Colesevelam Hydrochloride (Cholestagel)

A New, Potent Bile Acid Sequestrant Associated With a Low Incidence of Gastrointestinal Side Effects

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Objectives: To compare colesevelam hydrochloride (Cholestagel), a nonabsorbed hydrogel with bile acid–sequestering properties, with placebo for its lipid-lowering efficacy, its effects on laboratory and clinical safety parameters, and the incidence of adverse events.

Methods: Following diet and placebo lead-in periods, placebo or colesevelam was administered at 4 dosages (1.5, 2.25, 3.0, or 3.75 g/d) for 6 weeks with morning and evening meals to men and women with hypercholesterolemia (low-density lipoprotein cholesterol level >4.14 mmol/L [=160 mg/dL]). Patients returned to the clinic every 2 weeks throughout the treatment period for lipid parameter measurements and adverse event assessments. Samples were collected for serum chemistry profiles, hematologic studies, coagulation studies, and vitamin level assessment at baseline and at 6 weeks of treatment.

Results: Among the 149 patients randomized, 137 completed the study. Low-density lipoprotein cholesterol concentrations decreased in a dosage-dependent manner by 0.11 mmol/L (4.2 mg/dL) (1.8%) in the 1.5-g/d colesevelam treatment group and up to 1.01 mmol/L (39 mg/dL) (19.1%) in the 3.75-g/d colesevelam treatment group. Low-density lipoprotein cholesterol concentrations at the end of treatment were significantly reduced from baseline levels in the 3.0- and 3.75-g/d colesevelam treatment groups (P=.01 and P<.001, respectively). Total cholesterol levels demonstrated a similar response to colesevelam treatment, with an 8.1% decrease from baseline in the 3.75-g/d treatment group (P<.001). High-density lipoprotein cholesterol levels rose significantly in the 3.0- and 3.75-g/d colesevelam treatment groups, by 11.2% (P = .006) and 8.1% (P = .02), respectively. Median triglyceride levels did not change from baseline, nor were there any significant differences between treatment groups. The incidence of adverse events was similar among all groups.

Conclusions: Colesevelam therapy is effective for lowering low-density lipoprotein cholesterol concentrations in persons with moderate hypercholesterolemia. It lacks the constipating effect of other bile acid sequestrants, demonstrating the potential for increased compliance.

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PATIENTS AND METHODS

PATIENTS

Men and women aged 18 years or older who had elevated LDL cholesterol levels were screened for participation in the study at 1 of 6 clinical research centers. Individuals were ineligible if they had tendinous xanthomas, thyroid disease, clinically significant liver or renal disease, vasculitis, human immunodeficiency virus infection, poorly controlled diabetes, poorly controlled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >105 mm Hg), unstable cardiac disease, recent myocardial infarction or cardiac bypass surgery (within 2 months of screening), any evidence of active malignant neoplasm, any clinically significant unstable medical condition, or any serum chemistry or hematologic abnormalities at screening. Patients were also excluded from participation if they had a history of dysphagia, swallowing disorder, or motility disorder of the intestines. Individuals who used probucol in the prior year, used fibrates in the month before screening, or had a recent history of ethanol or drug use were also ineligible. Pregnant women and nursing mothers were excluded from participation, and women of child-bearing potential were required to undergo a urine pregnancy test and to be adequately protected against pregnancy.

Patients could not take lipid-lowering medications concurrently. Patients were asked to avoid intentional changes in diet during the study, such as fasting or binge eating; if they were taking fiber supplements (ie, cellulose, methylcellulose, psyllium, polycarbophil, or bran), patients were also asked to maintain constant intake levels throughout the study.

This study was conducted in accordance with the US Code of Federal Regulations for clinical studies (21 CFR) and the Declaration of Helsinki. Before the study started, the investigators at each site forwarded copies of the protocol and consent form of the study to an appropriately constituted institutional review board that reviewed and approved the informed consent and the protocol. Signed informed consent was obtained from each patient prior to entering the study.

STUDY DESIGN

This was a multicenter, randomized, double-blind, placebo-controlled study divided into 4 periods: (1) screening to determine patient eligibility for the trial, (2) diet/washout (6 weeks for patients currently receiving lipid-lowering medication and 4 weeks for others) to normalize the effect of diet on lipid profiles and to allow for the washout of other lipid-lowering drugs, (3) placebo run-in (4 weeks) to assess compliance prior to randomization, and (4) drug treatment (6 weeks) to compare the safety and efficacy of colesevelam therapy with placebo.

At the time of screening (week −8), all lipid-lowering medications were discontinued, and patients were instructed to follow a National Cholesterol Education Program (NCEP) Step 1 diet (total fat intake ≤30% of total energy, saturated fat intake ≤10% of energy, and cholesterol intake <300 mg/dL) for 4 weeks. Participants were provided with copies of the educational booklets, Step by Step: Eating to Lower Your High Blood Cholesterol15 and The 2D Food Portion Visual.16 Nutrient intake was estimated using the University of Minnesota Nutrition Coordination Center’s Nutrition Data System, version 2.8 (Minneapolis, Minn, 1996). Twenty-four–hour dietary recalls were centrally administered by telephone by the Nutrient Analysis Center at the Chicago Center for Clinical Research on 2 nonconsecutive days within the last 2 weeks of both the diet lead-in period and the treatment period.

After the NCEP Step 1 diet stabilization period, patients returned to the clinic (week −4) for measurement of fasting lipid profiles. Placebo was administered (single-blind) to be taken as 5 capsules twice per day with meals for 4 weeks. Patients returned to the clinic after 2 weeks of the placebo run-in period (week −2) and again at the end of the placebo run-in period (week 0) for lipid profile measurements, treatment compliance review, and safety assessment. Criteria for entrance into the double-blind treatment period required at least 80% compliance with placebo in the final 2 weeks of the placebo run-in period and mean (weeks −4 and −2) LDL cholesterol (4.14 mmol/L [160 mg/dL]) and TG (3.39 mmol/L [300 mg/dL]) levels. Furthermore, the difference between the 2 lipid measurements at weeks −4 and −2 had to be 12% or more. If the difference was greater than 12%, a third measurement was obtained and the mean of the 3 measurements was used to determine eligibility.

At week 0, the study drug was dispensed to patients meeting all lipid and nonlipid criteria in a double-blind fashion according to a computer-generated randomization scheme. Patients were randomized to receive placebo or colesevelam hydrochloride in dosages of 0.75 g twice daily for both trihydroxy and dihydroxy bile acids in the in...
per day (1.5 g/d), 1.125 g twice per day (2.25 g/d), 1.5 g twice per day (3.0 g/d), or 1.875 g twice per day (3.75 g/d) for 6 weeks. Colesevelam was supplied as tasteless, hard gelatin capsules containing 375 mg of colesevelam hydrochloride. Placebo capsules identical in appearance to the colesevelam capsules contained 350 mg of microcrystalline cellulose. The study drug was administered as 5 capsules (placebo alone, colesevelam alone, or placebo and colesevelam to arrive at the exact dose) taken with the morning meal and 5 capsules taken with the evening meal. If a patient missed a meal, he or she was instructed to take the study drug with a snack. Missed doses were not to be made up by doubling the next dose. Patients were also instructed to take the study drug with a sufficient amount of liquid to ensure that the capsules cleared the oral cavity and esophagus.

During the 6-week treatment phase, patients returned to the clinic at weeks 2, 4, and 6. At each visit, vital signs were taken, fasting lipid profiles were measured, and patients were questioned regarding adverse events and concomitant medication use. Compliance with study medication was assessed by counting the number of pills returned. Additionally, at week 6, physical examinations were performed and samples were collected for serum chemistry profiles, hematologic studies, coagulation studies, and vitamin level assessments.

LIPID ANALYSES

Total and HDL cholesterol and TG levels were measured in fasting (no food or drink other than water or non-sweetened clear liquids for a minimum of 9 hours) serum, according to previously described procedures and the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute. All laboratory analyses were performed by Smith-Kline Beecham Clinical Laboratories (Van Nuys, Calif). Low-density lipoprotein cholesterol levels (milligrams per deciliter) were calculated using the equation described by Friedewald et al. 

SAFETY MONITORING

A complete physical examination and clinical laboratory assessment, including serum chemistry profiles and hematologic tests, were completed during the initial screening (week −8), at the time of randomization (day 0), and at the end of treatment (week 6). At each clinic visit, the patient's weight, pulse, and blood pressure were measured and adverse events were assessed. Additionally, prothrombin time, partial thromboplastin time, and vitamin A, vitamin E, and estradiol levels in women were measured at the time of randomization and at the end of the treatment period. Thyroid-stimulating hormone levels were assessed at the time of screening.

STATISTICAL METHODS

The statistical analyses presented are for the intent-to-treat population. Intent-to-treat patients were all those who were randomized, took at least 1 dose of study medication, and had at least 1 postbaseline efficacy evaluation. Missing data were handled using a carry forward approach. All tests for main effects were 2-sided and were conducted at the α = .05 level of significance, while tests for interaction effects were conducted at the α = .10 level of significance. The comparability of the groups at baseline was assessed using analysis of variance (ANOVA) for continuous variables and the Fisher exact test for categorical variables. Analyses of lipid data were performed using all fasting blood draws. The mean percentage change and the mean change from baseline (week 0) to end point (week 6) in cholesterol concentrations were analyzed using a paired t test. The difference in percentage change and change across groups were analyzed using a 2-way ANOVA with factors for treatment, center, and treatment-by-center interaction. A covariance model was tested for both change and percentage change in LDL cholesterol levels with covariates of baseline LDL cholesterol levels, change in total fat in the diet, change in body mass index (weight [kg]/[height (m)]²), and age. Since the distribution for changes in TG levels was not normal, a Wilcoxon signed rank test was used to test the change from baseline, and a Kruskal-Wallis test was used to test between-group comparisons.

Safety evaluations were performed on all patients who received study treatment after randomization (safety population). The percentage of patients with adverse events was compared across treatment groups using the Fisher exact test. Changes in hematologic and chemical parameters from week 0 to week 6 were analyzed using a paired t test. Between-group changes in laboratory parameters were compared using a Kruskal-Wallis test, and changes in vital sign variables were compared using ANOVA with factors for treatment, center, and treatment-by-center interaction.

The study was also designed to investigate the effects of colesevelam therapy on high-density lipoprotein (HDL) cholesterol and triglyceride (TG) concentrations.

RESULTS

Among the 275 persons screened, 149 were randomized into 5 treatment groups of similar sizes (colesevelam therapy administered at dosages of 1.5 g/d [n = 30], 2.25 g/d [n = 30], 3.0 g/d [n = 31], or 3.75 g/d [n = 29] or placebo [n = 29]). Treatment groups were comparable with respect to demographic characteristics (Table 1). The mean age of all groups combined was 56 years (range, 31-80 years), with a distribution of 44% men and 56%
women. Eighty-two percent of the patients were white. Baseline (week 0) lipid levels did not differ across treatment groups. The baseline mean ± SD total cholesterol level of all groups combined was 7.29 ± 0.87 mmol/L (282 ± 34 mg/dL); LDL cholesterol, 5.13 ± 0.82 mmol/L (198 ± 32 mg/dL); HDL cholesterol, 1.32 ± 0.32 mmol/L (51 ± 12 mg/dL); and the baseline median TG, 1.78 mmol/L (159 mg/dL).

Among the 149 patients randomized, 137 (92%) completed the study. The dropout rates were similar among treatment groups: 0 in the placebo group, 2 in the 1.5-g/d colesevelam group (withdrawal of consent after randomization [n = 1] and lost to follow-up [n = 1]), 3 in the 2.25-g/d colesevelam group (adverse event [n = 1], lost to follow-up [n = 1], and other [n = 1]), 5 in the 3.0-g/d colesevelam group (withdrawal of consent after randomization [n = 2], noncompliance [n = 1]), and 2 in the 3.75-g/d colesevelam group (adverse event [n = 1] and withdrawal of consent after randomization [n = 1]). Overall compliance was more than 93% for all treatment groups.

**DIET**

Dietary intake of total energy and selected nutrients did not differ among treatment groups at baseline or at the end of treatment. On average, dietary compliance decreased after week 0, as evidenced by an 11% increase in total fat intake, from 45 to 50 g/d, and a 23% increase in saturated fat intake, from 13 to 16 g/d. Mean energy intake increased 4%, from 6439 to 6720 kJ/d (1533 to 1600 kcal/d). These changes were similar across all treatment groups.

