Teaching laboratory medicine with a problem-solving approach

KUSUM KUMAR, MB, BS
ALLAN FOX, DO

To learn cost-effective, appropriate use of laboratory testing, students must begin laboratory medicine studies early in an osteopathic medical school curriculum. In their second year, osteopathic medical students at Michigan State University are taught laboratory medicine as a distinct course, with a problem-solving approach. Various illustrative case studies are used in lectures, laboratory sessions, and small-group discussions to teach clinical interpretation and practical application of laboratory testing. Laboratory sessions that deal with various aspects of clinical pathology are conducted with active student participation. This course has been taught as described since 1982. It has been found to foster active independent learning and problem solving. As evaluated by subjective and objective criteria, learning laboratory medicine with a problem-solving approach in an active manner results in a better understanding of the rationale and usefulness of laboratory testing.

Rapid advances in biomedical knowledge and technology, as well as the need to practice cost-effective medicine, make it imperative that the appropriate teaching of laboratory medicine begin early in the course of a medical school curriculum. Wallach¹ believes that "faculty and administrators still assume that this essential area of medicine can be learned intuitively," and that most medical schools lack adequate teaching of laboratory medicine.

The rationale for obtaining appropriate tests in various clinical situations can be taught best by

organizing several illustrative case studies around clinical problems and laboratory tests.² The intent is to stimulate students to think in terms of differential diagnosis and to construct an appropriate "decision tree" or algorithm for abnormal laboratory findings.

Textbooks of pathology, as well as most instructors of pathology, organize information around a particular organ system or a specific disease rather than a particular clinical problem. Traditionally, the students are taught in terms of pathogenesis of diseases, whereas, as clinicians, they must reason in terms of differential diagnosis.

It has become more apparent that clinical problem solving is a complex process that can be developed by students if they are actively engaged in their own education.³ The 1984 report of the panel on the General Professional Education of Physicians (GPEP)⁴ recommended that medical students be active, independent learners and problem solvers rather than passive recipients of factual information transmitted to them in lecture rooms. Speicher and Smith⁵ described a problem-solving approach to laboratory studies, including strategies to solve clinical problems.

The laboratory medicine course at the Michigan State University College of Osteopathic Medicine has been taught with a problem-solving approach, which was designed according to the principles that subsequently were recommended by GPEP.⁴ This article outlines some of the major concepts and measures used to teach this course.

Course objectives

The primary objective of the laboratory medicine course is to encourage students to learn to use the laboratory effectively for diagnosis and management of patients. Upon completion of the course, the students should be able to do the following:

(1) Select appropriate laboratory tests, interpret the reported results, and synthesize the data into a useful and coherent clinical context.

(2) Perform venipuncture, prepare a peripheral blood smear, perform a WBC count and differential analysis, interpret the findings in all formed elements of the blood.

(3) Perform routine urinalysis and interpret its results.

(4) Understand the basic laboratory procedures used in hematology, coagulation, clinical chemistry, blood bank, microbiology, body fluid analysis, and pregnancy testing.

(5) Understand cost concepts and reimbursement systems to make cost-effective and efficient use of the laboratory.

The laboratory medicine course is taught as a required subject in the second year to approximately 130 students. It consists of ten lectures and five laboratory exercises, which are supplemented by study of prepared self-instructional materials in unscheduled time.

The textbook used is the fourth edition of *Clinical Laboratory Medicine: Clinical Applications of Laboratory Data*, by Ravel.⁶ Lecture topics include basic laboratory tests in hematology, coagulation, clinical chemistry, blood bank, urinalysis, microbiology, body fluid analysis, and diagnosis of pregnancy. The lectures focus on the effective use of information in the diagnostic process.

The first lecture in the series sets the tone by discussion of the need for testing. It is based on the following questions: (a) Why should a test be done? (b) When should the test be done? (c) What physiologic and pathologic mechanisms underlie the test and its results? (d) If there is a potential danger in performing the test, what is the expected benefit/risk ratio? and (e) What will the result mean in relation to the patient's overall clinical problem? The focus is on teaching the significance of obtaining a test and on using the information in making a diagnosis by utilizing the problem-solving approach.

Reference laboratory values, including the definition of normal and discussion of nonpathologic variations from normal are presented in the first lecture, as are Bayes' theorem of predictive values of positive tests and of prevalence of disease, costs, and reimbursement. Factors that determine the clinical significance and the costs of the laboratory tests are discussed in the introductory as well as the subsequent lectures. The students also become acquainted with the third-party reimbursement system, governmental regulation affecting reimbursement, and the impact of various health maintenance organizations on laboratory testing.

