Sitosterolemia: Opposing Effects of Cholestyramine and Lovastatin on Plasma Sterol Levels in a Homozygous Girl and Her Heterozygous Father

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Sitosterolemia is a genetic disorder characterized by sitosterol accumulation in plasma and clinically accelerated atherosclerosis. Under a condition of metabolic control with a 30% fat, low-sitosterol diet, we compared the effects of monotherapy and dual-drug treatment with lovastatin and cholestyramine on plasma sterol parameters and endogenous cholesterol synthesis in a homozygous sitosterolemic patient with concomitant heterozygous familial hypercholesterolemia (FH), her obligate heterozygous father, and hyperlipidemic control subjects. We found that for both the sitosterolemic homozygote and heterozygote, cholestyramine plus lovastatin dual therapy proved not to be superior to either drug treatment alone. In the homozygous patient, cholestyramine accounted for the decrease of plasma sterol (ie, lovastatin was ineffective), whereas in the heterozygote, lovastatin represented the margin of difference (ie, low-dose cholestyramine was relatively ineffective). Thus, the best treatment option for this homozygote child and her heterozygote father appears to be monotherapy with cholestyramine and lovastatin, respectively. Stimulation by bile acid malabsorption produced a dramatic decrease of plasma sterols in the homozygote, without increasing endogenous cholesterol synthesis, but this therapy was ineffective in the heterozygote. Decreasing endogenous cholesterol synthesis with lovastatin was effective in the heterozygote, but ineffective in the homozygote. In suspected sitosterolemia, a poor sterol response to lovastatin and a dramatic response to cholestyramine may differentiate homozygous from heterozygous and other familial forms of hyperlipidemia.

SITOSTEROLEMIA is an extremely rare genetic disorder characterized biochemically by elevated plasma levels of plant sterols, mainly sitosterol, and clinically by xanthomatous lesions and premature coronary heart disease.[1-5] Most studies suggest that the major biochemical defects in sitosterolemia include indiscriminate intestinal sterol absorption coupled with reduced hepatic sterol excretion and abnormally low cholesterol biosynthesis.[1-3,5-8] However, a rigorous low-sterol diet to curtail input has not proved an effective treatment in all patients.[8,9]

Drug treatments of sitosterolemia have shown some success; bile acid–sequestering resins such as cholestyramine (Questran; Mead Johnson Laboratories, Evansville, IN) have been shown to decrease plasma sterols (both cholesterol and sitosterol), but constipation may limit compliance.[10,11] Belamarich et al[12] reported dramatic and rapid reductions in plasma sterols in one 11-year-old sitosterolemic boy following therapy with cholestyramine and a low-sterol diet. In another trial, plasma cholesterol levels failed to decline during treatment with lovastatin (Mevacor; Merck, Sharp and Dohme, Rahway, NJ) in a homozygote without dietary sterol restriction.[11] Although both studies[11,12] suggested that the degree of responsiveness to diet and drug therapies is under genetic regulation, they lacked strict metabolic-ward diet control.

Similar to sitosterolemia, familial hypercholesterolemia (FH) is characterized by markedly elevated sterol levels, xanthomatous lesions, and premature coronary heart disease, but plasma sitosterol levels remain normal. The hallmark of FH is defective low-density lipoprotein (LDL)-receptor binding.[13-15] Our homozygote is unique in showing characteristics common to both sitosterolemia and FH, including markedly elevated plasma sterol concentrations (both cholesterol and sitosterol), decreased LDL-receptor binding, and xanthomas.[16] Since dual treatment with both bile acid–binding resins and lovastatin results in striking reductions of plasma cholesterol levels in FH,[17-19] the individual and combination therapies were studied under a condition of metabolic control in our sitosterolemic homozygote with FH, her heterozygote father, and hyperlipidemic controls. Two independent measures of endogenous cholesterol synthesis were related to sterol parameters to define underlying biochemical mechanisms that distinguish the sitosterolemic homozygote from the other forms of hyperlipidemia.

SUBJECTS AND METHODS

The index case was a 10-year-old white girl, homozygous for sitosterolemia, whose history and preliminary responses to diet and drug have been previously reported.[9,16] Fibroblast studies conducted by Dr J.L. Goldstein (University of Texas Southwestern Medical Center, Dallas, TX) showed that LDL binding and LDL-mediated stimulation of cholesteryl oleate formation were depressed by 56% and 65%, respectively, as compared with levels in normal cells, confirming a concomitant diagnosis of heterozygous FH.[16] On physical examination, the presence of tuberous xanthomata was noteworthy in this patient.

Previously reported blood-group studies confirmed the parentage of the patient's father, and fibroblast studies showed heterozygous FH.[16] Table 1 shows clinical characteristics of the homozygous patient and her heterozygous father, measured at baseline and while on the ad libitum low-sterol diet, and four heterozygous FH

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Table 1. Sitosterolemic Homozygote and Obligate Heterozygote Characteristics, Plasma Sterols, and Lipoprotein Distribution on Ad Libitum Low-Fat Diet

Patient	Weight (kg)	Sterols (mg/dL)		Lipids (mg/dL)		Sterol Distribution (mg/dL)		
		Cholesterol*	Sitosterol*	Total Sterol†	TG	VLDL	LDL	HDL
Sitosterolemic homozygote (index case)	30 ± 1	303 ± 71	37 ± 8	348 ± 14	69 ± 9	27 ± 16	264 ± 4	56 ± 7
Sitosterolemic heterozygote (obligate parent)‡	110 ± 2	280 ± 14	0.4 ± 0.1	286 ± 20	208 ± 55	47 ± 9	208 ± 17	30 ± 4
Hyperlipidemic patients (n = 4): ages 8-10, females§	27 ± 2	309 ± 78	0.2 ± 0.1	315 ± 83	72 ± 16	14 ± 4	243 ± 34	48 ± 7

NOTE. Age- and sex-matched hyperlipidemic patients are presented for comparison. Values represent the mean ± SD of at least 3 determinations. Total sterol = total cholesterol + sitosterol.

Abbreviations: TG, triglycerides; NA, not available.

*Determined by gas liquid chromatography.

†Determined enzymatically.

‡Ad libitum diet: 38% fat, 190 mg sitosterol, 420 mg dietary cholesterol per day.

§Ad libitum diet: 30% fat, 120 mg sitosterol, <300 mg dietary cholesterol per day.

patients who were age- and sex-matched to our homozygote and seen concurrently at the Rockefeller University Clinic for comparison.

The metabolic diet consisted of natural foods prepared in the Clinical Research Kitchen and weighed to ±0.1 g. The metabolic diet composition was initially calculated from food tables,[20] and then an aliquot of the homogenized diet was analyzed for actual nutrient composition and fatty acid content[21] by an independent laboratory (Industrial Chemical Analysis Laboratory, New York, NY). This basal low-sitosterol diet consisted of 29.7% fat (polyunsaturated to saturated ratio, 0.45), 51.9% carbohydrate, 18.4% protein and contained 223 mg cholesterol, 26 mg sitosterol, 5 mg campesterol, and 2 mg minor plant sterols (ie, 24-methylcholestanol + stigmasterol + 24-ethylcholestanol) per 2,000 kcal. The diet was strictly fed for 13 weeks; each diet-drug period was separated by a 2- to 3-week washout phase during which the homozygote and heterozygous patients returned to an ad libitum low-sterol diet administered in the hospital without drug therapy. For comparative purposes, the four FH patients were counseled concurrently at the Rockefeller University Clinic to follow an American Heart Association 30% fat diet containing less than 300 mg sterol/d.

The diet-drug treatments were conducted on The Rockefeller University Metabolic Unit under metabolically controlled inpatient conditions, with single blinding (homozygote and heterozygote patient) for the lovastatin-placebo phases. Body weight was maintained within ±1 kg throughout the study for the homozygote, her father, and four FH controls. Informed consent was obtained from all participants after review by the Institutional Review Board.

This study incorporated four metabolic diet-drug phases: diet-placebo (4 weeks), diet-lovastatin monotherapy (3 weeks), diet-cholestyramine monotherapy (3 weeks), and diet–lovastatin-cholestyramine combined therapy (3 weeks) (Fig 1). With the basal diet, a mirror-image lovastatin-placebo tablet was administered to equalize baseline dietary and treatment conditions over a 28-day period in both the homozygote and heterozygote. During week 4 of the diet-placebo period, the following were obtained: (1) three to four blood samples for determination of plasma sterol parameters, (2) three 24-hour urine specimens for quantitation of urinary mevalonate excretion, and (3) daily stool collections for fecal neutral and acidic sterol excretion. At the end of the subsequent diet-drug phases, repeat corresponding blood and urine specimens were collected for analysis.

To establish a maximum safe dosage for the lovastatin treatment phase in the homozygote patient, lovastatin was administered with the basal metabolic diet in doses of 10, 20, and 30 mg (which correspond to approximately 0.3, 0.7, and 1.0 mg/kg body weight, respectively) for 14 days each. At the end of the dose-response study, the homozygote patient was maintained on the highest

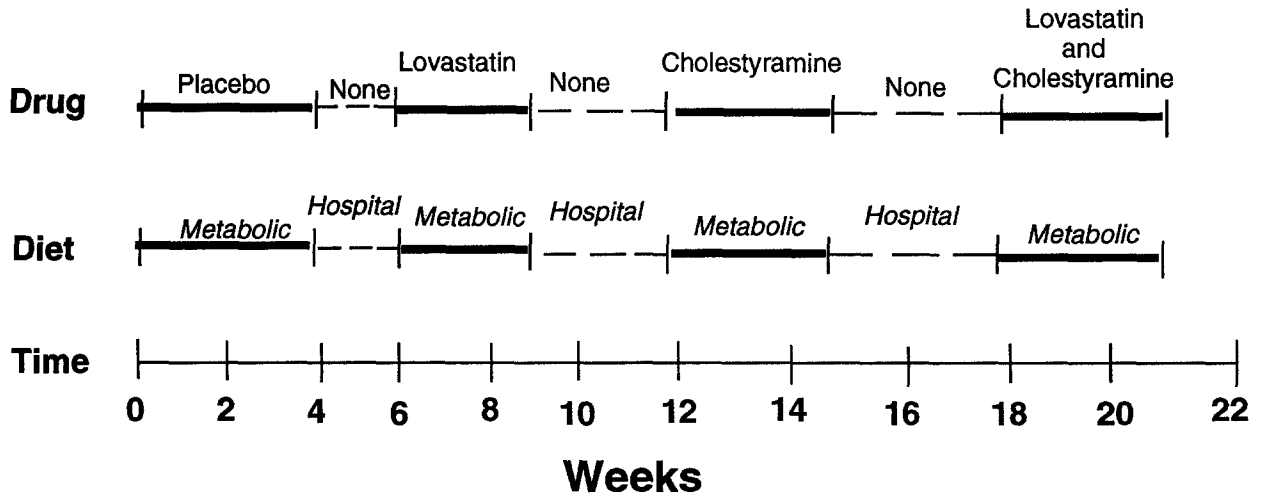

Fig 1. Study design. (■) Metabolic drug period; (---) washout period.

lovastatin dosage of 30 mg/d (equivalent to 1 mg/kg/d) with the metabolic diet for an additional week, completing the 3-week diet-drug study period. Only data for the highest lovastatin dosage are presented. Diet-drug treatment in the sitosterolemic heterozygote was paired with that of the homozygote; he was treated with a lovastatin dosage of 60 mg/d (a near-maximal dosage, equivalent to 0.5 mg/kg/d) for 3 weeks.

The homozygote and heterozygote were each treated with cholestyramine resin (2.5 g/10 kg/d) for 21 days, equivalent to 9 and 27 g/d, respectively. During the final diet-drug period, the homozygote and heterozygote were treated with combined (dual-therapy) lovastatin and cholestyramine. The homozygote received lovastatin 1 mg/kg/d combined with cholestyramine 2.5 g/10 kg/d, and the heterozygous father received lovastatin 0.5 mg/kg/d combined with resin 2.5 g/10 kg/d.

Laboratory Analysis

Antecubital blood samples were collected after a 12-hour fast for determination of plasma sterol and apolipoprotein (apo) B during the final week of each diet-drug period. Plasma was separated at 4°C by centrifugation at 2,500 rpm for 20 minutes. Dietary and plasma sterol distributions were determined from aliquots of diet homogenate (1 g)[22] or plasma (1 mL)[23] by capillary gas-liquid chromatography. After saponification, neutral sterols were extracted, dried, and trimethylsilylated as previously described. Aliquots were redissolved with internal standards and injected into a Hewlett-Packard model 5890 gas chromatograph equipped with a wax-coated CP-Wax-57 capillary column (0.32 mm ID × 26 m, 0.45 mm OD; Chrompak, Bridgewater, NJ).

Plasma sterol (cholesterol plus plant sterols) lipoprotein distribution was assayed enzymatically as described previously.[24,25] The high-density lipoprotein (HDL) sterol level was quantified following dextran-sulfate-magnesium precipitation and ultracentrifugation; LDL sterol concentration was determined by difference. Plasma aliquots were assayed for apo B levels by sandwich enzyme-linked immunosorbent assay.[26]

At the end of the 4-week diet-placebo period, stools were collected for 4 days, weighed, homogenized with an equal volume of water, and frozen at −70°C.[27] As previously validated at the Rockefeller University Metabolic Unit, chromic oxide was used as an internal marker of fecal steroid excretion, with corrections made for day-to-day variations in fecal flow as described by Grundy et al.[28] For analysis, the fecal homogenate was thawed, and an aliquot was lyophilized and analyzed for fecal neutral and acidic steroids by methods previously described.[23] Trimethylsilyl ether derivatives of the bile acid methyl esters and neutral sterol were injected onto CP-Sil-5 CB and CP-Wax-57 CB fused silica capillary columns (Chrompack), and retention times were compared with standards.[23] A comparison was made between sterol-balance data collected on the Rockefeller Metabolic Unit from the homozygote and her heterozygous father, a homozygous FH patient (age 5) and normolipidemic brother (age 6), and 10 unrelated hyperlipidemic control subjects aged 14 to 58 years and weighing 47 to 58 kg. These controls were housed at the Rockefeller University Metabolic Unit and fed a strictly controlled low-sterol diet, as reported previously by McNamara et al[29] and the senior investigator.[28]

Urinary mevalonic acid excretion was determined as previously described[30,31] in three 24-hour urine specimens collected on the metabolic unit in the homozygote and her heterozygous father and compared with that in hyperlipidemics with FH on a low-fat diet.[19] Completeness of urine collection was determined by measuring 24-hour urine creatinine clearance on the metabolic unit. Mevalonate acid concentrations were determined by the radioenzymatic method of Popjak et al.[31]

Descriptive statistics and a one-way ANOVA with repeated measures were calculated using the Biomedical Computer Programs (copyright University of California, 1985). A Tukey post hoc procedure[32] with a 5% significance level was used to test for differences among the periods.

RESULTS

Table 2 shows the effects of the 30% fat metabolic diet–placebo on plasma sterol distribution in the homozygote and heterozygote and diet-counseled age- and sex-matched hyperlipidemic patients. Plasma levels of sitosterol, campestrol, and 5α-stanols remained markedly elevated in the homozygote compared with the heterozygous parent and the controls, with sitosterol accounting for 11% of total plasma sterol. Plasma cholesterol levels in our homozygote were elevated as compared with normolipidemic reference standards.[33] Endogenous cholesterol synthe-

Table 2. Effects of Basal Metabolic Diet and Placebo on Plasma Sterols, Fecal Acidic and Neutral Sterol Excretion, and Endogenous Cholesterol Synthesis (sterol balance)

	Plasma Sterol Distribution (mg/dL)						Fecal Sterol Excretion, (mg · kg · d^{-1})		
Patient	Cholesterol	Sitosterol	Campesterol	Sitostanol	Campestanol	Cholestanol	Acidic Sterols	Neutral Sterols	Cholesterol Balance (endogenous cholesterol synthesis)
Sitosterolemic homozygote	287 ± 35	38 ± 6	18 ± 14	5 ± 1	3 ± 1	4 ± 1	1.3 ± 0.6	5.0 ± 1.5	3.1 ± 1.1
Sitosterolemic heterozygote	249 ± 13	0.5 ± 0.4	—	—	—	0.2 ± 0.1	2.7 ± 1.3	12.2 ± 2.1	12.2 ± 2.8
Hyperlipidemic patients (n = 4): ages 8 to 10, females)*	285 ± 65	0.3 ± 0.1	—	—	—	0.2 ± 0.2			
Familial hypercholesterolemic (age 5)†							4.2 ± 2.0	17.8 ± 3.4	14.6 ± 3.4
Normolipidemic subject (age 6)							1.1 ± 0.3	NA	9.2 ± 2.8
Hyperlipidemic patients (n = 10: ages 14 to 56)‡							4.3 ± 1.3	13.1 ± 1.4	13.5 ± 5.2

NOTE. Values represent the mean ± SD of at least 3 determinations.

*Hyperlipidemic age- and sex-matched patients counseled to eat a 30% fat diet containing <300 mg sterol per day.

†Homozygous FH patient and normolipidemic sibling fed a metabolic low-sterol diet.[29]

‡Hyperlipidemic subjects fed a metabolic low-sterol diet as reported previously.[28]

sis in the homozygote was depressed by over 66% as compared with levels in the heterozygous father (3.1 *v* 12.2 mg/kg/d), a homozygous FH patient (14.6) and normolipidemic sibling (9.2), and 10 hyperlipidemic controls (13.5) fed a low-sterol metabolic diet, predominantly due to decreased neutral sterol output[28-29] (Table 2). These findings were supported by the other independent determination (Table 3): 24-hour urinary mevalonate excretion was depressed by 62% and 43%, respectively, in the homozygote compared with the hyperlipidemic controls and the heterozygote. The sitosterolemic heterozygote maintained elevated plasma cholesterol, based on age- and sex-matched reference standards,[33] and negligible levels of sitosterol and cholestanol on the 30% fat diet. Endogenous cholesterol synthesis measured by sterol balance in the heterozygote was similar to that in hyperlipidemic controls.

Table 3 shows effects of the diet-drug treatments on urinary mevalonate excretion and plasma parameters in the homozygote, heterozygote, and hyperlipidemic controls. A preliminary lovastatin dose-response relationship was established in our sitosterolemic homozygote. No qualitative changes in plant sterols or lipoprotein distribution were induced with increasing dosages of lovastatin from 0.3 through 0.7 (data not presented) and 1.0 mg/kg/d (Table 2); no adverse effects were noted with any dosage. However, plasma cholesterol levels actually increased steadily with increasing lovastatin dosages, achieving statistical significance only at the highest lovastatin dosage (+11%, $P < .05$); this included a steady increase in LDL and HDL sterol, with net increases of up to 18% versus the diet-placebo treatment. There was no appreciable influence of lovastatin monotherapy on the LDL/HDL sterol ratio or apo B levels.

Plasma sitosterol levels in the heterozygote remained near zero through all diet and drug therapies (Table 3). In contrast to the homozygote, dramatic plasma cholesterol reductions were seen in the heterozygote only with administration of lovastatin. Lovastatin therapy (0.5 mg/kg/d) produced significant reductions in plasma cholesterol, LDL, and apo B concentrations of 31%, 44%, and 52%, respectively. With HDL unaffected, the LDL/HDL ratio was significantly reduced by 44% versus diet-placebo levels.

However, in the homozygote, cholestyramine resin monotherapy produced dramatic reductions in plasma sterol, as compared with the diet-placebo, decreasing plasma sitosterol, cholesterol, and LDL sterol proportionately by 29%, 31%, and 41%, respectively. Resin treatment also significantly improved the LDL/HDL sterol ratio by 33%. Compared with levels attained by lovastatin monotherapy, cholestyramine treatment significantly reversed the elevated plasma cholesterol levels by 38% and LDL and HDL sterols by 41% and 16%, respectively. Unexpectedly, cholestyramine therapy failed to stimulate cholesterol synthesis, which remained depressed by over 20% as compared with the diet-placebo control level.

Low-dose cholestyramine therapy was far less effective than lovastatin in reducing LDL in the heterozygote, effecting a modest reduction of 8% ($P < .05$) compared

Table 3. Effects of Drug Therapy and Diet/Placebo on Urinary Mevalonate Excretion, Plasma Sterols, Apo B Levels, and Lipoprotein Distribution in a Sitosterolemic Homozygote and Heterozygote and in Hyperlipidemic Controls

	24-Hour Urinary Mevalonate Excretion		Plasma Distribution (mg/dL)								
			Sterols			Lipids		Sterol Distribution			
Patient	nmol/kg/d	%Δ	Cholesterol	Sitosterol	Apo B	Total	TG	VLDL	LDL	HDL	LDL/HDL
Sitosterolemic homozygote											
Placebo	13.2 ± 1	0	287 ± 35	38 ± 6	168 ± 9	343 ± 18	83 ± 1	39 ± 4	247 ± 10	57 ± 4	4.5 ± 0.1
Lovastatin	6.7 ± 1	−49	318 ± 15*	35 ± 3	176 ± 11	367 ± 10	63 ± 10	34 ± 4	265 ± 14	67 ± 2*	4.0 ± 0.2
Cholestyramine	8.5 ± 1	−36	198 ± 22*†	27 ± 2*	159 ± 3	221 ± 11§‖	69 ± 5	28 ± 6	146 ± 10§‖	48 ± 2†	3.0 ± 0.3*
Lovastatin + cholestyramine	7.2 ± 1	−46	190 ± 14*	25 ± 3*	117 ± 21*†	233 ± 14§‖	65 ± 2	21 ± 10†	130 ± 13§‖	75 ± 5*†‡	1.8 ± 0.2§‖¶
Sitosterolemic heterozygote											
Placebo	23.0 ± 2	0	249 ± 13	.2 ± .4	157 ± 2	251 ± 8	155 ± 8	45 ± 11	180 ± 6	25 ± 2	7.2 ± 0.2*
Lovastatin	10.0 ± 1	−57	172 ± 29§	.1 ± .3	76 ± 5§	160 ± 6§	84 ± 7	34 ± 6	101 ± 2§	26 ± 2	4.0 ± 0.1*
Cholestyramine	30.1 ± 2	+31	229 ± 12	.2 ± .3	121 ± 2	224 ± 4	130 ± 20	31 ± 7	166 ± 5*	25 ± 2	6.1 ± 0.5
Lovastatin + cholestyramine	7.4 ± 1	−68	166 ± 10§	.1 ± .2	83 ± 18§	156 ± 11§	119 ± 10	29 ± 6	99 ± 8§	26 ± 2	3.7 ± 0.5*
Hyperlipidemic Patients (n = 14; ages 29-63)											
Low-fat diet	35 ± 9	NA	NA	NA	NA	387 ± 51	303 ± 49	31 ± 3	303 ± 49	49 ± 12	6.7 ± 2

NOTE. Values represent the mean ± SD of at least 3 determinations.
Abbreviation: NA, not available.
*$P < 0.05$ *v* placebo.
†$P < 0.05$ *v* lovastatin.
‡$P < 0.05$ *v* cholestyramine.
§$P < 0.01$ *v* lovastatin.
‖$P < 0.01$ *v* placebo.
¶$P < 0.01$ *v* cholestyramine.

with the diet-placebo. The sterol-lowering influence of lovastatin was maintained, but cholestyramine showed no additive benefit. Dual therapy in the heterozygote failed to elevate HDL levels or improve the LDL/HDL ratio beyond concentrations attained with lovastatin alone.

Dual therapy with both lipid-lowering medications in our homozygote did not reduce plasma sitosterol or LDL sterols as compared with cholestyramine monotherapy. The single most significant effect of dual therapy was the 56% increase ($P < .01$) in the HDL sterol component over that achieved with cholestyramine alone, representing the highest HDL sterol level achieved by any treatment.

All drug therapies further diminished the already low baseline 24-hour urinary mevalonate excretion in our homozygote. Urinary mevalonate levels decreased with every lovastatin dosage. Lovastatin monotherapy produced the greatest reductions (−49%) in urinary mevalonate excretion (Table 3). While the reductions in urinary mevalonate excretion induced by cholestyramine therapy were unexpected (ie, decreased by 36%), dual-drug therapy depressed mevalonate excretion to the level achieved by lovastatin monotherapy in the homozygote.

In the heterozygote, endogenous cholesterol synthesis as measured by urinary mevalonate excretion (Table 3) was not significantly different from that in hyperlipidemic subjects. Lovastatin monotherapy decreased mevalonate excretion by 57%, whereas cholestyramine monotherapy inversely (and expectedly) increased excretion by 31%. Dual therapy produced a 68% decline in mevalonate excretion, a marginally better response than achieved with lovastatin alone in the heterozygote.

DISCUSSION

Following the low-sterol, metabolically controlled diet, our sitosterolemic homozygous patient, as compared with her heterozygous father, maintained both markedly increased plasma sterols (11% sitosterol) and abnormally low endogenous cholesterol biosynthesis. Cholestyramine monotherapy significantly decreased the patient's plasma sterols and had no stimulatory effect on endogenous synthesis, whereas lovastatin increased the patient's plasma sterol and further depressed endogenous synthesis. Dual therapy (lovastatin plus cholestyramine) also failed either to stimulate greater endogenous synthesis or to decrease plasma sterol levels as compared with cholestyramine alone. In contrast, the patient's father, an obligate heterozygote, maintained modestly increased plasma sterol levels (99% cholesterol) during diet-placebo and relatively normal levels of endogenous synthesis that were subsequently stimulated by cholestyramine and inhibited by lovastatin. Lovastatin also produced the expected decrease of plasma sterol concentrations, but cholestyramine alone failed to significantly affect plasma sterols as compared with diet-placebo. Dual therapy failed to decrease plasma sterol levels below those seen with lovastatin therapy alone.

Sitosterolemic Homozygote

Total fecal neutral sterols, measured under steady-state conditions, plus bile acids minus dietary sterols were used to calculate endogenous cholesterol synthesis.[34] Cholesterol synthesis was dramatically depressed with diet-placebo alone in the homozygote patient, compared with the heterozygote and hyperlipidemic controls. It was remarkable, then, that plasma sterol levels remained elevated during this time, probably reflecting an impediment to clearance.[8,22] In seven other homozygotes from four unrelated families, extremely low cholesterol synthesis, 3 to 7 mg/kg/d, was measured by sterol-balance or isotope kinetic methods.[3,7-10,35]

Since mevalonic acid is the first committed precursor in the cholesterol biosynthetic pathway, the lower the endogenous cholesterol synthesis, the lower the urinary mevalonate excretion. Urinary mevalonate excretion, unlike balance measurements, does not require steady-state conditions and is therefore more reliable for evaluating changes in cholesterol synthesis during these drug treatments. In our sitosterolemic homozygote, mevalonate excretion was equally depressed by lovastatin and resin monotherapy and dual treatments as compared with diet-placebo. In two sitosterolemic subjects treated with lovastatin or colestipol monotherapy, monocyte HMG-CoA reductase activity was decreased by 47% and 30%, respectively.[11] Since monocyte HMG-CoA reductase activity is another measure of cholesterol synthesis, these findings in two unrelated sitosterolemics are in agreement with our results with drug monotherapy.

Lovastatin therapy in our homozygote reduced neither plasma cholesterol nor sitosterol levels, a finding concordant with that in another sitosterolemic patient treated with lovastatin.[11] The resultant increase in plasma LDL and HDL sterol in our homozygote following lovastatin therapy was remarkable. Other drug therapies such as fibrates increase LDL and HDL levels by modifying VLDL composition and lipoprotein kinetics in hyperlipidemia.[36,37] It is thus possible that lovastatin treatment in the homozygote may modify sterol distribution and account for the concomitant increase in both LDL and HDL sterol levels. A similar response was noted when a sterol-free diet was fed to another sitosterolemic homozygote.[8] A lack of sterol response, or even a "reverse" response to lovastatin (as seen in our patient) has been reported previously.[9]

The effectiveness of low-dose cholestyramine in our homozygote (ie, a 41% and 16% decrease in LDL sterols and HDL sterols) has been reported in some hyperlipidemics treated with resin therapy.[38] Cholestyramine-induced bile acid malabsorption appears to favor uptake and conversion of plasma sterols, rather than stimulation of endogenous cholesterol synthesis, for bile acid replacement.[39] In other studies, bile acid malabsorption induced either by cholestyramine or by ileal bypass surgery reduced plasma cholesterol from 20% to 50% with a proportionate plasma sitosterol decline in homozygote patients.[11] Hidaka et al[4] reported a still greater reduction in cholesterol in several Japanese sitosterolemic patients, again indicative of the therapeutic effect of cholestyramine.

In the sitosterolemic homozygote, lovastatin plus cholestyramine therapy was not better than cholestyramine alone in decreasing plasma sterol; however, a redistribution of

sterol among component subfractions was suggested. The clinical relevance of these findings is uncertain for our homozygous sitosterolemic patient, as these results are in contrast to the dramatic lipid-lowering effects of dual therapies in patients with only the heterozygous FH defect.[17-19]

Sitosterolemic Heterozygote

After the 28-day low-sterol diet phase, the heterozygote was able to produce cholesterol normally (Table 2). The amount and direction of change in urinary mevalonate excretion found in the heterozygote was nearly identical to those previously reported in hyperlipidemic patients treated with lovastatin and cholestyramine monotherapy and dual therapy.[19] Heterozygotes, including ours, show some sitosterol absorption from the gut (15% *v* 5% in normal subjects). However, plasma concentrations and body pools are not enlarged, because excretion is rapid (ie, 10 times the rate seen in homozygotes[35]).

In the heterozygote, the modest decline in plasma cholesterol following low-dose cholestyramine monotherapy along with increases in 24-hour urinary mevalonate excretion suggest stimulated cholesterol synthesis and utilization of plasma sterols for bile acid synthesis. Thus, the small reduction in LDL in the heterozygote reflects the balance between upregulated endogenous synthesis induced by bile acid malabsorption and increased utilization of hepatic and plasma cholesterol pools.

In the heterozygous father, it appears that dual therapy is marginally better than lovastatin alone in depressing cholesterol synthesis. However, the additional efficacy of this combined therapy in decreasing plasma sterol levels was small compared with that of lovastatin alone.

Relevance of Concomitant Heterozygous FH Defect

Our patient has the unusual defects of homozygosity for sitosterolemia and heterozygosity for FH. Lovastatin therapy in patients with homozygous FH does not reduce plasma LDL levels,[40] yet is effective in the heterozygous state. This finding supports the view that the primary influence of lovastatin is to stimulate an increase in the number of LDL receptors, not to inhibit the synthesis of lipoproteins. In our patient homozygous for sitosterolemia and heterozygous for FH, lovastatin monotherapy failed to decrease plasma LDL sterol concentrations, a finding concordant with that of homozygosity for sitosterolemia and FH.

Although no kinetic studies have been reported in sitosterolemics treated with drug therapies, lovastatin treatment in patients heterozygous for FH but without sitosterolemia alters LDL density and composition.[37] Thus, it is possible that the elevation in LDL sterol concentration following lovastatin treatment in our sitosterolemic homozygote patient with concomitant FH may result from a modification of LDL sterol particle composition and poor clearance by LDL receptors.

Summary

Overall, for both the sitosterolemic homozygote patient and her heterozygous father, cholestyramine plus lovastatin dual therapy proved not to be superior to either drug treatment alone. In the sitosterol homozygote, cholestyramine accounted for the decrease of plasma sterol (ie, lovastatin was completely ineffective), but in the sitosterolemic heterozygote, lovastatin represented the margin of difference (ie, cholestyramine was relatively ineffective). Thus, the best treatment option for our homozygous patient and her heterozygous father appears to be monotherapy with cholestyramine and lovastatin, respectively. In the dual therapies, the component that proved therapeutic remained in the combination regimen, with no added benefit from the complementary component.

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