Schamberg's disease: Report of a case

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Schamberg's disease is a benign progressive pigmentary disease which usually presents on the legs. Occasionally, lesions can be present on the trunk and hips. The case reported is unique because of the lesions being confined to the wrists.

Progressive pigmentary dermatosis (Schamberg's disease) was first described in 1901 by Jay Frank Schamberg.¹ The disorder is characterized by tiny, discrete, punctate, reddish-brown, often purpuric-like macules.² The color may vary from brown to yellow, and the lesion resembles a grain of cayenne pepper³ (Figs. 1 and 2). The condition, which most frequently is found in adults, usually develops slowly on the legs, although lesions on the arms, trunk, and hips do occur.^{4,5}

We present the case of a patient with Scham-

berg's disease whose only lesions appeared on her right wrist and forearm. To our knowledge, this is the first case to be reported in which the lesions were confined to those areas.

Report of a case

A 30-year-old white woman was seen in consultation with a 2-year history of multiple pinhead-sized, reddish macules occurring over the dorsum of her right wrist. Several older lesions had faded but were still visible over the extensor surface of her right forearm.

The patient stated that the first lesions had appeared approximately 2 years earlier, with subsequent eruptions occurring at 6-month intervals. The lesions never seemed to disappear, although they faded in color during the summer with tanning. She denied the use of any medications except a daily vitamin pill. Physical examination and all laboratory test results were normal.

Histologically, a 4-mm. punch biopsy specimen obtained from a representative skin lesion over the dorsum of the right wrist was interpreted as being highly sug-

Figs. 1 and 2. This patient presented with the characteristic lesions of Schamberg's disease, the pinhead-sized reddish puncta that resemble cayenne pepper. This patient was unique in that her lesions were confined to the right wrist and forearm.

Fig. 3. A biopsy specimen from the dorsum of the right hand exhibits irregular acanthosis and thinning of the epidermis, with areas of erosion of the basal cell layer and slight exocytosis. In the upper corium, edema and telangiectasia with inflammatory cell infiltrate are present ($\times 100$).

Fig. 4. Photomicrograph shows vasculitis and extravasated erythrocytes ($\times 250$).

gestive of pigmented purpuric eruption of Majocchi-Schamberg type. The specimen demonstrated irregular acanthosis and thinning of the epidermis, with areas of erosion of the basal cell layer and slight exocytosis (Fig. 3). Edema and telangiectasia, with inflammatory cell infiltrate, was present in the upper corium. Consisting of lymphocytic cells together with histiocytes, the infiltrate extended about the capillary blood vessels rather deeply into the corium. In addition, there were occasional foci of extravasation of a few red blood corpuscles (Fig. 4).

Comments

Schamberg's disease is a peculiar progressive pigmentary disease of the skin; its etiology is considered to be unknown. However, chronic irritation from wool, rubber boots, and stockings and ingestion of acetylsalicylic acid, carbromal, and meprobamate have been implicated as causes.^{6,7}

In our case, the prolonged history and the absence of other symptoms or manifestations tends to exclude the possibility of a purpuric drug eruption.

A review of the literature has revealed that this condition usually develops slowly on the legs, although lesions on the trunk and arms have been reported.^{4,5,8} To our knowledge, this is the first case of Schamberg's disease in which the lesions were isolated to the wrist and forearm. We are continuing to follow this interesting patient to see whether she will in time develop characteristic lesions over her lower extremities.

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4 Side Effects

Lorelco side effects are generally tolerable and of short duration.

Most frequent patient complaint is loose stools, which occur in about one in 10 patients and generally subside during therapy (see Prescribing Information for full discussion of side effects).

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Warnings, and Precautions.

5 Cost

The cost of Lorelco is significantly lower than that of the resins, ranging from one-third to about one-half their average price. Cost can be a significant factor when therapy may have to be continued long-term, perhaps for years.

Lorelco (probucol) presents a whole picture of hypercholesterolemia therapy.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

Brief Summary of Prescribing Information appears on the last page.

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Lorelco® Tablets (probucol tablets)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probucol) film-coated tablets for oral administration contain 250 mg of probucol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polyisobutyl 80, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(isopropylidenediethoxy) bis (2,6-di-*t*-butylphenol). Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY: Lorelco (probucol) lowers serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probucol exhibit a decrease in low density lipoprotein cholesterol. Cholesterol is reduced not only in the low density lipoprotein fraction, but also in some high density lipoprotein fractions with proportionately greater effect on the high density portion in some patients. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low density lipoprotein.

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of catabolism of low density lipoproteins. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol synthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/ml (± S.D.) ranging to 78.3 mcg/ml. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/ml (± S.D.) ranging to 62.0 mcg/ml.

At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 mcg/ml. Six weeks after cessation of therapy, the average had fallen by 60 percent. After six months the average had fallen by 80 percent.

In December 1984 a National Institutes of Health Consensus Development Conference Panel concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probucol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension and diabetes mellitus. Consideration should be given to the efficacy, safety and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient.

Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins) who have not responded adequately to diet, weight reduction and control of diabetes mellitus. Lorelco may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels should be periodically assessed. Small or transient changes in high density lipoprotein cholesterol may be due to inaccuracies in the method of determination. Substantial changes are sometimes seen with diet.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS: (See also PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (See ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Although Q-T prolongation can occur in patients on probucol, the arrhythmias observed in monkeys fed large doses of probucol added to an atherogenic diet have not been reported in man; nevertheless, the following precautions are deemed prudent:

1. At the start of treatment with Lorelco and throughout the treatment period, patients should be advised to adhere to a low cholesterol, low fat diet.
2. As part of an overall evaluation, a baseline, six month, and one year repeat ECG tracing should be considered. If marked prolongation of the Q-T interval (after correction for rate) occurs, the possible benefits and risks should be carefully considered before making the decision to continue the probucol administration.

Lorelco should not be used in patients with evidence of recent or progressive myocardial damage or findings suggestive of ventricular arrhythmias.

No instances of increase in ectopy attributed to Lorelco have been reported. However, patients with unexplained syncope while on Lorelco should have ECG surveillance.

PRECAUTIONS

General: Because Lorelco is intended for long-term administration, adequate baseline studies should be performed to determine that the patient has elevated serum cholesterol levels. Serum lipid levels should be determined before treatment and repeated during the first few months of treatment and periodically thereafter. A favorable trend in cholesterol reduction should be evident during the first three to four months of administration of Lorelco. Probucol lowers serum total and LDL cholesterol, and also lowers HDL-cholesterol in many patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease (see CLINICAL PHARMACOLOGY). Animal or human studies which could confirm or deny the hypothesis that drug induced alteration in HDL-cholesterol affects cardiovascular risk have not been carried out. It is not known whether probucol-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of probucol for the prevention of coronary heart disease, similar to the LRC-CPTT (See CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and should consider periodic electrocardiograms. (See WARNINGS.)

Elevations of the serum transaminases (glutamic-oxaloacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug-related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with probucol than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, probucol should be discontinued.

Drug Interactions: The addition of clofibrate to probucol is not recommended since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol. Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco. Monkeys fed a high fat, high cholesterol diet admixed with probucol exhibited severe toxicity. The toxicity observed in monkeys has not been reported in man. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.)

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Carcinogenesis, Mutagenesis, Impairment of Fertility

In chronic studies of two years duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy

Teratogenic Effects

Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probucol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

Labor and Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is secreted in human milk, but it is likely to be since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal

diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular

prolongation of the Q-T interval on ECG

Neurologic

headache, dizziness, paresthesias, insomnia, tinnitus, peripheral neuritis

Hematologic

ecchinopsia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic

rash, pruritus, ecchymosis, petechiae, hyperhidrosis, feticid sweat

Genitourinary

impotency, nocturia

Ophthalmic

conjunctivitis, tearing, blurred vision

Endocrine

enlargement of multinodular goiter

Idiosyncrasies

An idiosyncratic reaction observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain has been observed.

Other

diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE: There is a single report of a 15 kg, three-year-old male child who ingested 5 gm of probucol. Emesis was induced by ipecac. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdosage with Lorelco and no specific antidote is available. Probucol is not dialyzable. Treatment is symptomatic and supportive. Probucol has shown no identifiable acute toxicity in mice and rats. In these animals the LD₅₀ (oral) is in excess of 5 gm/kg of body weight.

DOSAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 500 mg (two tablets of 250 mg each) twice daily with the morning and evening meals.

HOW SUPPLIED: Each white film-coated tablet contains 250 mg probucol and is imprinted with the DOW diamond trademark over the code number 51. Bottles of 120 tablets, a 30-day supply for one patient (NDC 0068-0051-52)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well closed light-resistant container with child-resistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premortem syncope was frequently observed and was associated with a pronounced prolongation of the Q-T interval (30 to 50 percent longer than that observed in untreated monkeys). Serum levels of probucol greater than 20 mcg/ml were generally associated with some prolongation in the Q-T interval in the cholesterol-fed monkey. A 75 msec or greater increase in Q-T interval from control values was usually seen at 40 mcg/ml and above. Blood levels in humans receiving probucol average approximately 20 mcg/ml and not uncommonly reach levels of 40 mcg/ml and higher. Rhesus monkeys fed normal (low fat) chow and receiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration. In another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probucol, separated in time from the atherogenic meal, was carried out during the second year. Serum probucol levels ranged 20 to 50 mcg/ml in five of ten monkeys, and less in the remaining animals. Marked prolongation of the Q-T interval in the aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probucol. It should be emphasized that both HDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles) there were 12 fatalities. Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probucol has been studied, the dog is particularly with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probucol either before and after, or only after myocardial infarction induced by coronary artery ligation. In these studies there was no difference between probucol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probucol has shown no identifiable toxicity in mice and rats. In these animals the LD₅₀ (oral) is in excess of five gm/kg of body weight. In chronic studies of two-year duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs and monkeys, it is known that probucol accumulates slowly in adipose tissue. Approximately 90 percent of probucol administered orally unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days post surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated, probucol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPTT, hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol lowering diet experienced average total and low-density lipoprotein cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary and point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single-tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine was used in the above trial. Caution should be exercised in extrapolating these results to probucol since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency, effect on HDL-cholesterol, and possible toxicity. The effect of probucol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

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Product Information as of January, 1986

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