The remainder of the lectures provide basic in-

formation regarding selection of laboratory tests, interpretation of results, and synthesis of data in clinical context.

Following the lecture content, in the course syllabus, there are case study problems that the students are required to solve. The level of these exercises is planned so as to be commensurate with the knowledge and understanding of second-year students. These cases present specific clinical problems that require laboratory testing for diagnosis.

For example, one case study on renal function and urinalysis includes a short history of a 4-year-old girl with persistent vomiting and diarrhea of 24 hours' duration. Urinalysis reveals a pH value of 5 and negative protein, glucose, bilirubin, blood, and nitrite findings. Urinary ketones are positive (+ + +), and the urobilinogen level is 0.2 Ehrlich units/dL. The questions that the students have to answer are: What is/are the abnormalities in this urine? What is this condition called? What is the basis for the abnormal result? In which diseases might this condition be seen? What should be the next step in the management of this patient? By solving cases in this manner, students learn to focus on the problem with which the patient presents and to build the battery of tests in the proper sequence. These written case studies are critiqued by the instructors and returned to the students.

The content of the five laboratory sessions deals with phlebotomy, preparation and study of students' own peripheral blood smears, study of prepared normal and a few selected examples of abnormal blood smears, coagulation tests, blood banking, and urinalysis. All laboratory exercises require active student participation. A few students who have had a prior background in laboratory medicine (for example, medical technology) play roles as teaching assistants in these laboratory sessions.

Course evaluations by the students indicate that they find these laboratory sessions to be very profitable learning experiences. They especially cite the phlebotomy laboratory, where they draw blood from each other and prepare peripheral blood smears, which gives them hands-on experience. In addition, students study several previously prepared peripheral blood smears that illustrate abnormal RBCs, WBCs, and platelets. These abnormal smears accompany case studies, which are followed by a set of questions that start with the problem (the major abnormalities in the smear) and then proceed toward the diagnostic workup of the case. Abnormal RBC morphology includes iron deficiency anemia, sickle cell anemia, thalassemia major, megaloblastic anemia, and spherocytosis. Abnormal WBC morphology includes leukocytosis, left shift, toxic granulation, Dohle's inclusion bodies, hypersegmented neutrophils, agranulocytosis,

TABLE 1. RESPONSES OF STUDENTS TO VARIOUS ITEMS IN COURSES EVALUATION FORMS, 1987.

Items	Score* (% of responses)					Mean score
	1	2	3	4	5	
Stimulatory course	31.0	55.2	12.1	0	1.7	1.8
Increased awareness of the relevance of basic science to clinical problems	41.4	50.0	6.9	1.7	0	1.6
Improved ability to work out appropriate management of patients	32.8	56.9	5.1	5.2	0	1.8
Enhanced ability to use available data to generate diagnostic hypothesis	36.2	53.4	5.2	5.2	0	1.7
Increased understanding of the etiologic factors implicated in various diseases	25.9	56.8	12.1	5.2	0	1.9
Provided a framework that will help in organization and interpretation of clinical data	27.6	63.8	6.9	1.7	0	1.8
Good organization of topics	17.3	69.0	10.3	3.4	0	1.9
Content consistent with objectives/goals	25.9	62.1	8.6	3.4	0	1.8
Self-instructional materials informative	25.9	56.9	15.5	1.7	0	1.9
Overall mean score						1.77

*Scores were based on a 5-point scale, with 1 = strong agreement and 5 = strong disagreement with the statement.

and infectious mononucleosis. Abnormal platelet count emphasize changes in number, size, and shape.

The final laboratory session is focused completely on problem solving of specific clinical problems and abnormal results. This session is conducted first in small groups of seven or eight students, with each group being led by a teaching assistant.

Case studies then are discussed with the entire class by the instructor. As an example, one case study deals with the use of laboratory tests in the differential diagnosis of hypercalcemia. The brief history is that of a 40-year-old white man who is in apparently good health, but who has a chemistry profile revealing an unexpected serum calcium level of 12 mg/dL. The questions the students need to answer are: What other chemistry value(s) should be reviewed? Should the serum calcium determination be repeated, and, if so, how many times and with what patient preparation? In addition to tests in the routine profile, what other chemistry studies may be needed?

As a final exercise, students are required to construct an algorithm for the use of laboratory tests in the differential diagnosis of hypercalcemia. In this process, students need to use reason to determine the following: How can it be confirmed whether the value of serum calcium truly is elevated or due to sampling or technical error? What is the relation between serum proteins and calcium (total and ionized)? Should the serum proteins be evaluated, and, if so, by what tests? What pertinent findings in the history and physical examination are important? What are the various causes of hypercalcemia? If the patient is taking any drug that may cause hypercalcemia, what steps should be taken? What other specific tests should be obtained to arrive at the specific diagnosis? When is parathormone ordered?

