Effectiveness of Individualized Long-Term Therapy With Niacin and Probucol in Reduction of Serum Cholesterol

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A retrospective analysis was made of the results of the individualized office management of hypercholesterolemia in 37 patients (25 male, 12 female) with severe atherosclerosis (n = 35) or a predisposition to it (n = 2). The effects of diet instruction, diet and a niacin supplement, and diet plus the niacin supplement and probucol were assessed. Diet alone (n = 37) was prescribed for an average of 4.8 years; diet plus niacin (n = 37) for an average of 2.0 years; and diet plus niacin and probucol (n = 19) for an average of 2.9 years. Each patient served as his or her own control.

The maximum serum cholesterol at the beginning of the diet period was 8.69 ± 2.15 mmol/L (336 ± 83 mg/dL) (mean plus or minus standard deviation; n = 37). The goal cholesterol was <5.20 mmol/L (200 mg/dL). On diet alone the cholesterol level fell to 7.21 ± 1.27 mmol/L (279 ± 49 mg/dL) (P <.001); and goal cholesterol was reached by 12 of 37 patients (32.4 percent), but was maintained in none. On adding niacin, the mean cholesterol fell to 6.21 ± 1.16 mmol/L (240 ± 45 mg/dL) (P <.001). The goal cholesterol was reached in 22 of 37 patients (59.4 percent), but was maintained in only 7 of 37 (18.9 percent).

Nineteen of 37 patients on diet plus niacin also received probucol. Goal cholesterol was reached in 14 of 19 patients (73.6 percent), and was maintained in 11 of 19 (57.9 percent). The mean cholesterol fell to 5.20 ± 1.19 mmol/L (201 ± 46 mg/dL) (P <.02 when compared with the diet plus niacin period). In eight of 19 patients on this regimen, cholesterol levels fell to nadirs of 2.35 to 3.31 mmol/L (91 to 128 mg/dL), and it was necessary to reduce drug doses.

Visual evidence of regression of atherosclerosis was found in three patients who maintained goal-cholesterol levels for two to five years (two on diet plus niacin, and one on diet plus niacin and probucol).

T he purpose of lowering the high serum cholesterol levels in patients with atherosclerosis is to stop or retard the progression of atherosclerosis and, at best, to induce its regression. Because most clinical atherogenesis occurs at levels greater than 5.20 mmol/L (200 mg/dL), lowering cholesterol levels to less than 5.20 mmol/L seems prudent.

The purpose of the present study was to determine whether patients could be maintained on hypolipidemic

therapy for many years, and if this were possible, would it result in stopping the progression of atherosclerosis.

Although atherogenesis probably will not be arrested by hyperlipidemia control alone, experimental, clinical, and epidemiologic data emphasize that its clinical consequences can be ameliorated by this approach.[1]

Lowering the serum cholesterol by dietary intervention alone has proved difficult.[2] Improved methods and skills are required. According to a National Institutes of Health consensus conference, many physicians have not mastered these skills. The National Heart, Lung, and Blood Institute is now fostering educational programs to increase these skills.[3,4] In this regard individualizing the therapeutic approach to the needs of the patient is important.

The results of a method found useful in lowering the

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serum cholesterol in patients with clinical atherosclerotic disease are reported here. This method involves diet change, niacin and probucol, and tailoring the drug dosage to the requirements of each patient. In three patients, regression of atherosclerosis was demonstrated. As regression rarely occurs spontaneously,[5] this finding may be testimony to the usefulness of this approach.

METHODS

Patients

This study was not of a randomized, double-blind design, but was a retrospective analysis of 37 case studies of patients with hypercholesterolemia and other atherosclerotic disease that family physicians, internists, and cardiologists are likely to encounter. Each patient served as his or her own control. Each was given individualized treatment as would be done in any medical office. The people involved primarily in direct interactions with patients were the physician and an office assistant.

All patients were followed in the Ambulatory Cardiology facility of the University of Chicago Medical Center. With two exceptions, all had evidence of severe atherosclerotic disease. Clinical characteristics of the 37 patients are displayed in Table 1.

Niacin treatment was instituted in patients for whom dietary manipulations had not been successful in lowering their serum cholesterol. In those patients for whom diet plus niacin did not lower the serum cholesterol to goal levels, probucol was added. The maximum cholesterol levels ranged from 6.05 to 16.16 mmol/L (234 to 625 mg/dL).

Patients suffering from significant hepatic disorders or diabetes mellitus (with rare exceptions) were not treated with niacin, and therefore were excluded from the study.

Goals

The underlying goals were to reduce the serum cholesterol to a level of <5.20 mmol/L (200 mg/dL), to keep it there, and, it was hoped, to induce regression in the extent of atherosclerosis. The treatment regimen was individualized to accomplish these goals.

Treatment

Diet

Initially each patient was encouraged to follow in progressive order phase I to III of the American Heart Association diet. Dietary cholesterol was originally to be restricted to less than 250 mg/d, and when necessary, to 100 mg/d; fat was restricted to less than 30 percent of

TABLE 1. PATIENT CHARACTERISTICS AND NUMBER OF PATIENTS IN THE STUDY	
Characteristic	**No. of Patients**
Sex	
Male	25
Female	12
Age at start of study	
<40	2
40–49	5
50–59	16
60–69	10
>70	4
Cardiovascular diagnosis*	
Angina pectoris	9
Myocardial infarction	17
Status-post-coronary artery bypass graft surgery	15
Xanthoma tendinosum	3
Cerebral vascular accident	4
Aortic aneurysm	1
Intermittent claudication	4
Hypertension	12
Arrhythmia	4
Healthy but with familial heterozygous hypercholesterolemia	2
Type of hyperlipidemia	
Hypercholesterolemia	20
Hypertriglyceridemia	1
Mixed hyperlipidemia	16
* Several patients had multiple diagnoses	

total calories with a polyunsaturated-saturated-monounsaturated ratio of 1:1:1. Calories, sugar, and alcohol were restricted when appropriate. The assistance of a nutritionist was encouraged. In most cases, because of time and cost considerations, the seven rules of nutrition counseling pertinent to cholesterol lowering were left to the physician to administer. These rules are summarized in Table 2. A maximum of 10 percent decline in the mean cholesterol was anticipated by changing the diet.

Niacin

The diet changes rarely brought the serum cholesterol level to goal. Niacin was therefore prescribed. To reduce flushing (a common side effect), the following steps were taken: the niacin dose was increased slowly, a controlled-release preparation was prescribed at higher doses, niacin was to be taken with meals, and one aspirin daily was prescribed. The niacin dose was begun at 100 mg/d and slowly increased (100 mg/d/wk) over a six-month period to tolerance, or a maximum of 3,500 mg/d. Liver-function studies and glucose levels were checked approximately quarterly. If a chemical liver dysfunction or glucose intolerance occurred, the niacin dose was reduced to reverse

TABLE 2. SEVEN DIETARY RULES GIVEN TO PATIENTS WITH CLINICAL ATHEROSCLEROSIS

1. Remember that cholesterol is found only in animal foods
2. Reduce cholesterol intake to one meal daily
3. Learn the cholesterol content of meat, fish, and poultry, and consume on average 100 mg or less daily
4. Use about equal amounts of polyunsaturated oil, monounsaturated oil, and vegetable saturated fat in cooking. Avoid coconut oil
5. Myristic acid is a saturated fatty acid that raises cholesterol; it is found in milk fat, animal fat, and coconut oil
6. Reduce weight to optimal levels
7. Walk 2 miles a day for exercise. This is the caloric equivalent of about 17 pounds per year that will not be gained

TABLE 3. SUMMARY OF MEAN SERUM CHOLESTEROL LEVELS IN EACH PERIOD

Period	Serum Cholesterol in mmol/L (mean ± standard deviation)	
	Cholesterol	Percent Reduction
All patients (n = 37)		
Maximum level in initial diet period	8.69 ± 2.15	⎤ ---- 17.0*
Mean value in diet period	7.21 ± 1.27	⎦
Mean value in diet + niacin period	6.21 ± 1.16	⎤ --- 14.0*
Patients who received diet + niacin + probucol (n = 19)		
Maximum level in initial diet period	9.05 ± 2.17	⎤ ---- 15.4**
Mean value in diet period	7.65 ± 1.50	⎦
Mean value in diet + niacin period	6.59 ± 1.27	⎤ --- 13.9**
Mean value in diet + niacin + probucol period	5.20 ± 1.19	⎤ -- 21.2***

* $P < .001$
** $P < .05$
*** $P < .02$

these findings. Based on prior reports[6,7] it was anticipated that the average cholesterol reduction would be about 15 to 20 percent.

Probucol

In 19 patients probucol was added (500 to 1,000 mg/d). Based on previous reports[8,9] an additional reduction of about 15 to 25 percent was expected.

Other medications were prescribed and revised as dictated by clinical need and are not listed here.

COMPLIANCE

No attempt was made to determine compliance by standard pill-counting procedures. The patients obtained their medications from their local pharmacy. Niacin is available as an over-the-counter drug and was permitted. Possible lapses in compliance were monitored by observing the changes in cholesterol levels. If a marked increase in serum cholesterol was observed, the patient was contacted directly, and an attempt was made to determine whether the drugs were being taken as prescribed. The most common cause of marked increases was dietary lapse. Other causes included greater alcohol intake, not refilling prescriptions, the pharmacist arbitrarily substituting niacinamide for niacin, or an intervening illness. A lack of compliance often was signaled by the failure of the patient to have his or her cholesterol level checked. Compliance was more of a problem with the higher doses of niacin. On the combination of niacin and probucol, the side effects seemed to be less pronounced, and most patients adhered to the combined drug regimen.

ASSESSMENTS

Patients were asked to have their serum cholesterol levels measured monthly to quarterly. The triglycerides and high-density lipoprotein cholesterol levels were measured initially to establish the nature of the hyperlipidemia, and thereafter as deemed necessary to ensure that the trends in these values were appropriate. Liver function and glucose levels were assessed quarterly to monitor drug side effects.

To encourage adherence, those patients who lived at a distance from the clinic had their testing performed at a laboratory near their home. Of the 37 patients, nine (four on niacin alone; five on niacin plus probucol) had their cholesterol levels checked at an outside laboratory. Where such data are available, values from the outside laboratory were comparable to those obtained when the patient came to clinic. In most cases, to reduce costs, cholesterol alone was measured. Patients were encouraged to call about problems, and were told the results of all tests.

DATA ANALYSIS

The mean serum cholesterol concentrations were determined for each subject during three periods: diet alone, diet plus niacin, and diet plus cholesterol and probucol (Table 3). All values are reported as mean plus or minus standard deviation. Means were compared using the Student's *t* test. Group means were considered to be statistically different when $P < .05$. For all patients (n = 37), the maximum cholesterol value in the diet period was compared with the mean value on diet alone. All patients received niacin, and the mean for this period was compared with that of the diet-only period. Similar compar-
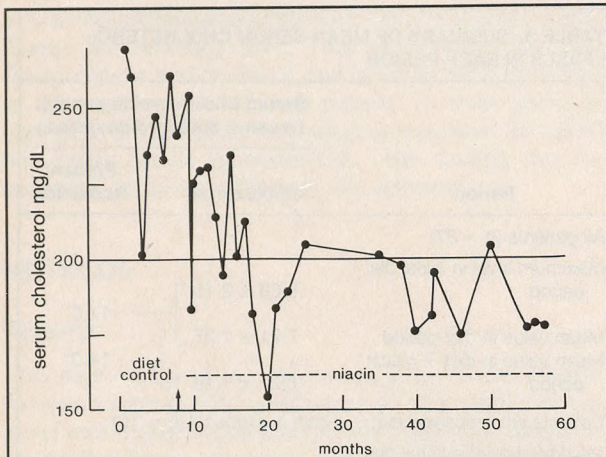
Figure 1. Lowering of serum cholesterol to goal with diet and niacin. This woman, who was to undergo a knee replacement, underwent repeat coronary arteriography after 50 months of dietary and niacin therapy. Regression of her coronary lesions occurred, which were visible to the unaided eye
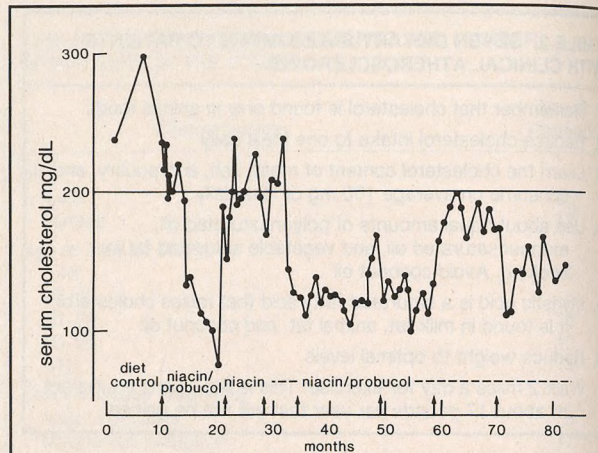

Figure 2. When first encountered, this man had angina at rest secondary to extensive coronary artery disease. He proved responsive to the medication in combination. After several years, repeat coronary arteriography showed no progression in his very advanced disease

isons were made for the 19 patients who received probucol in addition to niacin.

RESULTS

On diet alone the mean serum cholesterol fell 17.0 percent from the mean of the maximum values obtained at the beginning of the diet period (Table 3). The goal of <5.20 mmol/L (200 mg/dL) was achieved in 12 of 37 patients (32.4 percent), but none maintained this level. When niacin was added, the mean cholesterol fell an additional 14.0 percent from the mean of the diet period. The number reaching goal almost doubled (22 of 37; 59.5 percent), but only 7 of 37 (18.9 percent) maintained the goal. In Figure 1 the cholesterol changes in a patient who received only niacin are charted. In the 19 patients receiving diet, niacin, and probucol, the mean cholesterol fell an additional 21.2 percent; 73.6 percent reached goal, and the percentage maintaining goal over an almost three-year period was 57.9 percent. The potency of this combination became further evident when in 8 of 19 patients the cholesterol levels fell to 2.35 to 3.31 mmol/L (91 to 128 mg/dL). In these patients, the niacin and probucol dosages were reduced. Examples of this combined treatment are displayed in Figures 2 and 3. Two patients showed visible regression of coronary artery atherosclerosis. In one patient, an enlarging abdominal aortic aneurysm was re-

sected and found to be remarkably sparse in cholesterol content.

DISCUSSION

In 1979 Canosa et al[10] presented preliminary results showing a 19 percent reduction in serum cholesterol when niacin and probucol were given in combination and administered over a four-month period. The present work shows that this combination can lower the serum cholesterol about 32 percent below that achieved by diet alone and keep it low for years. Preliminary presentations of the present studies were made elsewhere.[11,12] No other reports of human or animal studies using this combination could be found.

Although a dietary approach is probably the safest and should be the first line of treatment,[4] it usually achieves a lasting effect in only a few patients. In the Multiple Risk Factor Intervention Trial,[2] despite individualized treatment by a devoted team of exhorters, the diet change altered the average cholesterol in the special intervention group by 0.47 mmol/L (18.0 mg/dL), a reduction of only 7.1 percent. Patients with atherosclerosis should nevertheless be encouraged to adhere to a diet low in cholesterol (100 mg/d) that provides a saturated fat content of no more than 10 percent of the total calories so as to keep the medication required to a minimum. In the patients
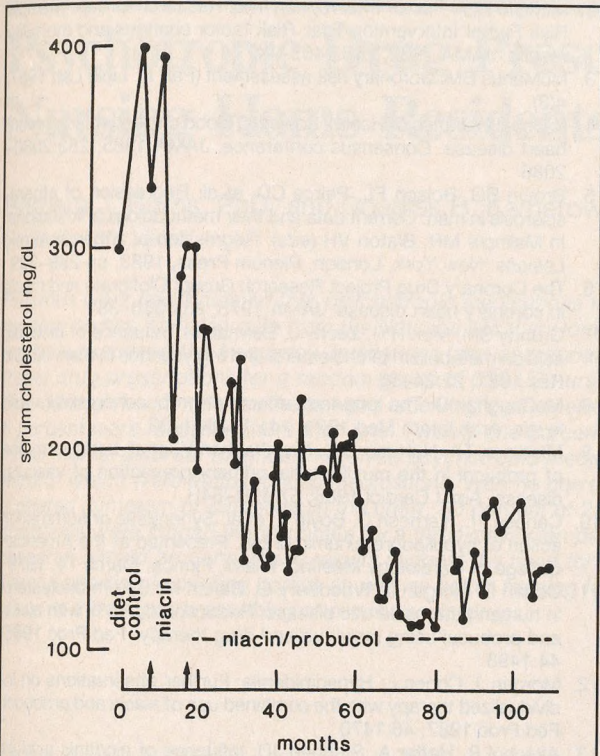
Figure 3. This man had complete obstruction of the right coronary artery and the left anterior descending artery. He was surviving on his circumflex artery. Repeat coronary arteriography, on two occasions done during the subsequent nine years, showed no progression of lesions in any of his arteries. Note that he also achieved a cholesterol level near 2.59 mmol/L (100 mg/dL), and the drug doses were reduced

with hypercholesterolemia or the mixed hyperlipidemia described here, it was possible to achieve a cholesterol level of <5.20 mmol/L (200 mg/dL) with diet alone in

12 of 37 patients (32.4 percent), but it could be maintained in none. Thus, diet change is necessary but insufficient to maintain a cholesterol level of <5.20 mmol/L.

Niacin was selected as the drug of choice for reasons shown in Table 4. The niacin effects on serum triglycerides, cholesterol, and lipoprotein concentrations are almost ideal. It has also been used as a hypolipidemic agent for more than 30 years.[6,13,14] Niacin is the least costly of available hypolipidemic drugs. On the other hand, flushing, biochemical liver dysfunction, and glucose intolerance often limit the dose that can be administered.

In the present study, adding niacin allowed 22 of 37 patients (59.4 percent) to achieve a cholesterol level of <5.20 mmol/L, but it could be maintained in only 7 of 37 patients (18.9 percent).

Probucol was selected as the second drug of choice because it is effective, well tolerated, and works by mechanisms different from those of niacin.[15] It has little effect on triglyceride levels, but it lowers the total and low-density lipoprotein cholesterol. It also reduces the high-density lipoprotein cholesterol. Although recent data raise questions about the need for concern regarding the lowering of the serum high-density lipoprotein cholesterol, this issue must be considered unsettled.[16]

When probucol was added to the diet and niacin regimen, the serum cholesterol was lowered to 5.20 mmol/L (200 mg/dL) or less in 14 of 19 patients (73.6 percent), and to less than 3.31 mmol/L (128 mg/dL) in 8 of 19 patients. It was possible to maintain goal levels in 11 of 19 patients (57.9 percent).

Currently it is doubtful whether any drug regimen will work without adherence to a diet that reduces the intake of cholesterol and saturated fat. Here are some additional noteworthy observations:

1. It is worth emphasizing that the diet, niacin, and probucol combination used here lowered the cholesterol in patients with hypercholesterolemia, mixed hyperlipidemia, and primary hypertriglyceridemia.

TABLE 4. ADVANTAGES AND DISADVANTAGES OF DIET AND MEDICATIONS

	Diet	Niacin	Probucol
Advantages	Safest approach	Lowers triglycerides, total cholesterol, and very low density, and low-density lipoprotein cholesterol. Raises high-density lipoprotein cholesterol	Lowers total cholesterol and low-density lipoprotein cholesterol
Disadvantages	Limited effectiveness because of noncompliance	Flushing* Liver dysfunction** Glucose intolerance***	Lowers high-density lipoprotein cholesterol Occasional diarrhea†

* Occurred in all patients at some time during treatment
** Occurred in 8 patients
*** Occurred in 4 patients
† This was not a problem in the 19 patients in this study

2. Niacin and probucol appear to have prevented a rise in serum cholesterol in one patient during the development of hypothyroidism and in another during a 20-pound weight gain.

3. Perhaps pertinent to the reduced mortality reported with previous niacin administration,[14] in the current series of patients with severe atherosclerosis, one patient died suddenly.

4. Since one patient developed an enlarging aneurysm of the abdominal aorta, which required surgical correction, it is important to consider what implications reducing serum lipids might have on the development and progression of such aneurysms.

In these patients arteriographic studies were performed only when required. One patient, a physician, requested repeat angiography to see the results of his efforts. One other had a repeat study prior to the placement of a knee prosthesis. Both showed visible regression in coronary artery narrowing. Two others showed no progression. As mentioned, one patient developed an abdominal aortic aneurysm. The surgical specimen was unusual because it showed a paucity of cholesterol. Although repeat coronary arteriography was not done on all patients, it seems noteworthy that three of 37 patients in this study showed visual evidence of lesion regression, an otherwise rare event.[5]

Acknowledgments

References

1. Blankenhorn DH, Nessim SA, Johnson RL, et al: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257:3233–3240

2. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. JAMA 1982; 248:1465–1477

3. McManus BM: Coronary risk assessment (Part II). Lipid Lett 1987; 4(3).

4. National Institutes of Health: Lowering blood cholesterol to prevent heart disease. Consensus conference. JAMA 1985; 253:2080–2086

5. Brown BG, Bolson EL, Peirce CD, et al: Regression of atherosclerosis in man: Current data and their methodological limitations. In Malinow MR, Blaton VH (eds): Regression of Atherosclerotic Lesions. New York, London, Plenum Press, 1983, pp 289–309

6. The Coronary Drug Project Research Group: Clofibrate and niacin in coronary heart disease. JAMA 1975; 231:360–381

7. Grundy SM, Mok HYI, Zechs L, Berman M: Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. J Lipid Res 1981; 22:24–36

8. McCaughan D: The long-term effects of probucol on serum lipid levels. Arch Intern Med 1981; 141:1428–1432

9. Miettinen TA, Huttunen JK, Naukkarinen V, et al: Long-term use of probucol in the multifactorial primary prevention of vascular disease. Am J Cardiol 1986; 57:49H–54H

10. Canosa FL, Yarnosh D, Boyle E, et al: Synergistic or summation action of hypolipoproteinemic drugs. Presented at the American College of Cardiology Meeting, Miami, Florida, March 14, 1979

11. Cohen L, Morgan J, Woodbury G, Barish M: Serum cholesterol in human atherosclerotic disease: Reduction by 50% with niacin and probucol using individualized drug therapy. Fed Proc 1985; 44:1498

12. Morgan J, Cohen L: Hyperlipidemia: Further observations on individualized therapy with the combined use of niacin and probucol. Fed Proc 1987; 46:1470

13. Altschul R, Hoffer A, Stephen JD: Influence of nicotinic acid on serum cholesterol in man. Arch Biochem Biophys 1955; 54:558–559

14. Canner PL, Berge KG, Wenger NK, et al: Fifteen-year mortality in coronary drug project patients: Long term benefit with niacin. J Am Coll Cardiol 1986; 8:1245–1255

15. Kesaniemi YA, Grundy SM: Influence of probucol on cholesterol and lipoprotein metabolism in man. J Lipid Res 1984; 25:780–790

16. Yamamoto A, Matsuzawa Y, Yokoyama S, et al: Effects of probucol on xanthomata regression in familial hypercholesterolemia. Am J Cardiol 1986; 57:29H–35H