Epidemiology of Hodgkin's disease

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Hodgkin's disease, although a relatively uncommon malignancy, is one that frequently affects adolescents and young adults. The cure rate is very high; however, treatment for advanced-stage disease with chemotherapy or radiation therapy (or both) can lead to significant immediate and long-term morbidity, and, while rare, increased mortality from the development of secondary malignancies. There have been numerous epidemiologic reports citing a number of factors associated with the increased risk for the development of Hodgkin's disease. Many of these factors are related to environmental, socioeconomic, and genetic conditions. This report describes the development of Hodgkin's disease in two brothers and discusses factors associated with the increased risk of development of Hodgkin's disease, particularly in these cases.

Hodgkin's disease is an uncommon malignancy making up 1.3% of all newly diagnosed cancers in the United States. Only 6900 cases were reported in 1986.¹ The incidence, however, appears to be increasing each year. In addition, because the average age of patients at diagnosis is 32 years, the economic impact with respect to total person-years of life lost for all lymphomas ranks fourth among all cancers.

Hodgkin's disease is also of great interest, not only because of the high curability rate, but because of the speculation that this disorder has a contagion etiology, perhaps due to an infectious agent. The implications, of course, are substantial. This report will discuss the epidemiology of Hodgkin's disease based on the cases of two brothers who had this lymphoma diagnosed within 1 year of each other.

Report of cases

In July 1982, Joseph, a 19-year-old man, had Hodgkin's disease, mixed-cellularity type, diagnosed after he had undergone a right cervical lymph node biopsy. Sym-

toms had begun 3 months before diagnosis with swelling of the left, then the right side of his neck with associated fevers (temperature $>101^{\circ}\text{F}$), night sweats and an approximate 8- to 16-lb weight loss. The disease was staged as stage IIB according to the Ann Arbor classification after bilateral cervical, bilateral supraclavicular, and bilateral axillary lymphadenopathy was found on physical examination.

A chest film and a computed tomography scan revealed an anterior and middle mediastinal mass (greater than a third of the intrathoracic diameter). Findings of liver-spleen scan, bipedal lymphangiogram, and gallium 57 scan (below the diaphragm), were normal, and results of bilateral bone marrow biopsies were negative. The patient achieved a complete clinical remission in February 1983 after undergoing six cycles of a chemotherapy regimen of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) combined with radiation therapy (3600 rad) administered by "sandwich" technique. He maintained his complete remission until October 1987, at which time his disease relapsed.

In June 1983, Joseph's 18-year-old brother had Hodgkin's disease, nodular sclerosing type, diagnosed after undergoing a right supraclavicular lymph node biopsy. His symptoms had begun 3 months earlier with vague, nondescript, retrosternal chest discomfort. During the interim, he experienced fevers with temperatures $>101^{\circ}\text{F}$ and night sweats, but had no significant weight loss ($>10\%$). At the time of diagnosis, he had increasing retrosternal chest discomfort. A chest x-ray film was obtained and revealed a widening of the mediastinum. His disease was staged as stage IIB after physical examination revealed right-sided supraclavicular and bilateral axillary lymphadenopathy, in addition to the chest radiographic findings. Computerized tomography scan of the abdomen and pelvis and gallium 57 scan (below the diaphragm) showed no abnormalities, and results of bilateral bone marrow biopsies were negative. The patient achieved a complete clinical remission in February 1984 after undergoing a similar combined chemotherapy (MOPP, six cycles) and radiation therapy (4000 rad) sandwich-technique regimen. He has maintained complete remission until the present.

Both brothers lived with four other siblings (total five brothers and one sister). Joseph has an identical twin, William. The order of birth (by age, from oldest to youngest) is: William, Joseph, John, James, Lori, and Kenney. There is no other family history of any type of lymphoma. Both patients had no history of tonsillectomy,

appendectomy, infectious mononucleosis, prior malignancy, immunosuppressive therapy, or other medication use (such as phenytoin or amphetamines). Both brothers are Catholic and grew up in a lower middle-class, single-family home with a total of seven or eight members (some family members were occasionally absent). Joseph had a very small circle of playmates while growing up whereas James had a large number of playmates. Both attended rather small parochial elementary and high schools, and both completed (and had their disease diagnosed while attending) community colleges. Hodgkin's disease developed in two elementary school classmates of James within the past year while they were attending college. Both of our patients' parents attended school only to the high school level.

Discussion

As stated, Hodgkin's disease is an uncommon malignancy. However, since 1832, when Thomas Hodgkin first described seven fatal cases of the disease that now bears his name, there have been frequent reports of clusters of cases, more so than would be otherwise expected, leading to speculation of the role of a "contagion" in the etiology. The two cases we described here may give credence to this speculation.

In 1982, Haim and associates² reported a statistically significant increased incidence of Hodgkin's disease in first-degree blood relatives. Four pairs of immediate relatives with Hodgkin's disease were found among 183 patients in whom the lymphoma was diagnosed over a 20-year period. The expected number during that period was 0.45. Consequently, close relatives of patients with Hodgkin's disease had a ninefold increased risk of the disease. In 1983, Kerzin-Storarr and coworkers³ reported a similar fourfold increase (six cases observed versus 1.4 expected). Furthermore, Grufferman and associates⁴ reported on an incidence survey of Hodgkin's disease in Greater Boston over a 14-year-period where the expected number was 0.7. The survey discovered five sibling pairs, younger than 45 years, thus showing a sevenfold increased risk in this group. Additionally, among 13 pairs of siblings, they identified 12 who were sex concordant, with an expected number of 6.8. The number of these cases plus similar cases in a literature review⁴ suggests that siblings of the same sex as an affected person have a risk of the development of Hodgkin's disease double that of siblings of the opposite sex. Therefore, the role of genetic susceptibility in the development of Hodgkin's disease must be considered; however, due to the lack of an identified pattern of inheritance, little is known.

In 1983, Berberich and associates⁵ reported the use of human leukocyte antigen (HLA) technique in studying familial cases of Hodgkin's disease. They found that the haplotype concordance among patients was greater than expected by chance alone, thereby providing a new method for assessing linkage of HLA and disease susceptibility, and new evidence for the genetic control susceptibility to Hodgkin's disease. Such susceptibility could possibly contribute to the unlikely event of Hodgkin's disease developing in two brothers. Interestingly, to date, Hodgkin's disease has not developed in Joseph's identical twin, William.

The number of siblings is thought to have an inverse relationship to the development of Hodgkin's disease, with the risk among patients with five or more siblings nearly half that of patients with none or one sibling.⁶ The number of our patients' siblings does not fit this trend. In addition, Gutensohn and Cole⁶ reported that the risk of Hodgkin's disease is reduced among patients of late birth order. This association apparently holds true for Joseph with his early birth order and increased risk of subsequent later development of Hodgkin's disease and also for Lori and Kenney with their later birth order and decreased risk of Hodgkin's disease, which to date has not developed.

Our patients and their family lived in a single-family housing unit. Gutensohn and Cole⁶ also reported that the risk of Hodgkin's disease in persons who lived in multiple-family dwellings was half that of persons in single-family homes. Perhaps this is an additional reason for both brothers having Hodgkin's disease.

Joseph had many playmates while growing up as a child, whereas James had fewer. It has been reported that the number of neighborhood playmates a child has at age 8 is inversely proportional to the risk of the development of Hodgkin's disease.⁷ The brothers' parents both continued their education only through high school, and their socioeconomic class could be classified as lower middle. Both of these variables are associated with increased risk of Hodgkin's disease in their offspring.⁷ The risk of Hodgkin's disease is twice as great in Jews as Catholics,⁶ but as already noted, our patients' family is Catholic.

The issue has been debated regarding the risk of Hodgkin's disease in persons who have undergone prior tonsillectomy.^{8,9} The general consensus appears to be that tonsillectomy is not a cause nor does it increase the risk of Hodgkin's disease. If it is a cause or increased risk factor, the effect is

complex and modified by factors related to family size. Neither brother had had a tonsillectomy. Persons with Hodgkin's disease have been found to have a higher incidence of prior appendectomy¹⁰; however, neither brother had had an appendectomy.

Long-term use of certain medications such as phenytoin has been associated with the development of lymphoma, especially Hodgkin's disease.¹¹ Neither brother had been taking phenytoin or any other medication on a long-term basis.

There is some evidence to suggest that chronic exposure to wood or wood dust may increase the risk of Hodgkin's disease. Milham and Hesser¹² analyzed the death certificates of 1594 white males who had died of Hodgkin's disease compared with those of matched controls and calculated the risk factor of 2.3 for those who were woodworkers. Long-term exposure to wood dust may be part of a casual pathway of providing a continuing antigenic stimulation. Neither brother had such exposure.