In addition to scheduled lectures and laboratory sessions, the course offers optional, supplemental,

self-instructional materials, which include short case studies accompanied by representative photomicrographs on slides that illustrate a finding, such as hypochromic microcytes in peripheral blood or RBC casts in urine sediment. These case studies are selected so that they represent common clinical problems that require laboratory tests for diagnosis and management. Following the case study, a quiz leads the student through an active process of diagnostic decision making.

Examinations in this course further emphasize the problem-solving approach. A midterm quiz is designed from a clinical perspective; short histories of patients are presented along with the results of a few initial laboratory tests. The students are expected to write brief answers that state the most likely diagnosis and to list a few additional key laboratory tests that need to be performed for diagnosis confirmation. The final examination uses multiple choice questions, which are drawn to some extent from the Group for Research in Pathology Education (GRPE) question pool. Nearly all questions relate to clinical application and interpretation.

Course evaluation

The laboratory medicine course has been evaluated annually by written student evaluations. Osteopathic medical students' response to this course has been enthusiastic. Table 1 presents the percentage of results of the various items in the forms returned by the students. The response choices ranged from 1 (strongly agree with the statement) to 5 (strongly disagree with the statement). The composite average of the ratings for all items was 1.77.

More than 90% of the students indicated that the course increased their awareness of the relevance of basic science to clinical problems and provided them with a framework that will help in organization and interpretation of the clinical data.

The students also were given the opportunity to write open-ended comments about the course in the evaluation forms.

It is quite clear that the course gives students an understanding of "why, how, and when" in terms of laboratory testing. These second-year students are taught system biology courses, of which laboratory testing is an integral part. The laboratory medicine course provides them with a strong basic background and, thus, better understanding of the systems courses. In addition, house staff and faculty members from medicine and other disciplines (pediatrics, neurology, obstetrics and gynecology, and surgery) have reported that the students have a better understanding of laboratory testing after this course.

Further objective evaluation of the course—a pre-test of second-year students and a post-test of third and fourth students—is under ongoing consideration.

Discussion

Laboratory medicine has been taught in the manner described for the last five years, and the course has been rated highly by the students. They learn how to make effective use of the information provided by the laboratory. We believe that this understanding results in an efficient use of laboratories by these students when they become physicians.

Laboratory medicine is not emphasized in most medical school curricula. Presently, laboratory medicine constitutes a separate required course in pathology in only 11% of medical schools. It is integrated with anatomic pathology in 55% of schools and is not part of the required curriculum in 10% of schools. It is part of another department's scores or another interdisciplinary cause in the remaining 24% of schools.⁷

It is not known how many of the schools teaching laboratory medicine use a problem-solving approach.⁸ Few osteopathic colleges use this method. Problem solving is an efficient way for students to develop knowledge and reasoning skills simultaneously.⁹ This course fosters problem solving, active learning, and independent study, all of which are among the elements recommended by GPEP.⁴ The instructional approach using illustrative case studies in this course encompasses the many proposals by Mistry² to teach efficient and effective utilization of the clinical laboratory.

Even though hands-on experience is provided in the laboratories in this course, it is thought that students would benefit further if they had rotations in small groups in the hospital clinical laboratories. Limited access to the hospital laboratories is a major reason for the lack of this experience for

students. Presently, an hour's guided tour of a hospital laboratory is optional.

Third- and fourth-year students may opt for a three-week clerkship in laboratory medicine under the supervision of a pathologist at one of several hospitals affiliated with Michigan State University College of Osteopathic Medicine. Approximately 5% of students choose this optional clerkship.

Another feature lacking in the course presently is the use of computer technology. The use of this very important tool, especially in the study of self-instructional materials (during unscheduled time), will be accomplished in the near future.

Summary

This paper describes the teaching of laboratory medicine as a distinct course in the second year at Michigan State University College of Osteopathic Medicine. Various illustrative case studies are utilized in lectures and laboratory sessions as well as in small group discussions to teach the clinical interpretation and practical application of laboratory tests. Laboratory sessions that deal with various aspects of clinical pathology are conducted with active student participation. This course has been taught as described since 1982. It has been found to foster active independent learning and problem solving. Learning laboratory medicine with a problem solving approach in an active manner results in a better understanding of the rationale and the usefulness of laboratory testing.

1. Wallach JB: *Interpretation of Diagnostic Tests: A Synopsis of Laboratory Medicine*. Boston, Little Brown & Co., 1986, p 8.

