Workshop VI
Drug Therapy

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Drug Therapy

Background. During the past decade, research has amply demonstrated that drug treatment of hypercholesterolemia can favorably modify the risk of developing coronary heart disease as well as the progression of atherosclerotic lesions in patients with symptomatic coronary heart disease (see Workshop V). During this period, investigators have learned how to use available agents more effectively, both singly and in combination. In addition, new drugs with increased potency and patient tolerability have become available. It is now feasible to reduce the level of low density lipoprotein (LDL) cholesterol to average or below-average levels in most hyperlipoproteinemic individuals. Consequently, the use of cholesterol-lowering drugs is rapidly increasing in the United States.

Drugs currently approved for use as hypolipidemic agents include the bile-acid sequestrants, cholestyramine and colestipol; niacin; two fibric-acid derivatives, clofibrate and gemfibrozil; probucol; and the cholesterol synthesis inhibitor, lovastatin.

The bile-acid sequestrants act by binding acids in the intestine, thereby increasing the rate of catabolism of cholesterol to bile acids in the liver. This process, in turn, increases the number of LDL receptors on hepatocytes, which increases the uptake of LDL and some LDL precursors from the blood. Prescribed alone, the resins can reduce LDL cholesterol levels by as much as 25%, but efficacy is limited by a compensatory increase in hepatic cholesterol synthesis and by the inability of many patients to tolerate full dosage because of gastrointestinal side effects. The sequestrants frequently aggravate hypertriglyceridemia in patients with pre-existing elevations of very low density lipoproteins (VLDL). Therefore, the sequestrants are used almost exclusively in patients with isolated elevations of LDL, including those patients with heterozygous familial hypercholesterolemia.

Nicotinic acid (niacin) appears to act mainly by inhibiting the secretion of VLDL from the liver. This drug also inhibits lipolysis in adipose tissue, but the effect is reduced with sustained administration. Niacin is poorly tolerated by patients because of cutaneous flushing and gastrointestinal distress unless therapy is initiated with small doses, with a gradual increase over a period of weeks to months. When niacin is given in this manner, it is well tolerated by many patients, and it can reduce LDL cholesterol levels by 20–25%. Niacin also effectively reduces VLDL levels and is therefore considered by many to be the drug of first choice in patients with combined elevations of LDL and VLDL, as in those with familial combined hyperlipidemia (multiple-type hyperlipoproteinemia). Niacin is also an effective drug in the treatment of hyperlipidemic patients with familial dysbetalipoproteinemia.

The fibric-acid derivatives, clofibrate and gemfibrozil, appear to have multiple effects on lipoprotein biosynthesis and catabolism. They consistently appear to increase the activity of lipoprotein lipase in hydrolyzing VLDL-triglycerides and thereby promote the formation of LDL from VLDL. They may also inhibit VLDL formation, so that their effect on LDL levels is variable. In normotriglyceridemic patients, the fibric-acid derivatives can reduce LDL cholesterol levels by 10–15%, but in patients with moderate to severe hypertriglyceridemia, LDL levels are frequently increased as VLDL levels are reduced. These drugs are generally well tolerated, but they increase the lithogenicity of bile and therefore may increase the incidence of cholelithiasis. In a major clinical trial, clofibrate appeared to increase the incidence of gastrointestinal malignancy, but a similar finding has not been reported with gemfibrozil. In the past, these drugs have been used mainly in the treatment of hypertriglyceridemia and in patients with familial dysbetalipoproteinemia, but the use of gemfibrozil in the treatment of hypercholesterolemia is now likely to increase as a result of the Helsinki Heart Trial (see Workshop V).

Lovastatin belongs to a class of fungal products that are potent competitive inhibitors of B-
hydroxy-B-methylglutaryl coenzyme A (HMG CoA) reductase, the major rate-limiting enzyme of cholesterol biosynthesis. Lovastatin’s cholesterol-lowering action results from inhibition of cholesterol synthesis in the liver, which leads to increased activity of hepatic LDL receptors and increased removal of LDL and some LDL precursors from the blood. Lovastatin and other drugs of this class are generally well tolerated. When used as monotherapy, this group of drugs is the most effective in lowering LDL cholesterol, reducing levels by 35–40%. They are also effective in patients with combined elevations of VLDL and LDL, but less effective than niacin or drugs of the fibric-acid class in reducing VLDL levels.