There has been much speculation as to an association between an infectious agent and the development of Hodgkin's disease based on early epidemiologic studies of close contacts among individuals and the later development of Hodgkin's disease. Initial reports¹³⁻¹⁵ of clusters of Hodgkin's disease in schools and classrooms exceeding the expected rates of development of the disease sparked the concern of a viral contagion as an etiologic agent. Because Hodgkin's disease predominately affects adolescents and young adults, the Epstein-Barr virus, the causative agent of infectious mononucleosis, has been implicated. The debate continues.

Vianna and associates^{13,14} and Zack and associates¹⁵ suggested evidence of transmission of Hodgkin's disease in schools, with an increased risk of development among classmates. Grufferman and associates¹⁶ and Smith and coworkers,¹⁷ however, showed no excess development of Hodgkin's disease between classmate pairs that might have occurred otherwise by chance. Joseph and James both attended the same elementary and high schools, with 2 years intervening their entry. In addition, two elementary school classmates of James have since had Hodgkin's disease develop while in college.

A report of clusters of cases of Hodgkin's disease in school and military cohorts¹⁸⁻²¹ led to the suggestion of involvement of an infective agent in the etiology. The Epstein-Barr virus has been implicated for two main reasons: (1) There is an increased incidence of lymphomas developing after

infectious mononucleosis compared with control subjects who have not had this disease; and (2) patients with Hodgkin's disease more so than control subjects without this lymphoma have elevated antibody titers against Epstein-Barr virus. No true virus, however, has been found in tumor specimens from patients with Hodgkin's disease. Neither brother had a history of infectious mononucleosis.

The increased incidence of malignant disorders has been observed in renal allograft transplant recipients. The most frequently occurring malignancies are cancer of the skin and lip (35% of cases), followed by lymphoma (27%).²² The most common lymphoma is large-cell non-Hodgkin's lymphoma (NHL), followed by Kaposi's sarcoma.²² Hodgkin's disease infrequently is associated as a tumor developing subsequent to transplant procedures. It was thought that the association between transplant recipients and the development of cancer is related to the immune suppression brought on by immunosuppressive medication, (ie, azathioprine, cyclophosphamide, or prednisone) required by the patient after transplantation.²² There is no evidence of preexisting neoplasms in either the donors or the recipients prior to transplantation. Lymphoreticular tumors are also known to occur with increased frequency among patients with primary immunodeficiency disorders.²²

A similar relationship probably exists between patients with the acquired immune deficiency syndrome (AIDS) and their high risk for malignancies, namely, Kaposi's sarcoma and NHL (Burkitt's lymphoma, Burkitt's-like lymphoma-diffuse undifferentiated NHL, and immunoblastic sarcoma).²³ Again, Hodgkin's disease is an infrequent occurrence.

Neither patient had a history of primary immunodeficiency disorder nor a human immunodeficiency virus (HIV) infection or exposure.

Summary

It appears two brothers had Hodgkin's disease develop 9 months apart. Certain risk factors or associations with the increased risk for Hodgkin's disease were noted, including first-degree blood relatives, sibling-pairs, sex-concordance, early birth order (Joseph), single-family housing unit, small cohort of childhood playmates (James), lower level of parent's educational attainment, middle-class status, and increased clustering of cases in school populations.

Our paper notes the factors associated with the risk for Hodgkin's disease, a malignancy which,

though rare, and fortunately highly curable, still has great impact in a young population.

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‡See Contraindications, Warnings, and Animal Pharmacology and Toxicology.

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DESCRIPTION: Loirelco (probuco) film-coated tablets for oral administration contain 250 mg or 500 mg of probuconol 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, polysorbate 80, talc, and titanium dioxide. Loirelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(1,1-dimethyl-ethylene)bis[3-(thio)bis[2,6-bis(1,1-dimethyl-ethylene)phenyl]]bis[2,6-bis(1,1-dimethyl-ethylene)phenyl]. Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY: Loirelco lowers total serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probuconol exhibit a decrease in low-density lipoprotein (LDL) cholesterol. Cholesterol is reduced not only in the LDL fraction, but also in the high-density lipoprotein (HDL) fraction with proportionately greater effect on the high-density portion. Epidemiologic 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 (VLDL).