2. Mistry FD: Using case presentations to augment instruction in laboratory medicine. *J Med Educ* 1982;57:804-806.

3. Glaser R: Education and thinking: The role of knowledge. *Am Psychol* 1984;39:93-104.

4. Muller S (chairman): Physician for the 21st century: Report of the Project Panel on the General Professional Education of the Physician and College Preparation for Medicine. *J Med Educ* 1984;59:1-200.

5. Speicher CE, Smith JW Jr (eds): *Choosing Effective Laboratory Tests*. Philadelphia, WB Saunders Co, 1983.

6. Ravel R (ed): *Clinical Laboratory Medicine: Clinical Applications of Laboratory Data*, ed 4. Chicago, Year Book Medical Publishers, 1984.

7. Newsletter 68. Association of Pathology Chairmen, Inc. West Virginia University Medical Center, Morgantown, West Virginia 1986.

8. Cardiff RD: Teaching problem solving in pathology. General Professional Education of Physicians (GPEP) anticipated. *Arch Pathol Lab Med* 1986;110:780-783.

9. Barrows HS, Tamblyn RM: Problem based learning: Rationale and definition, in Barrows HS, Tamblyn RM: *Problem Based Learning: An Approach to Medical Education*. New York, Springer Publishing Co, pp 1-18, 1986

From the Department of Pathology, Michigan State University, East Lansing, Mich.

Reprint requests to Dr Kumar, Department of Pathology, Michigan State University, A-622 E Fee Hall, East Lansing, MI 48824.

When the Goal Is to Reduce Elevated Blood Cholesterol...

LORELCO®
PROBUCOL 250 mg
tablets

Prescribing Information appears on the last page.

Choose

LORELCO **PROBUCOL**
250 mg tablets

as an adjunct to diet

Effectively Lowers Serum Cholesterol with a Unique Combination of Benefits

Consider the Whole Picture.

Efficacy

Lorelco works! You can prescribe it with confidence. Lorelco can virtually double the cholesterol-lowering efficacy of diet alone.¹ Total cholesterol-lowering efficacy *beyond diet* ranges from 10.7% to 27% in reported studies.¹⁻⁴

Indications

Lorelco is specifically indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who have not responded adequately to diet.

Merrell Dow

#1 selling lipid-lowering agent in the world

3 Compliance

The reasons for excellent compliance with Lorelco become clear with the taste and texture test.

This

Questran daily dose (one 9-gram packet one to six times daily)

Water (2 to 6 ounces with each packet)

or This

Lorelco daily dose (2 tablets twice daily with meals)

Tablet counts in a 7 year study of Lorelco indicated that patients took over 90% of their scheduled dosage.⁵

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, lovastatin, and niacin tablets USV.

Cost can be a significant factor when therapy may have to be continued long-term, perhaps for years.

10 years of outstanding Lorelco performance⁶ Now prescribed in 27 countries

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.

Prescribing Information appears on the last page.

References:

- LeLorier J, et al: Diet and probucol in lowering cholesterol concentrations: additive effects on plasma cholesterol concentrations in patients with familial type II hyperlipoproteinemia. Arch Intern Med 1977; 137:1429-1434.
- Mellies MJ, et al: Effects of probucol on plasma cholesterol, high and low density lipoprotein cholesterol, and apolipoproteins A1 and A2 in adults with primary familial hypercholesterolemia. Metabolism 1980; 29:956-964.
- Polachek AA, et al: Probucol in the long-term treatment of hypercholesterolemia. Curr Med Res Opin 1973; 1:323-330.
- Baker SG, et al: Treatment of homozygous familial hypercholesterolemia with probucol. S Afr Med J 1982; 62:7-11.
- McCaughan D: The long-term effects of probucol on serum lipid levels. Arch Intern Med 1981; 141:1428-1432.
- Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

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, polysorbate 80, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-[isopropylidenedithio]bis (2,6-di-*n*-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 ($\pm$ 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 ($\pm$ 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 alterations 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:

- 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.
- 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 low-density lipoprotein 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-CPP2 (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-oxalacetic 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 serious toxicity. The toxicity observed in monkeys has not been reported in man. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.)

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

eosinophilia, 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

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 overdose 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, or LORELCO 250. 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 intervals (30 to 50 percent greater 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_c interval in the electrocardiogram or syncope behavior was never observed over the entire one-year treatment period. Regression of gross 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 peculiar 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 is 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-CPP2, 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 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, 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.

REFERENCES:

- Consensus Development Panel. Lowering blood cholesterol to prevent heart disease. JAMA 253: 2080-2086, 1985.
- The Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results. 1. Reduction in incidence of coronary heart disease. JAMA 251: 351-64, 1984.

Product Information as of April, 1986

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow