PRODUCT MONOGRAPH

[Pr]CHOLESTYRAMINE-ODAN

Light Powder
(Cholestyramine for Oral Suspension, USP)
4g/sachet

Antihypercholesterolemic and Antidiarrheal

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(Cholestyramine for Oral Suspension, USP)

THERAPEUTIC CLASSIFICATION

Antihypercholesterolemic and Antidiarrheal

ACTION AND CLINICAL PHARMACOLOGY

Cholestyramine is a quaternary ammonium anion exchange resin with a polystyrene polymer skeleton. As the chloride salt, it binds bile acids both in vitro and in vivo, exchanging chloride for bile acid. Cholesterol is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholestyramine resin absorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

The increased fecal loss of bile acids due to cholestyramine resin 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 in man cholestyramine resin produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

INDICATIONS AND CLINICAL USE

CHOLESTYRAMINE-ODAN (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.

CHOLESTYRAMINE-ODAN 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-ODAN is indicated as a symptomatic control of bile acid induced diarrhea due to short bowel syndrome.

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

CONTRAINDICATIONS

CHOLESTYRAMINE-ODAN (cholestyramine resin) is contraindicated in patients with complete biliary obstruction where bile is not excreted into the intestine and in those individuals who have shown hypersensitivity to any of its components.

WARNINGS

CHOLESTYRAMINE-ODAN (cholestyramine resin) SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX CHOLESTYRAMINE-ODAN WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

SINCE CHOLESTYRAMINE-ODAN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4-6 HOURS AFTER CHOLESTYRAMINE-ODAN (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

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 pregnancy or lactation requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and the child.

Use in Children

The effects of long term drug administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. A pediatric dosage schedule has not been established.

The National Cholesterol Education Program (NCEP) Expert Panel recommends, however, that drug therapy be considered in children 10 years or older, who have previously undergone an adequate trial of diet therapy but still have unacceptable high serum cholesterol levels. In certain situations where a young child has extremely high serum cholesterol levels, drug treatment may even be initiated before 10 years of age. If the child is started on drug therapy, a carefully assessed diet therapy should also be continued in order to obtain optimal results.

Because bile acid sequestrants may interfere with absorption of fat-soluble vitamins, appropriate monitoring of growth and development is essential if cholestyramine is used in children.

Geriatrics

Appropriate studies on the relationship of age to the effects of cholestyramine have not been performed in the geriatric population. However, patients over 60 years of age may be more likely to experience gastrointestinal side effects.

Carcinogenesis and Mutagenesis

Studies were conducted in rats in which cholestyramine resin was used as a tool to investigate the role of various intestinal factors (e.g. fat, bile salts, GI flora). The incidence of intestinal tumors, induced by potent carcinogens, was observed to be greater in cholestyramine resin treated rats, than in control rats.

This observation was not evident in all studies conducted in rats, as results from one 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

Before instituting therapy with cholestyramine resin, an attempt should be made to control serum cholesterol by appropriate dietary regimen, weight reduction, and the treatment of any underlying disorder such as hypothyroidism, diabetes mellitus, nephrotic syndrome, dysproteinemias and obstructive liver disease which might be the cause of hypercholesterolemia. In addition, the current medications of the patient should be reviewed for their potential to increase serum LDL-C or total cholesterol. A favorable trend in cholesterol reduction should occur during the first month of cholestyramine therapy. The therapy should be continued to sustain cholesterol reduction.

There is a possibility that prolonged use of cholestyramine resin, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher.

Cholestyramine resin may produce or worsen pre-existing constipation. Dosage should be reduced or discontinued in such cases. Fecal impaction and aggravation of hemorrhoids may occur. Every effort should be made to avert severe constipation and its inherent problems in those patients with clinically symptomatic coronary artery disease.

Cholestyramine potentially may cause steatorrhea or accentuate pre-existing steatorrhea and this may require reduction and adjustment of dosage.

Effect on Vitamin Absorption

Because cholestyramine binds bile acids, it may interfere with normal fat digestion and absorption and thus may prevent absorption of fat soluble vitamins such as A, D and K. When cholestyramine resin is given for long periods of time, concomitant supplementation of water-miscible parenteral forms of vitamins A and D should be considered.

Chronic use of cholestyramine resin may be associated with increased bleeding tendency due to hypoprothrombinemia associated with vitamin K deficiency. This will usually respond promptly to parenteral vitamin K1 and recurrences can be prevented by oral administration of vitamin K1.

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.

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 (See PHARMACOLOGY)

Since cholestyramine resin is an anion-exchange resin, it may have strong affinity for anions other than the bile acids. Drug that are affected by co-administration of bile acid sequestrants vary widely in pharmacologic effect and mechanisms, magnitude of doses, and chemical characteristics. Therefore, it is not possible to predict *a priori* whether or not co-administration with cholestyramine will interfere with absorption. It should be assumed that concomitantly administered drugs have the potential interacting with cholestyramine unless clinical studies have shown otherwise.

Cholestyramine resin may delay or reduce the absorption of concomitant oral medication such as thyroid and thyroxine preparations, warfarin, chlorothiazide (acidic), phenylbutazone, phenobarbital, tetracycline, penicillin G, and digitalis. The discontinuance of cholestyramine could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to maintenance level while the patient was taking cholestyramine. The concomitant drug should be re-titrated to avoid over-dosage when cholestyramine is discontinued. Also, cholestyramine resin may interfere with the pharmacokinetics of drugs (e.g., estrogens) that undergo enterohepatic recirculation.

Drug Interaction studies have been conducted with cholestyramine and various HMG-CoA reductase inhibitors. Although cholestyramine has been shown to reduce the bioavailability of HMG-CoA reductase inhibitors, the clinical cholesterol-lowering effects of an HMG-CoA reductase inhibitor and cholestyramine have been shown to be additive.

SINCE CHOLESTYRAMINE-ODAN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER CHOLESTYRAMINE-ODAN (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPENDING THEIR ABSORPTION.

ADVERSE REACTIONS

The most frequent adverse effect of cholestyramine resin is constipation. When used as a cholesterol lowering agent predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old). Most instances of constipation are mild, transient, and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy.

Less frequent adverse reactions: Abdominal discomfort, flatulence, nausea, vomiting, diarrhea, heartburn, anorexia, dyspepsia and steatorrhea, bleeding tendencies due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (night blindness has been reported rarely) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perinatal area.

Occasional calcified material has been observed in the biliary tree, including calcification of the gallbladder, in patients to whom cholestyramine resin has been given. This may be manifestation of the liver disease and not drug related.

One patient experienced biliary colic on each of three occasions on which he took cholestyramine. One patient diagnosed with acute abdominal symptom complex was found to have a "pasty mass" in the transverse colon X-ray.

Other adverse reactions (not necessarily drug related) reported in patients taking cholestyramine resin include:

Gastrointestinal:	gastrointestinal-rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from known duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis, and eructation.
Laboratory Test Changes:	Liver function abnormalities.
Hematological:	Decreased or increased 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 odour of urine and diuresis.
Eye:	Uveitis.
Hypersensitivity:	Urticaria, asthma, wheezing and shortness of breath have been reported.
Miscellaneous:	Weight loss, weight gain, increased libido, swollen glands, edema, and dental caries.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

One case of overdosage with cholestyramine resin has been reported in a patient taking 150% of the maximum recommended daily dosage for several weeks. No ill effects were observed. Should overdosage occur, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction, and the presence or absence of normal gut motility would determine treatment.

For management of drug overdose, contact the regional poison control centre.

DOSAGE AND ADMINISTRATION

To familiarize the patient with CHOLESTYRAMINE-ODAN Light Powder and to minimize gastrointestinal side effects, it is desirable to begin all therapy with one dose daily. Dosage is then increased within a day or two to the desired level for effective control.

Motivation of the patient to continue the prescribed regimen in spite of gastrointestinal problems is important. Physician encouragement and supervision are essential for successful management.

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.

CHOLESTYRAMINE-ODAN Light Powder is administered orally and should not be taken in its dry form (See WARNINGS). Always mix the powder with water or other fluids before ingestion (see Preparation Instructions).

Preparation

The color of cholestyramine resin may vary somewhat from batch to batch but this variation does not affect the performance of the product.

