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REDUCTION OF SERUM CHOLESTEROL IN HETEROZYGOUS PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

Additive Effects of Compactin and Cholestyramine

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Abstract We studied the effects of the bile acid sequestrant cholestyramine, alone and in combination with the experimental agent compactin (ML-236B), a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, on serum levels of lipoproteins in 10 heterozygous patients with familial hypercholesterolemia. After cholestyramine treatment alone for 2 to 16 months, serum total and low-density lipoprotein cholesterol decreased by 20 and 28 per cent, respectively. With the addition of compactin for 12 weeks there was a 39 per cent total decrease in serum cholesterol from the control value — from 356 ± 14

to 217 ± 10 mg per deciliter (9.27 ± 0.36 to 5.64 ± 0.26 mmol per liter [mean \pm S.E.M.]; $P < 0.001$) — and a 53 per cent decrease in low-density lipoprotein cholesterol — from 263 ± 13 to 125 ± 10 mg per deciliter (6.84 ± 0.34 to 3.25 ± 0.26 mmol per liter; $P < 0.001$). High-density lipoprotein cholesterol, which had increased during cholestyramine treatment, remained at its higher level. No adverse effects were observed. If long-term safety can be demonstrated, the compactin-cholestyramine regimen may prove useful in heterozygous familial hypercholesterolemia. (N Engl J Med. 1983; 308:609-13.)

FAMILIAL hypercholesterolemia is an autosomal dominant disorder characterized by elevated levels of low-density lipoprotein (LDL) cholesterol, tendon xanthomas, and premature coronary atherosclerosis.¹ The disorder results from a complete or partial defect of the LDL receptor that normally controls the degradation of LDL.^{2,3} Heterozygous patients with familial hypercholesterolemia have only half the normal number of receptors; they degrade a normal amount of LDL through their receptors by doubling their plasma LDL levels.^{2,3} Thus, the LDL cholesterol levels in these patients are 2.5 times the normal level.⁴

The goal of therapy in familial hypercholesterolemia is to reduce the concentration of LDL in plasma without disrupting cholesterol delivery to cells.⁵ The ideal cholesterol-lowering agent would be one that enhanced production of LDL receptors. Two classes of drugs are known to increase LDL receptors in vivo. One class consists of the bile acid-binding resins, cholestyramine⁶ and colestipol,⁷ which have been used for two decades in the treatment of familial hypercholesterolemia. These drugs increase fecal excretion of bile acids, which increase conversion of cholesterol to bile acids in the liver. To obtain additional cholesterol, the liver augments the synthesis of cholesterol by increasing the activity of a rate-limiting enzyme, 3-hydroxy-3-

methylglutaryl coenzyme A (HMG-CoA) reductase, and produces larger numbers of LDL receptors. This raises the fractional catabolic rate for LDL and causes plasma LDL levels to fall.⁸

The other class of recently discovered drugs consists of compactin (ML-236B)⁹ and mevinoлин (monacolin K),^{10,11} which are competitive inhibitors of HMG-CoA reductase. These new drugs lower plasma LDL by decreasing the rate of LDL production and stimulating the production of LDL receptors in the liver, thereby increasing the fractional catabolic rate for LDL. Both drugs are effective in lowering serum cholesterol in human beings.¹²⁻¹⁵

When these two classes of LDL-receptor-promoting drugs were given together to dogs, hepatic LDL receptors increased threefold and plasma LDL levels decreased by 75 per cent.⁷

We studied the effects of the combination of a bile acid-binding resin and compactin in the treatment of heterozygous patients with familial hypercholesterolemia.

METHODS

Ten heterozygous patients with familial hypercholesterolemia were chosen for this study. All were Japanese. Patients 3 and 8 were brother and sister. The diagnosis of familial hypercholesterolemia had been based on the following two criteria: the presence of primary hypercholesterolemia with tendon xanthomas, and the presence of primary hypercholesterolemia with or without tendon xanthomas in a first-degree relative of a patient with familial hypercholesterolemia. Tendon xanthomas were diagnosed by radiographic measure-

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Table 1. Clinical Data in 10 Heterozygous Patients with Familial Hypercholesterolemia.