Probucol1,2,4,5,7 is a highly lipophilic agent chemically related to butylated hydroxytoluene. Probucol frequently reduces LDL cholesterol levels by 10–15% and is generally well tolerated although it can prolong the QT interval. Probucol, unlike other approved hypolipidemic drugs, lowers high density lipoprotein (HDL) levels and is also effective in reducing both xanthomas in patients with familial hypercholesterolemia and the appearance of atherosclerotic lesions in hypercholesterolemic rabbits. Recent studies have shown that probucol is a potent lipophilic antioxidant and can inhibit oxidative modifications of LDL that otherwise lead to active uptake of LDL into macrophages. In LDL receptor-deficient rabbits with marked hypercholesterolemia, probucol inhibits the rate of appearance of atherosclerotic lesions, despite little reduction of lipoprotein-cholesterol levels. Whether this effect is related to its antioxidant property is unknown.

All the available drugs also affect HDL cholesterol levels. Modest increases are observed with bile-acid sequestrants and lovastatin, moderate increases with the fibric-acid derivatives, and moderate-to-marked increases with niacin. By contrast, probucol lowers HDL levels, often by substantial amounts. Whether the increases in HDL cholesterol are beneficial with respect to atherogenesis has not been established, although the results of the Helsinki Heart Trial have shown a relation between increases in HDL cholesterol levels and reduced risk of clinical sequelae of coronary heart disease.8 Likewise, it is unclear whether the reduced HDL levels observed with probucol have any adverse effects; in fact, there is some evidence that reduction of tendonous xanthomas in familial hypercholesterolemic heterozygotes is directly related to the extent of reduction of HDL cholesterol levels, a finding that is consistent with the promotion of reverse cholesterol transport.9

Beneficial effects on the course of clinical coronary heart disease or coronary atherosclerotic lesions have been shown for cholestyramine, colestipol (given with niacin), niacin, and gemfibrozil.10,11 Studies of the effects of probucol and reductase inhibitors on human atherosclerotic lesions are in progress, but no results of these studies are yet available. Use of these drugs must take into account hypolipidemic efficacy, demonstrated efficacy in reducing atherosclerotic lesions or clinical sequelae of atherosclerosis, acceptability to patients, toxicity, and cost. The use of hypolipidemic drugs is increasing rapidly as a result of the favorable reports of several intervention trials during the past few years, and these drugs are currently being taken by millions of Americans.

The wide use of these drugs has increased the urgency of research to determine their efficacy in specific situations and to define and understand their toxicity with long-term use. In addition, it is apparent that the discovery of additional drugs, including drugs with different mechanisms of action, as well as improved types of formulations of existing classes of drugs, may increase the ability to lower lipid levels to a range associated with a low risk of coronary heart disease and other forms of atherosclerotic vascular disease.

**Research Needs**

**Standardized Protocols**

**Background.** As indicated above, several classes of drugs have been shown to lower total and LDL cholesterol. There are, however, only limited data to guide the physician on the efficacy of different drugs in specific forms of hyperlipoproteinemia. There is clearly a need for systematic studies to determine the response to different classes of drugs and to drugs within a given class in different hyperlipidemic states.

**Recommendations.** 1) In clinical studies, patient populations should be characterized with respect to lipoprotein disorder. Classification of patient populations in terms of apolipoprotein (apo) polymorphisms, such as apo E and Lp(a), should also be considered in the design of controlled clinical trials. 2) The effects of various classes of drugs should be compared in specific lipoprotein disorders (e.g., fibrates versus niacin). 3) Drugs within individual classes should be compared in specific lipoprotein disorders (e.g., different fibric-acid derivatives and nicotinic-acid derivatives or preparations).