**SERUM LIPIDS**

Low-density lipoprotein cholesterol concentrations decreased in a dosage-dependent fashion in response to colesevelam treatment. Low-density lipoprotein cholesterol concentrations at week 6 were reduced from baseline by 0.11 mmol/L (4.2 mg/dL) to 1.01 mmol/L (39 mg/dL) for the lowest to highest colesevelam dosages (Table 2). In the 2 groups receiving the highest dosages of colesevelam therapy, this represented a significant change from baseline (P = .01 and P < .001 for the 3.0-g/d and 3.75-g/d colesevelam therapy groups, respectively). Low-density lipoprotein cholesterol concentrations were reduced by 1.8%, 4.9%, 9.0%, and 19.1% in the 1.5-g/d, 2.25-g/d, 3.0-g/d, and 3.75-g/d colesevelam groups, respectively (Figure 2). The percentage of LDL cholesterol level reduction was statistically different from baseline for the 2 groups receiving the highest dosages of colesevelam (P = .01 and P < .001 for the 3.0-g/d and 3.75-g/d colesevelam groups, respectively). Individual LDL cholesterol level responses for all subjects are shown in Figure 3.

The greatest reduction in LDL cholesterol levels occurred rapidly within the first 2 weeks of the treatment period (Figure 4). During the second 2 weeks of treatment, the 1.5-g/d and 3.75-g/d colesevelam groups exhibited additional modest decreases, but the 2.25-g/d and 3.0-g/d colesevelam groups demonstrated relatively constant effects. During the final 2 weeks of treatment, there

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**Figure 1. Chemical structure of colesevelam hydrochloride (Cholestagel).**

**Table 1. Baseline Patient Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 29)</th>
<th>1.5 (n = 30)</th>
<th>2.25 (n = 29)</th>
<th>3.0 (n = 30)</th>
<th>3.75 (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>57.1 ± 11.6</td>
<td>54.1 ± 11.3</td>
<td>54.8 ± 11.7</td>
<td>56.3 ± 12.0</td>
<td>57.9 ± 8.4</td>
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<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (45)</td>
<td>13 (43)</td>
<td>18 (62)</td>
<td>10 (33)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (55)</td>
<td>17 (57)</td>
<td>11 (38)</td>
<td>20 (67)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>21 (72)</td>
<td>27 (90)</td>
<td>21 (72)</td>
<td>25 (83)</td>
<td>27 (93)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (14)</td>
<td>3 (10)</td>
<td>6 (21)</td>
<td>4 (13)</td>
<td>1 (3)</td>
</tr>
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<td>Hispanic</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Weight, kg†</td>
<td>73.9 ± 15.3</td>
<td>77.8 ± 12.9</td>
<td>79.8 ± 14.9</td>
<td>72.5 ± 14.5</td>
<td>80.5 ± 14.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td>26.7 ± 4.1</td>
<td>27.6 ± 3.8</td>
<td>27.9 ± 4.8</td>
<td>26.4 ± 4.3</td>
<td>28.2 ± 4.9</td>
</tr>
</tbody>
</table>

* There were no significant differences among treatment groups.
† Mean ± SD.
was a slight increase in LDL cholesterol levels in the 1.5-g/d, 2.25-g/d, and 3.0-g/d colesevelam groups. However, in the 3.75-g/d colesevelam group, mean percentage decreases in LDL cholesterol levels remained constant between the 2 intervals (19.2% decrease from week 0 to week 4 vs 19.1% decrease from week 0 to week 6).

Using analysis of covariance, baseline LDL cholesterol level and colesevelam treatment group were found to be predictive of the change in LDL cholesterol levels. Higher baseline LDL cholesterol levels and higher colesevelam dosage led to greater absolute reductions in LDL cholesterol levels at the end of treatment. Colesevelam treatment group was the only significant factor that predicted percentage change in LDL cholesterol levels. Other covariates (ie, sex, change of total fat in the diet, change of body mass index, and age) were not significant in either the change or percentage change in LDL cholesterol levels.