PATIENT NO.	AGE (YR) SEX	HEIGHT <i>cm</i>	WEIGHT <i>kg</i>	CHOLESTEROL * <i>mg/dl</i>	TRIGLYCERIDE * <i>mg/dl</i>	PHOSPHOLIPID * <i>mg/dl</i>	ACHILLES TENDON THICKNESS † <i>mm</i>
1	54/M	162	63	382	96	245	16.5
2	57/M	174	60	315	106	277	11.0
3	43/M	167	64	420	102	280	26.0
4	60/M	157	54	366	114	309	9.0
5	61/M	171	74	352	86	254	16.5
6	36/M	164	55	327	127	286	9.0
7	44/M	165	65	469	231	357	19.0
8	48/F	152	71	370	44	252	11.5
9	53/F	149	51	377	208	312	19.0
10	54/F	155	59	398	130	285	12.0
<i>Mean ± S.E.M.</i>	<i>51 ± 3</i>	<i>162 ± 3</i>	<i>62 ± 2</i>	<i>378 ± 14</i>	<i>124 ± 18</i>	<i>286 ± 11</i>	<i>15.0 ± 1.7</i>

*To convert cholesterol, triglyceride, and phospholipid values to millimoles per liter, multiply by 0.026, 0.01129, and 0.324, respectively.

†Normal value in Japanese subjects, 6.3 ± 0.2 mm (mean ± S.E.M.).

ment of the thickness of the tendon.¹⁶ None of the patients had clinical or laboratory evidence of cardiovascular, renal, hepatic, or endocrine disorders. The clinical and laboratory data are summarized in Table 1.

All patients were given instructions for a diet low in cholesterol (less than 200 mg per day) and in saturated fat (15 per cent protein, 70 per cent carbohydrate, and 15 per cent fat). After four to eight weeks of stabilization on an optimal dietary regimen, drug therapy with cholestyramine was started (4 g three times daily). After 2 to 16 months of cholestyramine therapy and after the patients had given consent, additional therapy with compactin was started. By this time good adherence to the cholestyramine regimen had been confirmed. Patients were given 30 mg of compactin three times daily with meals for 12 weeks, after which compactin was withdrawn.

Blood samples, obtained in the morning after a 12-hour overnight fast, were allowed to clot at room temperature. Lipoprotein fractions were separated by serial ultracentrifugation at different densities, essentially by the method of Havel et al.,¹⁷ into very-low-density lipoprotein (VLDL; density < 1.006), intermediate-density lipoprotein (IDL; 1.006 to 1.019), LDL (1.019 to 1.063), and high-density

lipoprotein (HDL; > 1.063). Cholesterol¹⁸ and phospholipid¹⁹ concentrations were determined with enzymatic methods, and the triglyceride concentration with Fletcher's method,²⁰ in whole serum and in lipoprotein fractions. Lipid recovery in each lipoprotein fraction was 93 to 100 per cent. The day-to-day coefficient of variation of lipid measurement was less than 2.5 per cent for reference samples.

Statistical calculations were performed with Student's paired t-test. Throughout the study, surveillance for drug toxicity included the following analyses, performed at each visit: complete blood count; urinalysis; and measurement of blood glucose, urea nitrogen, uric acid, total protein, serum alkaline phosphatase, serum aspartate aminotransferase, serum alanine aminotransferase, and serum creatine kinase. Compliance with diet and medication was assessed by oral questioning.

RESULTS

Table 2 shows the concentrations of serum cholesterol, triglyceride, and phospholipid in 10 patients

Table 2. Serum and Lipoprotein Levels of Cholesterol, Triglyceride, and Phospholipid during the Sequence of Treatments.*