Place the contents of one pouch of CHOLESTYRAMINE-ODAN Light Powder on the surface of 120 mL - 180 mL of water, or non-carbonated beverage or a highly fluid food such as soup, apple sauce, yogurt and pudding. After 1-2 minutes mix thoroughly by stirring.

CHOLESTYRAMINE-ODAN Light Powder may also be mixed in highly fluid soups or pulpy fruits with high moisture content such as applesauce.

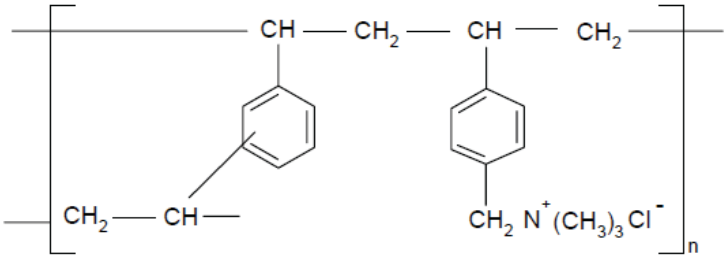
PHARMACEUTICAL INFORMATION

Drug Substance

Proper 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-coloured, fine, hygroscopic powder which may have a slight, amine-like odour and is insoluble in water and in alcohol.

Drug Product Composition

Each dose (sachet) contains 4 grams of anhydrous cholestyramine resin and the following nonmedicinal ingredients: carboxymethylcellulose sodium, colloidal silica, propylene glycol alginate, sodium saccharin and strawberry flavour.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

CHOLESTYRAMINE-ODAN Light Powder is available in cartons of thirty pouches (each pouch contains one dose of cholestyramine resin). Each dose (sachet) of CHOLESTYRAMINE-ODAN Light Powder contains 4 grams of cholestyramine resin (dried basis).

PIVOTAL EQUIVALENCE STUDIES

Cholestyramine-ODAN Light Powder (cholestyramine for oral suspension) 4 g/sachet has satisfied the in-vitro equivalence criteria in comparison to the Canadian Reference Product, Olestyr® Light Powder (cholestyramine for oral suspension USP) by Pendopharm, Canada.

INFORMATION FOR THE CONSUMER

This information sheet is to be used by persons taking CHOLESTYRAMINE-ODAN Light Powder.

CHOLESTYRAMINE-ODAN lowers the level of cholesterol, particularly Low Density Lipoprotein (LDL) Cholesterol, in the blood. CHOLESTYRAMINE-ODAN 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-ODAN 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-ODAN 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 breastfeed;
- you are taking any other medication.

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

Although CHOLESTYRAMINE-ODAN 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-ODAN 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.

In case you have taken too much CHOLESTYRAMINE-ODAN, contact a health care practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Proper Use of This Medication

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

Preparation of CHOLESTYRAMINE-ODAN Light Powder

CHOLESTYRAMINE-ODAN Light Powder should never be taken in its dry form as he can cause you to choke. Always mix CHOLESTYRAMINE-ODAN Light Powder with liquid before ingestion.

CHOLESTYRAMINE-ODAN Light Powder can be prepared in fluids or in highly fluid foods.

With fluid add the contents of one pouch of CHOLESTYRAMINE-ODAN Light Powder to 120 mL – 180 mL (4-6 ounces) of water or your favorite non-carbonated beverage, or a highly fluid food such as soup, apple sauce, yogurt and pudding. After 1-2 minutes mix thoroughly by stirring vigorously or using a shake. CHOLESTYRAMINE-ODAN is then ready to drink.

With highly fluid foods such as soups, applesauce, yogurt and puddings, pour the contents of one pouch of CHOLESTYRAMINE-ODAN Light 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-ODAN Light Powder to make up for missed doses.

Contents of CHOLESTYRAMINE-ODAN Light Powder

Each dose (sachet) contains 4 grams of anhydrous cholestyramine resin and the following nonmedicinal ingredients: carboxymethylcellulose sodium, colloidal silica, propylene glycol alginate, sodium saccharin and strawberry flavour.

Storage Recommendations
Store at room temperature between 15°C and 30°C. Protect from moisture.

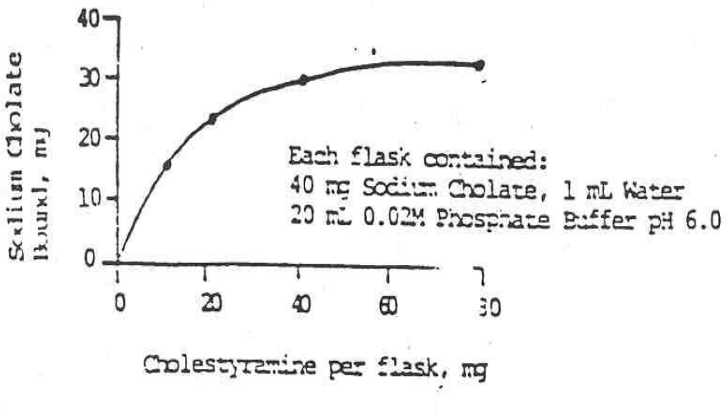
PHARMACOLOGY

Animal Pharmacology

Binding of Bile Acids

Since cholestyramine is an anion exchange resin, the chloride anion attached the quaternary ammonium groups of the resin can be replaced by other anions-usually those with a greater affinity for the resin than chloride. Bile acids are strongly bound by the resin as shown in vitro studies.

FIGURE 1: Binding of Sodium Chelate by Cholestyramine In Vitro



Huff et al reported a 3-fold increase in fecal bile acid excretion after 10 days. This effect continued during nine weeks' administration of a normal diet, containing 2% cholestyramine, fed to male albino rats of 130-140 g in weight.

Binding of Drugs

Since cholestyramine is an anion exchange resin, it has a strong affinity for acidic materials. It may also absorb neutral or, less likely, basic materials to some extent.

Eleven drugs have been studied *in vivo* and *in vitro* for possible binding with cholestyramine. These included:

Four Basic Drugs:
Chlorpheniramine maleates
Dextromethorphan
Dihydrocodeinone bitartrates
Quinidine sulfate

One Neutral Drug:
Digoxin

Six Acidic Drugs:
Acetylsalicylic Acid
Chlorothiazide
Phenobarbital
Phenylbutazone
Tetracycline
Warfarin

The basic and neutral drugs were not bound, or bound only slightly by cholestyramine *in vitro*. Those which were weakly bound were very easily washed from the resin with buffer at various pH levels.

Acetylsalicylic Acid, although an acidic drug, had much less affinity and was more easily eluted form cholestyramine than cholic acid. In support of these *in vitro* results, the blood level of salicylic acid was only moderately depressed in the first half hour following the concomitant oral administration of acetylsalicylic acid, at a dose of 4.65 mg/kg and cholestyramine, at a dose of 71.5 mg/kg, to rats. After two hours, blood salicylate levels were not affected by the resin. Similar *in vivo* and *in vitro* results were observed with phenobarbital and tetracycline.
The absorption of phenylbutazone may be delayed (but not decreased) when taken with cholestyramine, as suggested by studies in the rat.

No significant effects on chlorothiazide absorption or excretion were observed in dogs given chlorothiazide 30 minutes before the administration of cholestyramine.

In rats, the anticoagulant activity of a large single dose of warfarin was unaffected by the administration of cholestyrarnine, whether warfarin was given 30 minutes before or simultaneously within the resin. Plasma warfarin levels were lower when the two drugs were given together.

Fat Absorption

In a study with male weanling rats, the administration of 5% cholestyramine decreased the absorption of medium chain triglycerides by 3%, whereas absorption of the other dietary fats was more markedly affected. Five percent cholestyramine decreased net absorption of coconut oil by 15%, the highly unsaturated vegetable oils by 19 to 40%, olive oil by 40% and butter and lard by 47 and 55%, respectively.

Fat-Soluble Vitamins A and K Absorption

The inclusion of 1 or 2% cholestyramine in rations containing 5-20% fat and minimal levels of vitamin A led to decreased liver stores of vitamin A in young rats. No overt evidence of a nutritional deficiency of this essential vitamin was observed. Rates of weight gain and efficiency of caloric utilization were unaffected at the lower levels of dietary fat intake.

In studies of 1 to 8-day old chicks fed minimal or adequate amounts of menadione (a synthetic analog of vitamin K), the addition of 2% cholestyramine to the diet had no significant effect on prothrombin time after 2 or 4 weeks.

