This was supported by in vivo studies with rats where the blood level was only moderately depressed in the half hour following oral administration of acetylsalicylic acid, at a dose of 4.65 mg/kg, and cholestyramine, at a dose of 71.5 mg/kg. Two hours after dosing, blood salicylate levels were no longer affected by the cholestyramine resin.

Results of in vitro and in vivo studies with phenobarbital and tetracycline were similar to those obtained with acetylsalicylic acid.

Although in vitro chlorothiazide binding to cholestyramine occurs to the same extent as cholic acid, no significant effects on chlorothiazide absorption or excretion were observed in dogs given chlorothiazide 30 minutes before the administration of cholestyramine.

In vivo studies with rats have suggested that when phenylbutazone is administered with cholestyramine, phenylbutazone absorption is delayed rather than diminished.

In vivo studies with rats have shown that cholestyramine significantly lowers plasma warfarin levels up to 4 hours after treatment when these two drugs are administered simultaneously.

However, the anticoagulant activity of a large single dose of warfarin was unaffected by the administration of cholestyramine, whether warfarin was given 30 minutes before or simultaneously with the resin.

Binding Of Bile Acids

Because cholestyramine is an anion-exchange resin, the chloride anion bound to the quaternary ammonium groups of the resin can be replaced by other anions, usually those with a greater affinity for the resin than chloride. In vitro studies have shown that cholestyramine has substantial bile salt binding capacity.

Numerous in vivo studies with animals have shown that administration of cholestyramine in the diet, resulted in binding of bile acids and consequently significant increases in fecal bile acid excretion.

Fat Absorption

Gross steatorrhea was induced in two healthy subjects maintained on constant dietary intake and receiving 30 g of cholestyramine for 11-17 days. During the treatment period fecal fat excretion

increased 4-5 fold and returned promptly to pre-treatment values when cholestyramine was withdrawn.

Gross steatorrhea in five otherwise healthy subjects was induced by administration of 30 g cholestyramine/day but not by 15 g cholestyramine/day. Such steatorrhea was associated with deficient digestion and absorption of ingested triglyceride as shown by fat balance studies and I^{131}-triolein studies.

In contrast, in seven subjects maintained on a regular diet there was no interference with absorption of I^{131}-oleic acid during the period of resin administration when compared to the control period.

The studies suggest that the binding of bile acids by cholestyramine resin prevents their participation in the hydrolytic digestion of dietary triglycerides. This would, in turn, lead to steatorrhea induced by large doses of cholestyramine.

In studies of patients with partial biliary obstruction it has been demonstrated that serum bile acids, phospholipids, triglycerides, cholesterol and total lipids may be lowered during treatment with cholestyramine.

However, in another study it was reported that significant decreases in serum triglycerides occurred in 4 out of 15 patients.

Fat Soluble Vitamin Absorption

Logenecker and Basu reported that when 8 g of cholestyramine was administered to four healthy subjects with a normal meal and with 250 00 USP units of vitamin A acetate, the plasma vitamin A levels were significantly reduced as compared to control during a 9-hour post-prandial period. A 4 g addition of cholestyramine to the same diet had no significant effect.

Clinical Studies

Hypercholesterolemia

Numerous studies have shown that the administration of cholestyramine resin, in the proper dosage, usually results in a significant lowering of serum cholesterol levels. This results from the increased fecal loss of bile acids bound to the resin, and the compensatory formation of additional bile acids from cholesterol. These reductions in serum cholesterol levels have been shown in both normocholesterolemic subjects and in hypercholesterolemic patients.

In one early long-term metabolic study of ten hypercholesterolemic patients, cholestyramine was administered at dosage levels varying from 12-36 g/day to 7 patients for 12 months, and to 3 patients for 5 months. Cholestyramine treatment resulted in decreases of serum cholesterol ranging from 15 to 76% with a mean decrease of 43% of the average of pre-treatment values.

In another study, seventeen patients with varying types (II, III, and IV) of hypercholesterolemia were treated with 12-24 g of cholestyramine per day. Significant serum cholesterol reductions occurred with all patients: Type II 18.1%; Type III 23%; and Type IV 17.9%.

Fallon emphasized that basic difference in disease states may also account for variability in the response of the serum cholesterol level. Patients who have hypercholesterolemia associated with type II disease appear to respond to cholestyramine therapy at doses which did not produce significant lowering of cholesterol level in patients with other forms of hypercholesterolemia. He observed 13 patients with idiopathic hypercholesterolemia who experienced an average cholesterol reduction of 26% with dosages of 8 to 16 g of cholestyramine daily for a period of one month to two years.

The Lipid Research Clinic Coronary Primary Prevention Trail, a multicenter, randomized, double-blind study, tested the effect of lowering plasma cholesterol on reducing the risk of coronary heart disease and/or non-fatal myocardial infarction in 3806 asymptomatic middle-aged men with primary hypercholesterolemia (type II hypercholesterolemia). Their mean age was 47.8 years upon entering the study. All participants had a plasma cholesterol level of 265 mg/dL or greater and low density lipoprotein cholesterol (LDL-C) level of 190 mg/dL or greater. Major study exclusion criteria consisted of participants with coronary heart disease or conditions associated with secondary hypercholesterolemia, with high blood pressure, with other major illness, or response to diet therapy.

Both groups followed a moderate cholesterol lowering diet. The cholestyramine group experienced average plasma total and low density lipoprotein cholesterol (LDL-C) reduction of 13.4% and 20.3% respectively, which were 8.5% and 12.6% greater reductions than those obtained in the placebo group. The effect of total cholesterol on incidence of Coronary Heart Disease is presented below.