	DIET ALONE		DIET PLUS CHOLESTYRAMINE		DIET PLUS CHOLESTYRAMINE PLUS COMPACTIN				DIET PLUS CHOLESTYRAMINE
	Week 4 †	Final ‡	Week 4 †	Final ‡	Week 2	Week 4	Week 8	Week 12	Week 4
Cholesterol									
Serum	343 ± 9	356 ± 14	280 ± 8	285 ± 9	218 ± 10	220 ± 8	219 ± 6	217 ± 10	283 ± 7
VLDL		23 ± 6		17 ± 2		14 ± 2		15 ± 2	21 ± 4
IDL		17 ± 3		11 ± 1		10 ± 2		9 ± 2	15 ± 3
LDL		263 ± 13		190 ± 9		128 ± 8		125 ± 10	174 ± 7
HDL		36 ± 3		50 ± 2		49 ± 3		52 ± 2	52 ± 3
Triglyceride									
Serum	129 ± 20	150 ± 30	107 ± 14	93 ± 8	109 ± 16	78 ± 6	96 ± 8	99 ± 7	130 ± 9
VLDL		75 ± 23		45 ± 7		36 ± 5		50 ± 7	57 ± 5
IDL		13 ± 2		9 ± 1		9 ± 1		9 ± 1	13 ± 2
LDL		39 ± 4		23 ± 1		18 ± 1		20 ± 1	30 ± 4
HDL		14 ± 1		13 ± 1		11 ± 1		14 ± 1	16 ± 1
Phospholipid									
Serum	286 ± 9	269 ± 7	246 ± 6	258 ± 5	225 ± 8	226 ± 9	232 ± 6	222 ± 7	264 ± 5
VLDL		20 ± 5		20 ± 2		15 ± 2		15 ± 2	17 ± 2
IDL		10 ± 2		11 ± 1		10 ± 2		8 ± 1	12 ± 2
LDL		153 ± 7		122 ± 5		85 ± 6		81 ± 6	114 ± 6
HDL		69 ± 6		95 ± 3		102 ± 4		98 ± 3	102 ± 5

*All values are milligrams per deciliter and are given as means ± S.E.M. To convert cholesterol, triglyceride, and phospholipid values to millimoles per liter, multiply by 0.026, 0.01129, and 0.324, respectively.

†Values obtained before the "final" values.

‡The final values obtained during that treatment sequence.

with familial hypercholesterolemia, during sequential therapy with a diet low in cholesterol and saturated fat; the diet plus cholestyramine; and combined therapy with diet, cholestyramine, and compactin. The individual serum cholesterol responses are shown in Figure 1. Mean serum cholesterol levels fell by 20 per cent, from 356 ± 14 mg per deciliter (9.27 ± 0.36 mmol per liter [mean \pm S.E.M.]) to 285 ± 9 mg per deciliter (7.41 ± 0.23 mmol per liter) during cholestyramine treatment ($P < 0.001$). The addition of compactin to therapy produced a further reduction in serum cholesterol levels. Serum cholesterol fell by 24 per cent from the level observed during dietary and cholestyramine treatment (285 ± 9 mg per deciliter), to 217 ± 10 mg per deciliter (5.64 ± 0.26 mmol per liter) ($P < 0.001$), and by 39 per cent from the level observed during the diet alone (356 ± 14 mg per deciliter) ($P < 0.001$). These effects of compactin were maintained, without subsequent increases, throughout the treatment period (Fig. 1). Four weeks after the withdrawal of compactin, serum cholesterol returned to the levels previously present during cholestyramine and dietary treatment.

Mean serum triglyceride levels decreased slightly, from 150 ± 30 mg per deciliter (1.69 ± 0.34 mmol per liter) during dietary treatment alone, to 99 ± 7 mg per deciliter (1.12 ± 0.08 mmol per liter) during dietary, cholestyramine, and compactin therapy.

The mean serum phospholipid levels fell slightly — from 269 ± 7 mg per deciliter (87.2 ± 2 mmol per liter) during diet alone to 258 ± 5 mg per deciliter (83.6 ± 2 mmol per liter) during cholestyramine therapy. Compactin combined with diet and cholestyramine reduced the phospholipid level by 18 per cent from the level observed during diet alone (269 ± 7 mg per deciliter) to 222 ± 7 mg per deciliter (71.9 ± 2 mmol per

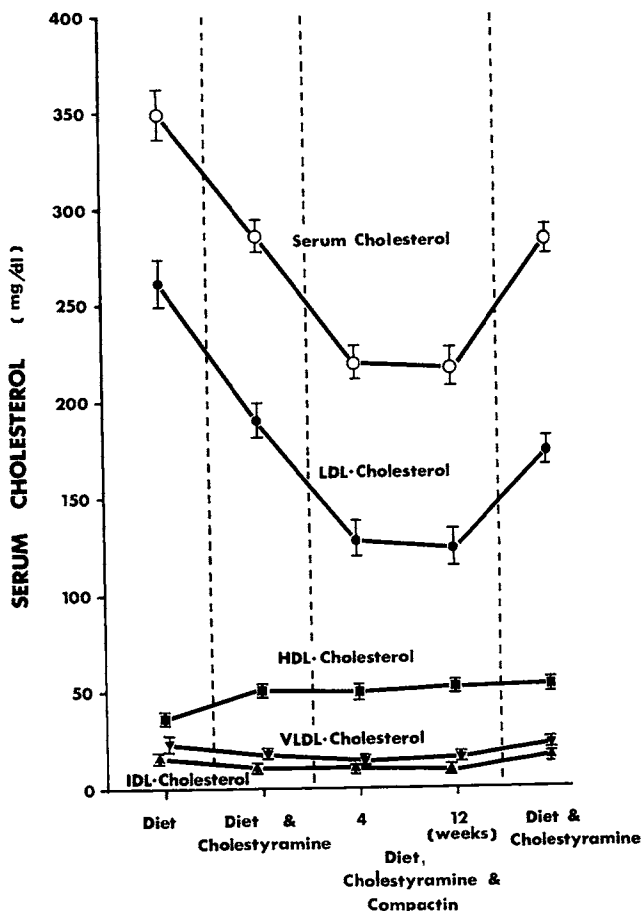


Figure 2. Effects of the Three Regimens on Serum Low-Density-Lipoprotein (LDL), High-Density Lipoprotein (HDL), Very-Low-Density Lipoprotein (VLDL), and Intermediate-Density Lipoprotein (IDL) Cholesterol Levels.

Data are means \pm S.E.M. To convert cholesterol values to millimoles per liter, multiply by 0.026.

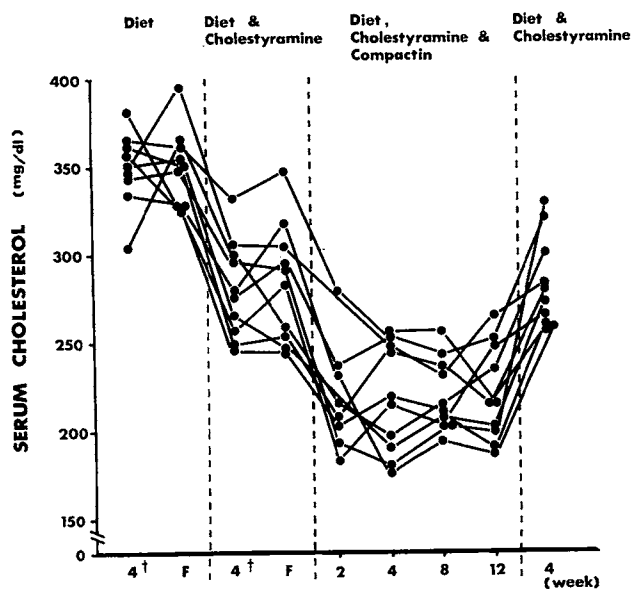


Figure 1. Cholesterol Levels during the Treatment Sequence. To convert cholesterol values to millimoles per liter, multiply by 0.026. "F" denotes the final determination made in that treatment period. † denotes values obtained before "F" values.

liter) ($P < 0.001$), and by 14 per cent from the level observed during cholestyramine treatment (258 ± 5 mg per deciliter) ($P < 0.001$). After the withdrawal of compactin the phospholipid levels returned to the previous values associated with diet and cholestyramine.

Table 2 and Figure 2 show the levels of lipids in lipoprotein fractions during sequential treatment. When compared with diet alone, cholestyramine reduced LDL cholesterol concentrations by 28 per cent, from 263 ± 13 mg per deciliter (6.84 ± 0.34 mmol per liter) to 190 ± 9 mg per deciliter (4.94 ± 0.23 mmol per liter) ($P < 0.001$). When compactin was used in combination with cholestyramine, LDL cholesterol levels fell by a further 34 per cent at the 12th week, from 190 ± 9 mg per deciliter to 125 ± 10 mg per deciliter (3.25 ± 0.26 mmol per liter) ($P < 0.001$). The total reduction from the values during diet alone was 53 per cent ($P < 0.001$). After the withdrawal of compactin, LDL cholesterol increased to the previous levels for diet and cholestyramine. HDL cholesterol increased significantly, to 50 ± 2 mg per deciliter (1.3 ± 0.1 mmol per liter) with cholestyramine treatment, as compared

with 36 ± 3 mg per deciliter (0.9 ± 0.1 mmol per liter) with diet alone ($P < 0.001$). This increased level of HDL cholesterol persisted after compactin treatment was added to the therapy. IDL cholesterol decreased from 17 ± 3 mg per deciliter (0.4 ± 0.1 mmol per liter) with diet alone to 9 ± 2 mg per deciliter (0.2 ± 0.1 mmol per liter) with diet, cholestyramine, and compactin ($P < 0.01$). VLDL cholesterol concentrations showed no significant changes.

LDL triglyceride fell significantly, from 39 ± 4 mg per deciliter (0.4 ± 0.1 mmol per liter) with diet alone to 23 ± 1 mg per deciliter (0.3 ± 0.01 mmol per liter) with diet and cholestyramine ($P < 0.01$) and to 20 ± 1 mg per deciliter (0.2 ± 0.01 mmol per liter) with diet, cholestyramine, and compactin ($P < 0.01$). VLDL, IDL, and HDL triglyceride concentration did not change significantly.

LDL phospholipid decreased significantly by 20 per cent, from 153 ± 7 per deciliter (49.6 ± 2.3 mmol per liter) with diet alone to 122 ± 5 mg per deciliter (39.5 ± 1.6 mmol per liter) with diet and cholestyramine ($P < 0.001$). When compactin was used in combination with cholestyramine, LDL phospholipid levels fell by a further 34 per cent, from 122 ± 5 to 81 ± 6 mg per deciliter (from 39.5 ± 1.6 to 26.2 ± 1.9 mmol per liter) ($P < 0.001$). The total decrease from values during diet alone was 47 per cent ($P < 0.001$). Concentrations of HDL phospholipid increased from 69 ± 6 mg per deciliter (22.4 ± 1.9 mmol per liter) to 95 ± 3 mg per deciliter (30.8 ± 1.0 mmol per liter) as a result of cholestyramine treatment ($P < 0.01$). The increased levels of HDL phospholipid were maintained throughout therapy with cholestyramine plus compactin. IDL phospholipid decreased slightly but significantly, from 11 ± 1 mg per deciliter (3.6 ± 0.3 mmol per liter) with diet and cholestyramine to 8 ± 1 mg per deciliter (2.6 ± 0.3 mmol per liter) with diet, cholestyramine, and compactin ($P < 0.05$). VLDL phospholipid concentrations showed no significant changes.

No side effects, such as gastrointestinal, hematologic, neurologic, or other abnormalities, were observed. Laboratory data showed no significant changes during therapy with cholestyramine and compactin.

DISCUSSION

In the Japanese population,²¹ as well as the European and American populations,¹ heterozygous familial hypercholesterolemia occurs at a frequency of about 1 in 500. It is closely associated with premature arteriosclerotic heart disease. The increased levels of LDL in familial hypercholesterolemia appear to accelerate atherogenesis.

For the treatment of heterozygous familial hypercholesterolemia, cholestyramine, colestipol, nicotinic acid, clofibrate, and probucol are effective in lowering serum cholesterol levels.²² According to the findings of Goldstein and Brown, familial hypercholesterolemia is a disorder resulting from decreased LDL catabolism by the receptor route and from loss of feedback regulation of cholesterol synthesis.² Thus, treatment

should increase LDL catabolism by stimulating the LDL pathway and should suppress cholesterol synthesis by inhibiting HMG-CoA reductase.⁵ Cholestyramine promotes LDL catabolism through its specific physiologic clearance pathway.⁶ As a result, the fractional catabolic rate of LDL is increased during treatment with cholestyramine in heterozygous patients with familial hypercholesterolemia.

Recently, a new class of cholesterol-synthesis inhibitors was found to lower the plasma level of LDL cholesterol in human beings and animals. Compactin, discovered by Endo et al., is a fungal metabolite isolated from *Penicillium citrinum* and a potent reversible inhibitor of HMG-CoA reductase.⁹

A structural analogue of compactin, mevinolin,^{10,11} is even more potent than compactin in inhibiting HMG-CoA reductase and has been found to be effective in lowering serum cholesterol.^{14,15} According to studies of [¹²⁵I]LDL turnover in young dogs, mevinolin lowers plasma LDL levels by a dual mechanism: suppression of LDL synthesis and stimulation of the receptor-mediated catabolism of LDL in the liver.⁷ In cultured porcine hepatocytes, an increase in receptor-mediated degradation of LDL was also demonstrated after 18 hours of incubation with compactin.²³

Treatment with compactin is ideal in familial hypercholesterolemia in that it reduces serum cholesterol by 22 per cent and LDL cholesterol by 29 per cent, but serum cholesterol and LDL cholesterol levels (303 ± 8 and 211 ± 11 mg per deciliter, respectively) still remain above normal at doses of 30 to 60 mg of compactin per day.¹³ No single drug, including bile acid resins, can normalize serum and LDL cholesterol levels in familial hypercholesterolemia.²²

Several combinations of drugs are more effective than individual drugs in the treatment of hypercholesterolemia. Kane et al. found that the combination of nicotinic acid and colestipol reduced LDL cholesterol levels to the normal range; these levels were actually significantly lower than those of a control population matched for sex and age.²⁴ The effectiveness of bile acid sequestrants has long been known to be blunted, however, because of compensatory increases in hepatic biosynthesis of cholesterol. Inhibition of cholesterol biosynthesis and VLDL production by nicotinic acid may be complementary to the effect of the bile acid-binding resins. Thus, the most effective regimen currently available for the treatment of heterozygous familial hypercholesterolemia is thought to be nicotinic acid with a bile acid-binding resin.²²

It would be expected, on theoretical grounds, that a specific inhibitor of cholesterol synthesis would act synergistically with a bile acid sequestrant in lowering plasma LDL levels.⁸ Kovanen et al. found that the combination of colestipol and mevinolin was synergistic in increasing hepatic LDL receptors and lowering plasma LDL levels in normal young dogs.⁷ This combination produced a synergistic threefold increase in the fractional catabolic rate for LDL. The average decrease in LDL cholesterol during treatment

with resin alone is reported to be about 15 to 30 per cent²⁵⁻²⁷; treatment with compactin alone decreases LDL cholesterol by 29 per cent.¹³ In the present study, the combination of cholestyramine and compactin decreased LDL cholesterol by 53 per cent — an effect comparable to that of the combination of colestipol and nicotinic acid (a decrease of 47 to 55 per cent).^{24,28} Moreover, compactin and its analogue, mevinolin, are well tolerated, and clinical and laboratory side effects are very mild and few.¹²⁻¹⁵

Serum triglyceride levels decreased with the addition of compactin. This decrease was due to reductions in the LDL fraction, as in our previous study with compactin.¹³ This drug reduced both serum cholesterol and phospholipid levels in dogs.²⁹ In the present study, serum phospholipid as well as LDL and IDL phospholipid concentrations decreased significantly. The cholesterol/phospholipid ratios in whole serum and LDL fractions in patients with familial hypercholesterolemia are known to be higher than those in normal subjects.⁴ After treatment with the combination of diet, cholestyramine, and compactin, these ratios decreased significantly, from 1.34 ± 0.03 to 0.98 ± 0.02 in whole serum ($P < 0.001$), and from 1.71 ± 0.03 to 1.55 ± 0.02 ($P < 0.001$) in LDL fractions. The abnormal levels of triglyceride and phospholipid observed in familial hypercholesterolemia may be secondary to a lack of regulation in the relevant enzymes normally regulated by LDL through LDL receptors.³⁰ Thus, the combination of compactin and cholestyramine normalizes both the concentrations and the compositions of serum LDL.

No long-term studies of compactin toxicity in animals or human beings have been reported, and any clinical use of this new agent will have to await such data. Nevertheless, on the basis of our studies to date, the compactin-cholestyramine regimen appears to be a promising form of therapy for heterozygous familial hypercholesterolemia.

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