Human Pharmacology

Binding of Bile Acids

Cholestyrarnine is a quarternary ammonium anion exchange resin with a polystyrene polymer skeleton. As the chloride salt, it binds bile acids both *in vitro* and *in vivo*, exchanging chloride for bile acid. When the resin is administered to certain animals used for experimental purposes and to man, it sequesters bile acids in the gut, preventing their reabsorption and thereby promoting their excretion in the feces.

Fat Absorption

Hashim et al induced gross steatorrhea in two healthy subjects by the administration of a large daily dose (30 g) of cholestyramine for 11-17 days. Fecal fat excretion increased by factors of 4 and 5, respectively, returning promptly to pretreatment values when cholestyramine was withdrawn.

Studies in 5 healthy subjects, maintained on regular diet and given radioactive labelled triolein, before and during administration of 30 g/day of cholestyramine, demonstrated that there was a depression in the level of blood radioactivity over the 8-hour sampling period, and significant increase in fecal radioactivity during the 48-hour period of cholestyramine administration.
In contrast, in 7 subjects maintained on regular diet and given radioactive labeled oleic acid, there was no significant difference in radioactivity of blood and feces between control and experimental periods.

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

Studies in a limited number of patients with partial biliary obstruction have demonstrated that serum bile acids, phospholipids, triglycerides, cholesterol and total lipids may be lowered during treatment with cholestyramine, although another investigator reported significant decreases in serum triglyceride levels in only 4 of 15 patients.

Fat-Soluble Vitamins A and K Absorption

Using four healthy young adult subjects, Longenecker and Basu reported that when 8 g of cholestyramine was ingested simultaneously with a normal meal with 250,000 U.S.P. Units of vitamin A acetate, during a 9-hour post-prandial period, the plasma vitamin A levels were significantly reduced (below the values obtained with the control meal). The 4 g addition of cholestyramine had no significant effect.

Clinical Studies

Hypercholesterolemia
In proper dosage, cholestyramine usually leads to a significant reduction (15% or more) in serum cholesterol levels. These results from the increased fecal loss of bile acids bound to the resin and the compensatory formation of additional bile acids from cholesterol. The lowering of serum cholesterol levels has been observed both in subjects with "normal" cholesterol levels (100-250 mg/100 mL) as well as in patients with elevated values.

In a careful, long-term metabolic study of 10 patients with hypercholesterolermia, Bressler et al. reported that over periods of 12 months for 7 patients and 6 months for 3 patients with varying dosage levels of cholestyramine (12-24 g/day) the decrease in cholesterol ranged from 15 to 76% of an average of pretreatment values. The mean decrease was 43%. Casdorph has reported studies on 17 patients with varying degrees of hypercholesterolernia, for most of whom he prescribed 4-8 g cholestyramine daily. (Two patients received 12 g/day). Significant cholesterol reductions occurred in many of these patients with an average reduction of 23.5%.

Fallon emphasized the importance of carefully determining the etiology of the hypercholesterolemia that is to be treated. He finds that patients who are truly idiopathic, and not basically hypertriglyceridemic, respond to cholestyramine with significant lowering of serum cholesterol. This investigator observed 13 patients with idiopathic hypercholesterolemia who experienced an average cholesterol reduction of 26% with dosage of 8 to 16 g daily, for a period of one month to two years.

The National Institutes of Health have concluded a 10-year randomized double-blind placebo-controlled study, in men, at 12 lipid research clinics on the effect of lowering plasma cholesterol on the risk of coronary heart disease defined as CHD death and/or non fatal myocardial infarction. The 3,806 participants who took part in this study were preponderantly

college- or high school-educated whites. 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 an LDL-C level of 190 mg/dL or greater.
Participants with coronary heart disease or conditions associated with secondary hyperlipoproteinemia were excluded from the study. The effect of Total-C on incidence of CHD is illustrated in Table I.

TABLE I
Cholesterol Lowering and Coronary Heart Disease

	N	Mean Total-C*	No. oh CHD cases**
Cholestyramine Group	1,906	251	155
Placebo Group	1,900	276	187

* Average of annual posttreatment levels for participants attending clinic. TOTAL-C indicates plasma total cholesterol.