Studies on the mode of action of Loirelco indicate that it increases the fractional rate of LDL catabolism. 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. Loirelco also exhibits inhibition of early stages of cholesterol biosynthesis 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 Loirelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Loirelco 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 of 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 Loirelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/mL (± S.D.) ranging from 7.8 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 from 6.2 to 90.1 mcg/mL. In a separate study in eight patients, blood levels averaged 19.0 mcg/mL at the end of 12 months of treatment. Six weeks after cessation of therapy, the average had fallen by 60%. After six months, the average had fallen by 80%.

In December 1984, a National Institute of Health Consensus Development Conference Panel¹ concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

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

Loirelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (Types I and IIb hyperlipoproteinemia).² whose elevated LDL-cholesterol has not responded adequately to diet, weight reduction, and control of diabetes mellitus. Loirelco may be useful to lower elevated LDL-cholesterol that occurs in those patients with combined hypercholesterolemia and hypertriglyceridemia (Type IIb) due to elevation of both LDL and VLDL, but it is not indicated where hypertriglyceridemia is the abnormality of most concern. After establishing that the elevation in serum total cholesterol represents a primary lipid disorder, it should be determined that patients being considered for treatment with Loirelco have an elevated LDL-cholesterol as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with elevated triglycerides or with markedly elevated HDL-cholesterol values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients, LDL-cholesterol may be estimated according to the following equation:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - [(0.16 \times \text{triglycerides}) + \text{HDL-cholesterol}]$$

When total triglycerides are greater than 400 mg/dL, this equation is less accurate. In such patients, LDL-cholesterol may be obtained by ultracentrifugation.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels, including HDL-cholesterol, should be periodically assessed.

The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

CONTRAINDICATIONS: (See also WARNINGS and PRECAUTIONS.) Loirelco is contraindicated in patients who are known to have a hypersensitivity to it. Loirelco is contraindicated in patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin.

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

Prolongation of the QT interval can occur in patients on Loirelco. Serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Loirelco alone and in patients on Loirelco and a concomitant antiarrhythmic drug. The following precautions are deemed prudent:

1. Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Loirelco and throughout the treatment period.
2. An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to continue Loirelco.

Loirelco therapy should be discontinued or not started if the QT interval at an observed heart rate on a resting ECG is persistently more than one of the values listed below:

Observed Heart Rate (beats/min)	QT Interval in sec (15% above the upper limit of normal) ^a	
	Males	Females
40	0.56	0.58
50	0.52	0.53
60	0.49	0.50
70	0.45	0.47
80	0.43	0.44
86	0.42	0.43
92	0.40	0.40
100	0.39	0.40
109	0.37	0.38
120	0.36	0.36
133	0.34	0.35

^aValues calculated from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia, PA: Lea and Febiger; 1958; p. 272 (Table 6).

3. Patients developing unexplained syncope or syncope of cardiovascular origin should have Loirelco therapy discontinued and should have ECG surveillance.
4. Drugs that prolong the QT interval are more likely to be associated with ventricular tachycardia after:
 - a. An increase in the dose of the drug.
 - b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines).
 - c. Hypokalemia or hypomagnesemia.
 - d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
 - e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Loirelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemia therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Loirelco:

- a. Hypokalemia.
- b. Hypomagnesemia.
- c. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
- d. Recent or acute myocardial infarction, ischemia, or inflammation.

PRECAUTIONS

General: Before instituting therapy with Loirelco, adequate baseline studies should be determined that the patient has persistently elevated total and LDL-cholesterol levels representing a primary lipid disorder, and that the increased cholesterol is not due to secondary conditions such as hypothyroidism, poorly controlled diabetes mellitus, obstructive liver disease, nephrotic syndrome, or dysproteinemias. Serum lipid levels, including HDL-cholesterol, should be determined after an overnight fast before treatment, during an adequate trial of diet and weight reduction therapy prior to addition of drug therapy, and periodically during combined diet and drug therapy, including assessment during the first several months of drug treatment. A favorable trend in lipid levels should be evident during the first three to four months of administration of Loirelco, and if satisfactory lipid alteration is not achieved, the drug should be discontinued. Loirelco lowers serum total and LDL-cholesterol, and also lowers HDL-cholesterol in most 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). Human studies which will attempt to confirm or deny the hypothesis that drug-induced alteration in HDL-cholesterol affects cardiovascular risk are currently under evaluation. It is not known whether Loirelco-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of Loirelco 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 Loirelco 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 to become pregnant for at least six months after discontinuing Loirelco and should not breast-feed their infants during that time with Loirelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and periodic ECGs. (See WARNINGS) Elevations of the serum transaminases (SGOT, SGPT), bilirubin, alkaline phosphatase, creatine phosphokinase, urea nitrogen, and blood glucose above the normal range were observed on one or more occasions in various patients treated with Loirelco. Most often these were transient and/or could have been related to the patient's clinical state or other therapy. Although the basis for the relationship between Loirelco and these abnormalities is not firm, the possibility that these are drug related cannot be excluded. In controlled trials, the incidence of abnormal laboratory values was no higher in patients treated with Loirelco than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, Loirelco should be discontinued.

