The role of hyperlipidemia therapy in preventive care

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The diagnosis and treatment of lipid disorders have progressed significantly within the last several years. The ability to define the exact metabolic derangement is now possible using sophisticated laboratory techniques. For the practitioner and the patient, however, the precise characterization of the underlying disorder is not always necessary. With a basic understanding of the approach to lipid disorders as outlined, and the accurate determination of the cholesterol and triglyceride levels, the physician can outline a potent strategy for the reduction of lipids in his or her patients. At present, multiple therapeutic options are available to the physician. These are discussed.

Evidence linking the elevation of serum cholesterol levels to atherogenesis is now firmly established.¹⁻³ A significant amount of data that demonstrates that treatment of hypercholesterolemia leads to a decline in the incidence of coronary artery disease has been accumulated.⁴ Additional data suggest that such treatment should begin in childhood.⁵

Since the completion of the Lipid Research Clinics Coronary Primary Prevention Trials,⁶ hypercholesterolemia has become an issue of paramount importance in preventive medicine and remains a focus of intensive epidemiologic research. To assist physicians in the Fort Worth community to keep abreast of recent advances in this field of medicine,⁷ the Texas College of Osteopathic Medicine (TCOM) founded the Heart Disease Prevention Clinic. This clinic is based on the model of Frohlich,⁸ who gradually expanded a small local clinic to a national referral center for blood lipid disorders in western Canada. The clinic at TCOM is designed to diagnose and treat plasma lipid abnormalities and to operate a clinical research pro-

gram. This article will review relevant aspects of lipid metabolism and summarize the approach taken in our clinic in managing these disorders.

Diagnosis

Hyperlipidemia is an increase in the plasma cholesterol or plasma triglyceride level or both beyond established normal limits. Until recently, severe hypercholesterolemia and moderate hypercholesterolemia have been defined as plasma cholesterol concentrations exceeding the 90th percentile and 75th percentile, respectively. Tables 1-3 show the new parameters for cardiovascular risk as recommended by the National Cholesterol Education Program of the National Heart, Lung and Blood Institute.⁴ Treatment should be initiated at the level of moderate risk.

The cholesterol values shown in Table 3 fall within the normal range of data sheets currently used by many commercial laboratories. Therefore, many patients who have not been classified previously as hyperlipidemics are, in fact, at risk for premature coronary artery disease.

Once cholesterol elevation is detected, medical evaluation is begun. A detailed family history is obtained first to ascertain whether other family members are affected similarly.⁹ For a man, the risk of myocardial infarction (MI) is increased five- to seven-fold if his father suffered MI before the age of 55 or his mother before age 65. For a woman, there is a 2.5- to seven-fold increase in risk when one parent has had premature MI.¹⁰

These epidemiologic data emphasize the importance of examining offspring of affected families, because they may indicate primary lipid disorders that have a genetic basis. Familial histories of xanthomas and diabetes mellitus also are elicited. The history taking is then directed toward systemic disorders that affect lipid metabolism, as shown in Table 4.

The diagnosis of hyperlipidemia associated with systemic diseases does not exclude the possibility

TABLE 1. CORONARY HEART DISEASE RISK FACTORS.*

Gender—Male sex
 Family history—coronary disease events prior to 55 years of age in a parent or sibling
 Cigarette smoking—currently smoking more than 10 cigarettes/day
 Hypertension—elevated blood pressure using JNC III guidelines
 Low HDL-cholesterol—levels <35 mg/dl (for treatment, not screening decisions)
 Diabetes mellitus
 History of stroke or peripheral vascular disease
 Obesity—30% or more overweight

*Reprinted from *Archives of Internal Medicine* (1988; 36-69).

TABLE 2. CLASSIFICATION OF TOTAL AND LDL CHOLESTEROL.*

Total cholesterol	Classification	LDL-cholesterol
<200 mg/dl	Desirable	<130 mg/dl
200 to 239 mg/dl	Borderline-high	130 to 159 mg/dl†
≥240 mg/dl	High	≥160 mg/dl

*Reprinted from *Archives of Internal Medicine* (1988; 36-69).