TABLE I

Cholesterol Lowering and Coronary Heart Disease

	No. of participants	MEAN TOTAL PLASMA CHOLESTEROL mg/dL	NO. OF CORONARY HEART DISEASE CASES
Cholestyramine group	1 906	251	155
Placebo group	1 900	276	187

The cholestyramine group experienced a 19% reduction in risk (P<.05) of the primary end point - definite coronary heart disease (CHD) death and/or definite non fatal myocardial infarction - reflecting a 24% reduction in definite CHD death and 19% reduction in non fatal myocardial infarction.

The cumulative 7 year incidence of the primary end point was 7% in the cholestyramine group vs. 8.6 % in the placebo group. In addition, the incidence rates for new positive exercise test, angina, and coronary bypass surgery were reduced by 25% , 20% and 21% respectively in the cholestyramine group.

In the Lipid Research Clinics trial, plasma cholesterol was lowered by a combination of a modest cholesterol lowering diet and cholestyramine resin. In this study a dose response relationship existed between the daily dose of cholestyramine resin, the lowering of total plasma cholesterol, and the reduction in coronary disease risk; (see table below).

TABLE II

Relation of Daily Dose of Cholestyramine to Reduction in Cholesterol and Reduction in Risk for Coronary Heart Disease

DOSE OF CHOLE-STYRAMINE	PACKAGE COUNT	PATIENT POPULATION	TOTAL CHOLESTEROL LOWERING	REDUCTION IN CHD RISK

0-8 g	0-2	439	4.4%	10.9%
8-20 g	2-5	496	11.5%	20.1%
20-24 g	5-6	965	19.0%	39.3%

Adherence to medication was associated with reduced incidence of Coronary Heart Disease only when accompanied by falls in total cholesterol and LDL cholesterol levels. No effect, however, was observed on all-cause mortality.

Partial Biliary Obstruction

Bile acids which emulsify fats in the digestive process are formed in the liver from cholesterol and secreted via the bile duct into the intestine. Here, they are involved in the digestive processes, emulsifying the fats and the fatty materials present in ingested foods. A large proportion of the bile acids may be reabsorbed and returned to the liver via the portal circulation. Very small amounts of bile acids are found in normal sera. However, when normal secretion of bile is partially obstructed the serum concentration may increase by 20 fold or greater which may result in a severe and intractable pruritus.

Cholestyramine resin is used in the treatment of pruritus associated with partial cholestasis. The resin provides symptomatic relief of pruritus associated with partial obstructive jaundice including primary biliary cirrhosis and other incomplete biliary obstruction; the effect of the drug on serum cholesterol in these patients is variable.

Cholestyramine resin usually has no effect on pruritus or serum bile acid concentrations in patients with relatively complete biliary obstruction, and the resin is ineffective in complete atresia in which no bile products reach the intestine. Relief of pruritus usually occurs within 1-3 weeks after initiation of therapy. Withdrawal of the drug usually results in an increase in serum concentration of bile acids and return of pruritus within 1-2 weeks.

These studies support the hypothesis of a causal relationship between high serum bile acid concentrations and the pruritus of jaundice. The lag periods of several days between administration of the resin and relief of itching and between withholding cholestyramine and the return of itching, suggest that the causative factor may not be bile acid in the serum, but that which accumulated in the skin or adjacent tissues.

Increased fecal bile acid excretion after cholestyramine administration to man has been consistently observed.

Datta and Sherlock reported an increase in fecal bile acids from a mean of 81 mg/day during a 10 day control period to 364 mg/day during 54 days of cholestyramine therapy (dosage 1.7-6.6 g/day).

Carey and Williams reported that cholestyramine treatment reduced the average serum bile acid concentration in 4 patients with pruritus associated with partial biliary obstruction from 25 mcg/mL to 6 mcg/mL with a concomitant alleviation of itching.

Diarrhea in Post Ileal Resection Patients

Hofmann et.al, reported that ten of twelve patients having less than 100 cm of distal ileum resected, and some remaining ascending colon, responded to cholestyramine, 16 g/day, with a significant decrease in fecal frequency or fecal weight or both. By contrast, none of eight patients having resection of more than 100 cm of ileum responded.

The degree of steatorrhea was also of predictive value since all eight patients with fecal fat excretion less than 20 g/day responded, whereas none of five patients with greater steatorrhea responded.

It was reported in a more recent study on fifteen patients with persistent diarrhea of more than one year's duration following ileal resection, that with an average dose of
5.4 g of cholestyramine per day, 13 patients had a 50% reduction in stool frequency and 14 patients had an improvement in consistency. Urgency, perianal soreness and flatus also decreased in most patients.

In another study with 11 patients, stool frequency was significantly decreased when 12 g of cholestyramine per day were added to the diet. There was a further decrease when medium chain triglyceride and lactose (Potagen) were substituted for part of the dietary fat.

TOXICOLOGY

Oral chronic toxicity studies lasting up to one year have been conducted in rats and dogs which were fed 0.5, 1 or 2 g of cholestyramine per kg of body weight/day and 5, 10 or 20 g/day respectively.

Hematological analysis, serum glucose, BUN, carbonate, chloride, sodium, potassium and pH measurements and urinary tests for protein, sugar, pH, chloride sodium and potassium were made periodically. No abnormal values attributed to cholestyramine resin administration were observed.

Reproduction and Teratology

Female Sprague-Dawley rats were fed a diet containing either 3%, 4% or 5% cholestyramine resin from at least 4 days prior to mating to the twentieth day of gestation. The inclusion of cholestyramine resin in the diet had no significant effect on weight gain, number of fetuses or fetal weight.

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