Drug Interactions: The addition of clofibrate to Loirelco is not recommended, since the lowering effect on mean serum 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 Loirelco on serum cholesterol. The dosage of agents is not usually modified when given with Loirelco.

Monkeys fed a high fat, high cholesterol diet administered with probuconol exhibited serious toxicity. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.) Prolongation of the QT interval can occur in patients on Loirelco and sinus arrhythmias have been seen in association with an abnormally long QT interval in patients on Loirelco. The addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines) increases the risk of serious arrhythmia. (See CONTRAINDICATIONS AND WARNINGS.)

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 probuconol. 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 the persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

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

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

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 QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), sudden death

Neurologic

Headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis

Hematologic

Neutropenia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic

Rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat

Genitourinary

Impotency, nocturia

Ophthalmic

Conjunctivitis, tearing, blurred vision

Endocrine

Enlargement of multinodular goiter

Idiosyncrasies

Observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain

diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Loirelco, 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 g of probuconol. Emesis occurred within 15 minutes, and the child remained well, apart from a brief episode of loose stools and flatulence. No specific treatment is available on the treatment of overdosage with Loirelco and no specific antidote is available. Probuconol is not dialyzable. Treatment is symptomatic and supportive. Probuconol has shown no identifiable acute toxicity in mice and rats. In animals the LD₅₀ (oral) is in excess of 5 g/kg of body weight.

DOSEAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 1000 mg daily given in two divided doses of 500 mg each (two 250 mg tablets or one 500 mg tablet) with the morning and evening meals.

HOW SUPPLIED: 250 mg round, white, film-coated tablets imprinted with either the DOW diamond trademark over code number 51 or LOIRELCO 250. Bottles of 120 (NDC 0068-0051-52) 500 mg capsule-shaped, white, film-coated tablets, marked LOIRELCO 500. Bottles of 100 (NDC 0068-0053-61) Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well-closed light-resistant containers with a desiccant.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys, administration of probuconol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premortem study was frequently observed and was associated with a pronounced prolongation of the QT intervals (50% longer than that observed in untreated monkeys). Serum levels of probuconol greater than 20 mcg/mL were generally associated with some prolongation of the QT interval in the cholesterol-fed monkey. A 75 mcg or greater increase in QT interval from control values was usually seen at 40 mcg/mL and above. Blood levels in humans receiving Loirelco average approximately 20 mcg/mL, and not uncommonly reach levels of 40 mcg/mL and higher. Rhesus monkeys fed normal (low fat) diets received probuconol 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. Another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probuconol, separated from the atherogenic diet meal, was carried out during the second year. Serum probuconol levels ranged from 20 to 50 mcg/mL in five monkeys, and less in the remaining animals. Marked prolongation of the QT interval in the ECG or syncope behavior was observed over the entire one-year treatment period. Regression of gross lesions comparable to that observed in a past group of monkeys receiving cholestyramine was seen in animals receiving probuconol. It should be emphasized that both cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year cholestyramine study involving 32 probuconol-treated dogs (beagles), there were 12 fatalities.

Subsequent experiments have indicated that probuconol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probuconol has been studied, the dog is peculiar with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the injections of epinephrine to epinephrine-treated monkeys did not induce ventricular fibrillation.

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

Probuconol has shown no identifiable toxicity in mice and rats. In these animals, the LD₅₀ (oral) is in excess of 5 g/kg of weight. In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs, and monkeys, it is known that probuconol accumulates slowly in adipose tissue. Approximately 90% of probuconol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance; 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 probuconol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

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

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPTT,³ hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol-lowering diet experienced average total and cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven incidence of the primary end 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, split 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 or 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 Loirelco since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency (LDL-cholesterol, and possibly toxicity). The effect of probuconol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

REFERENCES

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Product Information as of June, 1988

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