†Treat as "high" if CHD or ≥2 risk factors.

of an underlying primary disorder. Therefore, the patient is reexamined once the secondary (systemic) disorder has been brought under control (generally, three to six months after the initiation of treatment). Further, some secondary disorders, such as uremia, require specialized attention, because the lipid disorder often does not remit with either hemodialysis or peritoneal dialysis.¹¹

The history is completed by data on diet and lifestyle. An extensive dietary history is obtained to ascertain excessive caloric, alcohol, or saturated fat intake that requires modification. The patient records everything eaten during a three-day period on a food intake record sheet. The diary includes the time of the day when each meal was taken, the type and amount of food eaten, and the mode of preparation. The food intake data are analyzed by a registered dietician for the total number of calories consumed and the distribution of the intake among the macronutrients (proteins, carbohydrates, and fats). The amounts of cholesterol, vitamins, and minerals (especially table salt) also are computed.

An exercise history is obtained to assess the degree of aerobic fitness. Although exercise does not affect primary lipid disorders appreciably (MS Brown, MD, "You can't outrun cholesterol," medical grand rounds, Parkland Memorial Hospital, Dallas, 1986), it may be important in improving the sense of well-being for the patient, may promote compliance with medical therapy, and may aid in elevating high-density lipoprotein (HDL) levels.¹²

Physical examination is directed toward two areas: (1) the stigmata of hyperlipidemia (xanthomas, arcus senilis, and hepatic enlargement or sple-

nomegaly); and (2) assessment of the ravages of atherosclerosis. A baseline ECG also is obtained, and patients older than 35 years should undergo stress testing before an exercise regimen is recommended.

Laboratory examination involves a series of steps indicated by the history and physical examination. Considerable importance is placed on laboratory values, for the same reason that accurate blood pressure determinations are considered crucial—to avoid committing an apparently healthy patient to lifelong medical therapy based on erroneous data. Most important are accurate and reliable (reproducible) cholesterol, HDL-cholesterol, and triglyceride determinations. We have found that commercial and hospital laboratories often have provided data that were not accurate enough for a precise diagnosis; consequently, we now perform all lipid determinations in our own laboratory, which conforms to Lipid Research Clinics standards.⁵

The laboratory diagnostic strategy is based mainly on serum lipid determinations following a 14-hour fast. Observing the serum after overnight storage at 4°C allows the assessment of exogenous hypertriglyceridemia (presence of chylomicrons). Under some circumstances (with type III disease), agarose gel electrophoresis also is carried out to identify the broad β band. Further specific tests may be performed to make the exact etiologic diagnosis of a particular inherited lipid disorder.¹³

These include isoelectric focusing of apolipoproteins, immunoassays for apolipoproteins, plasma enzyme assays, ultracentrifugal analysis of lipoproteins, and access to gene probes for apoprotein analysis.

Clinical management of the patient is started with Fredrickson's classification. This system is used to establish the presence of a specific lipid pattern (Table 5)¹³ but not to identify the underlying cause. Such an approach may be misleading, especially with a patient under treatment. The diagnosis of lipid disorders is akin to the diagnosis of anemia—both are symptoms of respective underlying diseases, not diagnoses unto themselves. This is particularly true for the primary lipid disorders because they are of genetic origin, and, thus, they may affect several family members simultaneously. The function of the laboratory of our Heart Disease Prevention Clinic is to assist in developing a specific diagnosis, as listed in Table 5.

Major classes of hyperlipidemia

Type 1 hyperlipidemia is distinguished clinically by grossly lipemic serum chylomicron accumulation in the fasting state. Normally, chylomicrons are secreted into the circulation after a meal. The

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Rapid relief

The rapid action of Seldane has been shown both in clinical studies^{5,9} and histamine-induced skin wheal tests.^{5,10,11} Most hay fever patients (55%) experienced relief within 1 hour, and 84% within 2 hours, after Seldane administration. Seldane produced more than 50% reduction of skin wheal area within 1 to 2 hours and 90% reduction within 4 hours, as shown below.¹⁰

No development of tolerance

Seldane has been proven effective in through-the-season use without development of tolerance in four long-term clinical studies,⁵⁻⁸ one lasting six months.

Percent change in histamine wheal area resulting from a single dose of Seldane 60 mg or placebo.¹⁰

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Seldane is comparable to placebo in CNS effects, such as drowsiness, EEG activity, multiple sleep latency tests, and self-rated alertness.^{5,12,13} Even at 5 times the usual daily dose (600 mg in single or multiple doses) for up to 10 weeks, Seldane showed no sedative effect greater than that of placebo.⁵

See Prescribing Information for Contraindications, Precautions and Adverse Reactions.

Proven patient preference

87% of patients who start on Seldane refill their Seldane prescription, according to a nationwide study of nearly a thousand members of large-group prescription plans. Only 59% of those started on the next leading antihistamine refilled.⁵ In a major U.S. consumer study, 87% of patients said that Seldane worked as well as or better than other allergy medications previously taken. (63% said that Seldane worked better.)⁵

Convenient dosing for high compliance

Patients take Seldane only twice daily at any convenient 12-hour interval – a regimen that promotes high patient compliance.

Percent patient compliance by dosage schedule

A summary of 26 studies relating compliance and dosage schedules of various types of medications showed no significant difference in compliance rates between q.d. and b.i.d. dosing. There was significantly greater compliance with q.d. or b.i.d. dosing compared to t.i.d. or q.i.d. dosing ($p < 0.05$).¹⁴

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**The incidence of drowsiness reported in controlled clinical studies with Seldane 60 mg b.i.d. did not differ significantly from placebo, while chlorpheniramine 4 mg t.i.d./q.i.d. produced twice the incidence ($p < 0.02$).

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Seldane® (terfenadine) 60 mg Tablets

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients

Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenicity.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use

Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General

Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported

adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting			All Clinical Studies**	
	Seldane N = 781	Controlled Studies* Placebo N = 665	Control N = 626***	Seldane N = 2462	Placebo N = 1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress					
(Abdominal distress,					
Nausea, Vomiting,					
Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash					
and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (14 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of June, 1988

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Cincinnati, Ohio 45215, U.S.A.

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plasma triglyceride level is >1,000 mg/dL in this disorder. Type I hyperlipidemia often is associated with lipemia retinalis, recurrent episodes of abdominal pain, high risk of pancreatitis, and eruptive xanthomatosis of the skin.¹⁴

The primary cause of the disease is either a congenital deficiency of lipoprotein lipase or apolipoprotein C-II. Lipoprotein lipase is an enzyme located on the surface of capillary endothelial cells; it is responsible for the breakdown of very-low-density lipoprotein (VLDL) and chylomicrons, which are triglyceride transporting particles.¹⁴ Apolipoprotein C-II (a normal component of triglyceride-rich lipoproteins) is necessary for the functioning of lipoprotein lipase.

This disorder requires careful attention to the level of circulating triglycerides. Although severe hypertriglyceridemia generally is not associated with accelerated atherosclerosis, the recurrent episodes of pancreatitis that often accompany it exposes the patient to considerable morbidity.

Type II hyperlipidemia is an elevation in cholesterol secondary to low-density lipoproteins (LDL) accumulation in the blood, with or without triglyceride elevation. LDL is the main transporter of cholesterol in plasma. Cholesterol is needed to manufacture hormones and cellular membranes and, therefore, is necessary for life. Peripheral and hepatic cells are able to remove LDL particles from the blood via cell surface receptors. The work of Nobel prize laureates Goldstein and Brown¹⁵ has shown that some individuals lack the gene for functional LDL receptors and are unable to clear their plasma cholesterol without medical therapy. This condition is known as familial hypercholesterolemia (FH).

An autosomal dominant trait, FH occurs in the random population at the rate of 1 in 500 heterozygotes.¹⁵ The serum cholesterol level usually is in the range of 350 to 500 mg/dL. These patients inherit a gene that is a mutant, whereas the normal gene pair encodes for LDL receptors in the liver and in peripheral tissues.¹⁵ These receptors are nec-

essary to remove cholesterol from the circulation. When only a mutant gene is inherited (heterozygote), an approximately two-fold elevation in LDL is observed; this may lead to heart attacks in persons as young as 35 years.

Homozygotes, who are found at a frequency of 1 per 1,000,000 general population, have no detectable LDL receptors; they ultimately require liver transplants for survival. These patients develop advanced coronary artery disease as early as the first year of life.

Lack of diagnosis of this type II disorder often leads to mistreatment. General risk-reduction maneuvers, such as diet and exercise, cannot significantly influence the cholesterol levels. Therefore, life-long drug therapy is required, even for FH heterozygotes.

Another possible cause of Fredrickson's type II pattern is familial combined hyperlipidemia, which is thought to be caused by overproduction of apoprotein B.¹⁶ This condition is characterized by an elevation of both cholesterol and triglyceride levels. It is of genetic origin, although the exact mode of transmission is unknown. This disorder may be expressed differently within members of the same family, with some having type II and some type IV patterns. Goldstein and associates¹⁶ found this to be the most common lipid disorder in survivors of myocardial infarction; it may be present in 10% of all patients with coronary artery disease. Unlike familial hypercholesterolemia, tendon xanthomas are rare, as is elevation of cholesterol levels in childhood.

The type III pattern is also known as broad β disease because of its unique electrophoretic pattern. Clinically, it is characterized by yellowish fat deposits in the creases of the palms and xanthomas over the elbows and tibial tuberosities. Both serum cholesterol and triglyceride values are elevated, with the triglycerides being higher because of difficulty in metabolizing a unique cholesterol-rich VLDL, which results from an apolipoprotein defect.¹⁷

TABLE 3. TREATMENT OF ELEVATED LDL-CHOLESTEROL LEVELS.*

	Initiation	Goal
<i>Diet:</i>		
No CHD and <2 risk factors†	≥160 mg/dl	<160 mg/dl
Known CHD or ≥2 risk factors	≥130 mg/dl	<130 mg/dl
<i>Medications:</i>		
No CHD and <2 risk factors	≥190 mg/dl	<160 mg/dl
Known CHD or ≥2 risk factors	≥160 mg/dl	<130 mg/dl

CHD = coronary heart disease.
*Reprinted from *Archives of Internal Medicine* (1988; 36-69).
†See Table 1 for list of risk factors.

TABLE 4. SYSTEMIC DISEASES OFTEN ASSOCIATED WITH HYPERLIPIDEMIA.

Diabetes	Uremia
Hypothyroidism	Nephrotic syndrome
Biliary obstruction	Hepatitis
Multiple myeloma	Alcoholism
Systemic lupus erythematosus	Excessive estrogen levels
Cushing's syndrome	

TABLE 5. LIPOPROTEIN DISORDERS (ADAPTED FROM SCHAEFER AND LEVY¹³).

Increased chylomicrons (types I and V HLP*)	Increased VLDL* (type IV HLP)	Increased β -VLDL* (type III HLP)	Increased LDL* (type II HLP)
Familial hypertriglyceridemia	Familial hypertriglyceridemia	Apolipoprotein E2 phenotype	Familial hypercholesterolemia
Familial combined hyperlipidemia (increased chylomicrons)	Familial combined hyperlipidemia	Apolipoprotein E variants	Familial combined hyperlipidemia
Lipoprotein lipase deficiency		Apolipoprotein E deficiency	
Apolipoprotein C-II deficiency			

*HLP = hyperlipoproteinemia; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein.

Normally, chylomicrons are converted to cholesterol-rich remnant particles by the action of lipoprotein lipase and subsequently are removed from the circulation by the liver. The liver uses the lipids transported in chylomicron remnants and secretes another triglyceride-rich VLDL. This VLDL is cleared from the plasma by lipoprotein lipase; first, it is converted to intermediate density lipoprotein (IDL) and then to LDL. The molecular defect in type III hyperlipidemia is caused by an altered form of apolipoprotein E, which results in inefficient hepatic uptake and, thus, excessive accumulation of IDL in the plasma. These patients are also at risk for premature coronary artery disease. The disorder is more common in men than in women, perhaps because of a protective effect of estrogen.¹⁷

Type IV hyperlipidemia genetically results from a disorder referred to as familial endogenous hypertriglyceridemia, with triglyceride levels in the range of 300 to 1,000 mg/dL. The type IV pattern is due to either overproduction of VLDL¹⁸ or difficulty in its clearance from the circulation, which is secondary to either a lipoprotein lipase or apoprotein deficiency similar to the type I disorder. Type IV hyperlipidemia does not appear to be an independent risk factor for coronary artery disease. However, it often is particularly troublesome in people with secondary causes of hyperlipidemia, such as those listed in Table 4.

The type V pattern also has a genetic basis possibly related to an apolipoprotein deficiency.¹³ It is characterized by elevated triglycerides with chylomicrons in the serum. Diagnosis and clinical sequelae are similar to those in the type I pattern. This disorder commonly is associated with hyper-

tension, polyneuropathies, hyperuricemia, and diabetes mellitus.¹⁹

Treatment

Diet is the first step in the treatment of hyperlipidemic disorders. Patients in the moderate risk category often can be treated by diet alone, whereas those at high risk are likely to need concomitant lipid-lowering medication. The diet recommended by the American Heart Association²⁰ generally is effective. This regimen includes reducing fat to 30% of total caloric intake, with no more than 300 mg of total cholesterol ingested per day. If the patient is obese, decreased caloric intake to effect weight reduction also is recommended. More liberal fat intake, to give the diet more flexibility or to meet a budget, may be allowed in the form of monounsaturated fats, such as olive oil.²¹ Fats from vegetables are preferable to meat sources²² and may be less expensive. A vegetarian diet high in polyunsaturated fat also is desirable.²³ With the compliance with recommended diets remaining highly variable,¹ this area needs much further investigation. The suggestions made here are examples of how a higher level of compliance may be reached.

Children of patients at risk should be screened and started on a modified diet at an early age, as recommended by the American Heart Association²⁰: (1) The diet should be nutritionally adequate; (2) caloric intake should be adjusted for growth rate, activity, and weight; (3) total fat should be restricted to 30% of caloric intake (10% saturated, 10% polyunsaturated, and 10% monounsaturated fat); (4) cholesterol should be limited to 100 mg/1,000 kcal, with an upper limit of 300 mg/day; (5) protein should provide 15% of calories; (6)

carbohydrate should provide 55% of calories; and (7) salt should not be used at the table.

Because the human body can synthesize adequate amounts of endogenous cholesterol from other nutrients, diet is the cornerstone of any treatment. Samuel and associates²⁴ have provided a balanced review of dietary recommendations.

Drug treatment presently includes three types of medications taken alone or in combination. For elevated cholesterol (type II hyperlipidemia), treatment generally consists of a bile acid binding resin (cholestyramine or colestipol). These agents act by trapping bile acids in the intestine, which interrupts the enterohepatic circulation. Consequently, increased hepatic synthesis of bile acids from its precursor, cholesterol, is required. The liver, therefore, removes more cholesterol from the circulation, and serum cholesterol levels are lowered. This therapy has been demonstrated by the Lipid Research Clinics⁶ to reduce the incidence of coronary artery disease and generally has few (if any) long-lasting side effects.

Short-term side effects are encountered occasionally. The most common are gastrointestinal problems, especially constipation and bloating. Both cholestyramine and colestipol bind anionic drugs, including digoxin, thyroxine sodium warfarin, and thiazide diuretics. Additionally, these agents may cause an increase in plasma triglyceride levels, as well as elevated alkaline phosphatase and transaminase values.²⁵

Another agent that has been used to lower cholesterol is probucol. While this agent has been found to lower LDL cholesterol, it has also been found to lower HDL cholesterol at the same time.²⁶ Where the balance lies between one beneficial effect and one possible deleterious effect is unclear at present. The use of probucol may lie in synergism with other cholesterol agents, as probucol has been shown to have an antioxidant effect—the latter action may inhibit the deposition of LDL cholesterol in blood vessels independent of its cholesterol-lowering effects. This use, however, requires further study.

For those disorders involving either combined elevation of cholesterol and triglycerides or triglyceride elevation alone (types III, IV, and V), nicotinic acid is standard therapy. Nicotinic acid has been evaluated by the Coronary Drug Project,²⁷ which found that it decreases the incidence of coronary events. Nicotinic acid has a number of side effects, the most annoying of which is flushing. This can be decreased by taking the drug with meals or one adult aspirin. The dose required for a significant hypolipidemic effect is approximately 3 g/day. To avoid side effects, a starting dose of 100 mg twice a day, which is increased by 100 mg twice

a day every three to five days to 1 g/day and then increased by 500 mg increments, until the total dosage is reduced, is recommended. Mild elevation of uric acid may accompany this therapy, but it usually is asymptomatic. Glucose intolerance also may occur, which may require regulation of blood glucose levels in diabetics. In addition, there may be mild transaminitis, but this will not require discontinuation of the medication.

The third major drug currently available for the treatment of hyperlipidemia is gemfibrozil, which primarily is used for the treatment of type IV triglyceride disorders. The dosage is two 300-ml tablets twice a day. The drug is well tolerated and can be combined with nicotinic acid for recalcitrant cases. Although other hypolipidemic drugs (clofibrate, dextrothyroxine, and neomycin) are available, several trials have shown these drugs to have side effects that limit their routine usage.^{25,27}

Recently, gemfibrozil has been found to be beneficial in disorders involving cholesterol, whether or not the cholesterol elevation is accompanied by a derangement of triglycerides. In a randomized double-blind study involving 4081 men, gemfibrozil was found to significantly reduce the incidence of coronary events as compared to placebo, particularly those with both cholesterol and triglyceride elevations.²⁸ It appears to reduce the incidence of heart disease through a beneficial effect on HDL. Consequently, gemfibrozil should be considered in the armamentarium of agents for cholesterol disorders as well. It will be most useful in those patients who cannot comply with the binding resins or who find the side effects of nicotinic acid intolerable.²⁹

The last year has also seen the first of a new class of lipid-lowering agents derived from fungal metabolites. These agents work by interfering with 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), which is the liver's rate determining enzyme of cholesterol synthesis.²⁵ The only agent in this class presently available for use is lovastatin. This is indicated for those disorders involving the cholesterol elevation without concomitant triglyceride problems. This agent has the advantage of being in pill form and can exert its lipid-lowering effects even if taken once a day. While this agent may seem ideal for cholesterol disorders, there are some pertinent warnings. First, the drug does not have long-term survival data as does the binding resins. It is well known that two drugs that have the same effect may not have the same long-term benefit, as has been demonstrated in other blood pressure studies, for example. In taking lovastatin, one must be checked for cataracts, liver function abnormalities, and rhabdomyolysis on a regular basis, which can impose an additional ex-

pense on top of an already expensive agent. While this agent may prove to be a powerful tool in the prevention of coronary artery disease, its use must be tempered by the above.

Presently, much investigation is directed toward the beneficial effects of fish oil in lowering triglyceride and cholesterol levels. There is recent interest in the potential therapeutic effects of fish oil in type II and type V hyperlipidemia,³⁰ although the dose requirements have yet to be established. Overall, it is reasonable to ingest 3 g eicosapentaenoic acid (EPA) per day, either in supplement form or from fish itself (1/2 lb of salmon), although smaller quantities also may prove effective. Studies to determine the effectiveness of lower doses currently are in progress.³¹

Comment

The diagnosis and treatment of lipid disorders is at the stage where the hypertension field was a generation ago. The awareness of these disorders is increasing rapidly in the medical profession, but, at present, there are relatively few pharmacologic agents available for treatment. In addition to the elevation of lipid levels, other plasma lipid abnormalities, such as lipoprotein deficiency syndromes,³² may have serious clinical consequences.

Summary

The treatment of hyperlipidemia is undergoing rapid evolution. Recently, a more stringent guideline has been put forth. This mandates the physician to take a more aggressive approach to the treatment of lipid disorders with a basic understanding as outlined above. The physician now has the medications at his or her disposal to meet the challenge of these more stringent guidelines.

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