**New Markers**

**Background.** The current classification of lipoprotein species is based primarily on the major classes of VLDL, LDL, and HDL. It is now appreciated that each of these classes is heterogeneous, in both structure and function. Practical methods that can be used to evaluate the effects of drug treatment on different lipoprotein species, or subspecies, or specific lipoprotein properties are needed. Some examples include Lp(a), VLDL containing different apolipoprotein components, chylomicron remnants, and lipoprotein subspecies with specific reactivity to monoclonal antibodies, susceptibility of certain lipoproteins to chemical modification, and capacity of certain lipoproteins to accept cholesteryl esters.
Current information is not sufficient to justify recommendations for drug treatments to raise HDL (see Workshops I, IV, and V). There is, however, a pressing need to develop practical methods to quantify subspecies of HDL that may be specifically affected by drug treatment (see Workshop I).

**Reduction of Cholesterol in Lipoprotein Classes Other Than Low Density Lipoproteins**

**Background.** It is generally accepted that reduction of LDL, as measured by reduction of LDL cholesterol, is the most important measure of the efficacy of cholesterol-lowering drugs. However, there is a background of experimental clinical data linking triglyceride-rich lipoproteins, or subclasses thereof, to atherogenesis and coronary heart disease.

**Recommendation.** Additional research is needed to evaluate the effectiveness of the reduction of lipids in other lipoprotein classes, including VLDL and intermediate density lipoproteins, on the risk for coronary heart disease.

**Diet-Drug Interactions**

**Background.** Current recommendations state that all patients should receive maximal dietary therapy before drug therapy is considered and that dietary therapy must be continued during drug therapy. Data are limited to document the latter recommendation.

**Recommendations.** 1) Specific diet-drug interaction studies are needed for each class of drugs as applied to specific lipoprotein disorders. 2) Early phases of drug development research directed to safety assessment may not require stringent dietary control.

**Treatment of Children**

**Background.** There is little information on the safety of long-term hypolipidemic drug therapy in children.

**Recommendation.** There is a need to conduct well-controlled trials in children to assess the effects of various drugs on growth and development and to determine whether the safety profiles for drugs in children are similar to those in adults.

**Treatment With Combinations of Drugs**

**Background.** Evidence exists that certain combinations of hypolipidemic drugs have complementary effects in certain forms of hyperlipoproteinemia. Use of drug combinations has several potential advantages, including greater hypolipidemic efficacy, increased patient compliance, and, at least in some cases, reduced drug toxicity. The overall data base, however, is quite limited, especially for certain drug combinations.

**Recommendation.** There is a need to extend these studies in a systematic fashion to establish safety and efficacy.

**Criteria for Intervention Trials**

Four drugs (cholesterol, colestipol, nicotinic acid, and gemfibrozil) have been shown in intervention trials to favorably affect the risk for coronary heart disease (see Workshop V).

**Recommendations.** 1) Studies to evaluate the efficacy of drug treatment on the course of coronary heart disease are needed for probucol and drugs in the reductase-inhibitor class. However, such studies should not be required as part of the approval process for new drugs within a given class where beneficial effects on coronary heart disease risk have previously been shown. 2) Long-term safety studies should be required for each new drug, irrespective of its class.

**Genetic Determinants of Drug Response**

**Background.** It is now apparent that the expression of certain forms of hyperlipoproteinemia is affected by certain apolipoprotein polymorphisms (for example, apo E).

**Recommendations.** 1) Research is needed to determine the influence of apolipoprotein polymorphisms, such as apo E, apo B, and Lp(a), on drug response. 2) Appropriate specimens (such as plasma and white blood cells) for study of newly developed genetic markers should be routinely stored.

**New Drug Classes**

**Background.** Evaluation of the effect of lipid-lowering drugs on atherogenesis is often limited by the complexity of drug effects on different lipoprotein classes or other biologic systems (such as those affecting fibrin formation or dissolution, or platelet behavior). There is also a need for better-tolerated drugs where efficacy has already been established.