** Definite non fatal myocardial infraction or CHD death.

Plasma cholesterol was lowered by a combination of a modest cholesterol-lowering diet and cholestyramine. The dose response relationship between the amount of cholestyramine ingested daily, the lowering of total plasma cholesterol, and the reduction in CHD risk is summarized TABLE II.

TABLE II
Relation of Reduction of Cholesterol to Reduction
in Coronary Heart Disease Risk

Dose of Cholestyramine	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%

Partial Biliary Obstruction

Bile acids are formed in the liver from cholesterol and excreted via the bile into the intestine. Here they are involved in the digestive processes, emulsifying the fats and fatty materials

present in ingested foods. A large proportion of the bile acids is reabsorbed and returned via the portal circulation to the liver.

Very small amounts of bile acids are found in normal sera. When the normal secretion of bile is partially blocked, however, serum concentrations may increase 10 to 20-fold or more. When this occurs an intractable pruritus often intervenes. This pruritus may be so severe that some patients become extremely depressed.

Several recent reports show that administration of cholestyramine reduced serum bile acids and relieved pruritus in such patients. Withholding the resin for a few days led to a return of pruritus and increased serum bile acid levels.

These observations 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. Carey reported an increase in fecal bile acid from 54 to 500 mg/day, in a patient, following the ingestion of cholestyramine.

Datta and Sherlock observed 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 four patients with pruritus associated with partial biliary obstruction had an average serum bile acid concentration of 25 mcg/mL. During treatment with cholestyramine, the itching was relieved, and serum bile acids averaged only 6 mcg/mL.

Abundant data in human studies demonstrate conclusively that an important effect of cholestyramine is to increase fecal bile acid excretion and reduce serum bile acids.

Diarrhea in Post-Ileal Resection Patients

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

Williams et al observed that the stool frequency decreased in 11 patients when cholestyramine was added to the diet and was further decreased when Portagen was substituted for part of the dietary fat.

TOXICOLOGY

Oral chronic toxicity studies lasting for one year have been conducted in rats and in dogs. Dosages of cholestyramine greatly in excess of those used in man exhibited no toxic manifestations and caused no observable histological changes in either species. In these studies, the rats were fed 0.5, 1 or 2 g of cholestyramine per kg of body weight each day.
The beagle dogs received 5, 10, or 20 g daily. No adverse effects on weight or other gross clinical signs of toxicity were observed in either species.

In the dogs, periodic measurements of total red cells, hematocrit, hemoglobin, sedimentation rate and differential leucocyte counts were made. Serum glucose, BUN, carbonate, chloride, sodium, potassium and pH measurements were not remarkable; nor were urinary tests for protein, sugar, pH, chloride, sodium and potassium. Similar measurements were made on the rats during the year as far as samples of blood and urine could be obtained. No abnormal values attributable to cholestyramine administration were observed.

REPRODUCTION AND TERATOLOGY

Three successive litters of rats were bred, whelped and weaned from dams and sires fed 2 g of cholestyramine per kg of body weight daily, beginning 60 days before the initial breeding and continuing through all periods of pregnancy, lactation, and intervening rest. There was no evidence of gross toxicity among the parent animals. Reproductive performance was normal, and pregnancy and lactation proceeded smoothly. Fetal development was normal. No gross teratogenic effects were observed to be associated with cholestyramine administration. Pup growth rates, and body weights at birth and weaning were normal.

Occasional oral, nasal and ocular porphyrin discharges were observed both in control and treated animals. One treated animal exhibited corneal opacity, and another, a growth on the right side, toward the end of the 37-week study. Neither was considered unusual nor cholestyramine-induced. Other anomalous changes common in rats included hydronephrosis and diaphragmatic hernia in a few animals, observed in proportionately equivalent numbers among the control and experimental groups. No gross pathology due to cholestyramine was observed in any parental animals, and no evaluation of possible skeletal anomalies was made in the offspring.

Extra care was required to assure the nutritional adequacy of the ration for the cholestyramine-fed animals, as evidenced by decreased pup mortality when the standard diet was supplemented with vitamins.

Under the conditions of these studies, when cholestyramine was fed at levels 10 times the usual human dose, the only adverse effects were nutritional, due to sequestration of one or more essential vitamins by the agent.

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