**Recommendations.** 1) Development of drugs whose actions are limited to certain components of the lipoprotein system should be encouraged (e.g., drugs whose effect is directed specifically at the rate of production of apo B-100 or apo A-1 and drugs affecting the uptake or release of cholesterol in macrophages). 2) Development of drugs that are better tolerated (e.g., new preparations of niacin and bile-acid sequestrants) should be encouraged.

**Treatment of Secondary Hyperlipoproteinemia**

**Background.** In certain common forms of secondary hyperlipoproteinemia, coronary heart disease is a major cause of morbidity and mortality. However, there have been few systematic studies of the efficacy of available lipid-lowering drugs in these conditions (e.g., patients with type II diabetes mellitus, renal and cardiac transplant patients, patients with nephrotic syndromes or chronic renal failure, and patients on hemodialysis).

**Recommendations.** Systematic comparative studies of the effect of the various classes of drugs in the common forms of secondary hyperlipoproteinemia are needed.
Professional Education

First- and Second-Choice Drugs

Background. The National Cholesterol Education Program Adult Treatment Panel Guidelines proposed LDL cholesterol cut points for managing patients with high blood cholesterol. Bile-acid sequestrants and nicotinic acid were defined as “drugs of first choice,” the HMG CoA reductase inhibitors as “new drugs,” and other classes of drugs as “other.” These criteria were established primarily for treating elevated levels of LDL cholesterol and were based on their known efficacy in lowering LDL cholesterol, availability of long-term safety data, and documented evidence for reducing risk of coronary heart disease in clinical studies. Specific and extensive recommendations for the management of patients with other lipoprotein disorders were not made. These other lipoprotein disorders are common and frequently occur in patients with established coronary heart disease. The selection of appropriate drugs for treating other lipoprotein disorders differs from that of patients with elevated LDL cholesterol.

Recommendations. 1) Additional guidelines for the use of drugs in patients with lipoprotein disorders other than isolated elevation of LDL cholesterol are needed, including specific recommendations for first- and second-choice drugs. 2) There is a need to periodically update existing guidelines based on either new scientific data or availability of new therapeutic agents. For example, the findings in the Helsinki Heart Study suggest that changes in lipoproteins other than LDL are beneficial.

Diet-Drug Interactions

Background. The current recommendation is that maximum attempts at cholesterol lowering by diet should be attempted before initiating drug therapy and that diet therapy should be maintained during drug therapy. There is limited scientific data to document the validity of these recommendations.

Recommendation. It was recommended that although there is a need for careful studies of diet-drug interactions, the current recommendations, including those for continued dietary therapy in patients receiving drugs, should continue to be followed because there are logical bases for these recommendations.

Treatment of Children and the Elderly

Background. The treatment guidelines for the use of drugs are based almost exclusively on data obtained from studies in middle-aged men, and these data have been extrapolated to the treatment of women. The current guidelines exclude children and adolescents from consideration, and no specific recommendations have been made for the use of drugs in the elderly. In part, the lack of recommendations for these segments of the population reflects the lack of controlled evaluation of drug safety in children and a paucity of information in the elderly.

Recommendations. 1) Use of drug therapy before adolescence should be limited to those patients with the most severe forms of hyperlipidemia (i.e., homozygous familial hypercholesterolemia or heterozygous familial hypercholesterolemia with a strong family history of premature coronary heart disease). Such patients are best managed by referral to a specialized center. These restrictions can be relaxed somewhat from adolescence to age 20. Drug therapy should be individualized but should generally be limited to the use of bile-acid sequestrants. 2) It is appropriate to consider drug therapy in some elderly persons, but consideration must be given on an individual basis to additional factors such as life expectancy and the presence of other diseases requiring drug therapy. (See Workshop V regarding clinical trials in the elderly.)

Treatment of Patients With Established Coronary Heart Disease

Background. There is increasing evidence that the natural history of atherosclerosis in patients with established coronary heart disease can be modified by lipid-lowering drugs. For example, in the recently reported Cholesterol-Lowering Atherosclerosis Study, favorable effects of lipid-lowering drugs on atherosclerotic lesions were demonstrated, regardless of the pretreatment lipoprotein values.

Recommendation. More aggressive treatment of patients with established coronary heart disease in all age groups is recommended, in terms of lowering the threshold for initiating drug therapy and perhaps in trying to obtain greater decrease in lipoprotein levels. This recommendation applies particularly to those individuals who do not have other major risk factors as the precipitating cause for coronary heart disease.

Combined Drug Therapy

Background. Evidence is now available that certain drug combinations (e.g., resins plus either nicotinic acid or reductase inhibitors) are complementary in the treatment of hyperlipidemia.

Recommendation. Combined drug therapy is a rational approach to treatment, but it should be limited to combinations that have been demonstrated to be efficacious and safe. If the target goals for therapy are not achieved by such combination therapy, consideration should be given to referring these patients to a center specializing in the treatment of lipid disorders.

Toxicity

Background. The toxicities of individual drugs and classes of drugs are quite variable. Bile-acid sequestrants cause dose-dependent gastric distress and constipation, and niacin frequently causes cutaneous symptoms, especially facial flushing, early in the course of treatment. Major toxicities observed
with drugs other than bile-acid sequestrants include hepatic function abnormalities, hyperuricemia, hyperglycemia, and myopathy with increased creatine phosphokinase (CPK). While these abnormalities can be a cause for concern, they do not invariably require cessation of drug treatment.

**Recommendations.** 1) Liver function test abnormalities such as moderate increases in transaminases not more than twofold or threefold that of the upper limit of normal are not uncommonly observed with several classes of drugs. If transaminase levels do not exceed twice the upper limit of normal, therapy can be maintained, provided there are no other abnormalities in liver function in an asymptomatic patient. When transaminase levels exceed normal by threefold, the dose should be reduced or the drugs should be discontinued. 2) Routine monitoring of CPK is not recommended, but myopathy associated with elevated CPK is occasionally observed in patients treated with fibric-acid derivatives or reductase inhibitors. With certain drug combinations (reductase inhibitors plus gemfibrozil, niacin, or cyclosporine), the incidence of myopathy is greatly increased, and these combinations should be used cautiously. 3) Nicotinic acid administration can be associated with hyperglycemia and hyperuricemia, and routine monitoring is recommended. Asymptomatic and moderate elevations of uric acid do not require reduction of dosage or discontinuation of the drug, but development of fasting hyperglycemia is an indication for either reduction in dosage or discontinuation.

**Secondary Hyperlipoproteinemia Attributable to Other Drugs**

**Background.** A number of other drugs used for other therapeutic purposes can significantly modify lipid and lipoprotein levels. The major offenders among chronically administered drugs are steroid hormones and antihypertensive agents.

**Recommendations.** 1) Before initiating hypolipidemic drug therapy, the possibility that the lipoprotein disorder may be related to the administration of other drugs should be considered. If the patient has a lipoprotein abnormality and is receiving drugs with known lipid-altering effects (certain diuretics, β-blockers without significant intrinsic sympathomimetic activity, glucocorticoids, or estrogens), consideration should be given to a change in drug treatment.

**Other Forms of Secondary Hyperlipoproteinemia**

**Background.** Some commonly occurring disease states are associated with secondary hyperlipoproteinemia and increased risk for coronary heart disease. These include patients with type II diabetes mellitus, chronic renal failure necessitating dialysis, and nephrotic syndrome. Additionally, patients who have undergone either renal or heart transplants and are receiving many other medications frequently develop severe forms of hyperlipoproteinemia and accelerated atherosclerosis. Limited data are available to define the proper approach to hypolipidemic drug therapy in these patients.

**Recommendations.** 1) When possible, aggressive management of the underlying disease (e.g., type II diabetes mellitus) should be carried out. 2) With the exception of type II diabetes mellitus, drug therapy should be used cautiously in patients with these secondary forms of hyperlipoproteinemia because of an increased risk of severe drug toxicity. Consideration should be given to referral of such patients to specialized centers for management of the lipid disorder.

**References**

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