Colesevelam treatment also reduced total cholesterol concentrations (Table 2). Decreases from baseline to week 6 in total cholesterol levels ranged from 0.12 mmol/L (4.8 mg/dL) to 0.61 mmol/L (24 mg/dL) across the 4 colesevelam groups. These reductions from baseline were significant in the 2.25-g/d and 3.75-g/d colesevelam groups (P = .04 and P < .001, respectively) and nearly reached significance in the 3.0-g/d colesevelam group (P = .06). The percentage reductions from baseline in total cholesterol levels were modest (highest, 8.1%). These reductions were significant for the 2 groups receiving the highest doses of colesevelam (P = .05 and P < .001 for the 3.0-g/d and 3.75-g/d colesevelam groups, respectively) and approached significance in the 2.25-g/d colesevelam group (P = .05).

Table 2. Lipid Levels at Baseline (Week 0) and End of Treatment (Week 6), With Change From Baseline to End of Treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo†</th>
<th>1.5</th>
<th>2.25</th>
<th>3.0</th>
<th>3.75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 28)</td>
<td>(n = 26)</td>
<td>(n = 26)</td>
<td>(n = 25)</td>
<td>(n = 24)</td>
</tr>
<tr>
<td><strong>LDL Cholesterol Levels, mmol/L (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.01 ± 0.65 (194 ± 25)</td>
<td>5.03 ± 0.99 (195 ± 38)</td>
<td>5.21 ± 0.78 (202 ± 30)</td>
<td>5.16 ± 1.02 (200 ± 39)</td>
<td>5.22 ± 0.66 (202 ± 26)</td>
</tr>
<tr>
<td>Week 6</td>
<td>4.99 ± 0.75 (193 ± 29)</td>
<td>4.92 ± 1.04 (190 ± 40)</td>
<td>4.93 ± 0.94 (191 ± 37)</td>
<td>4.68 ± 1.34 (181 ± 52)</td>
<td>4.21 ± 0.70 (163 ± 27)</td>
</tr>
<tr>
<td>Change‡</td>
<td>-0.02 ± 0.59 (−0.8 ± 23)</td>
<td>-0.11 ± 0.52 (−4.2 ± 20)</td>
<td>-0.28 ± 0.73 (−11 ± 28)</td>
<td>-0.48 ± 0.90 (−18 ± 35)</td>
<td>-1.01 ± 0.61 (−39 ± 24)</td>
</tr>
<tr>
<td><strong>Total Cholesterol Levels, mmol/L (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.27 ± 0.85 (281 ± 33)</td>
<td>7.31 ± 0.99 (283 ± 38)</td>
<td>7.37 ± 0.80 (285 ± 31)</td>
<td>7.15 ± 1.03 (277 ± 40)</td>
<td>7.36 ± 0.67 (285 ± 26)</td>
</tr>
<tr>
<td>Week 6</td>
<td>7.25 ± 0.97 (280 ± 38)</td>
<td>7.18 ± 1.07 (278 ± 41)</td>
<td>7.06 ± 0.96 (273 ± 37)</td>
<td>6.81 ± 1.37 (263 ± 53)</td>
<td>6.75 ± 0.90 (261 ± 35)</td>
</tr>
<tr>
<td>Change</td>
<td>-0.02 ± 0.58 (−0.7 ± 22)</td>
<td>-0.12 ± 0.54 (−4.8 ± 21)</td>
<td>-0.31 ± 0.74 (−12 ± 29)</td>
<td>-0.34 ± 0.85 (−13 ± 33)</td>
<td>-0.61 ± 0.80 (−24 ± 31)</td>
</tr>
<tr>
<td><strong>Triglyceride Levels, mmol/L (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.38 ± 0.37 (53 ± 14)</td>
<td>1.34 ± 0.26 (52 ± 10)</td>
<td>1.34 ± 0.31 (52 ± 12)</td>
<td>1.23 ± 0.31 (47 ± 12)</td>
<td>1.31 ± 0.32 (51 ± 12)</td>
</tr>
<tr>
<td>Week 6</td>
<td>1.37 ± 0.39 (53 ± 15)</td>
<td>1.36 ± 0.26 (52 ± 10)</td>
<td>1.35 ± 0.29 (52 ± 11)</td>
<td>1.34 ± 0.30 (52 ± 12)</td>
<td>1.42 ± 0.44 (55 ± 17)</td>
</tr>
<tr>
<td>Change</td>
<td>-0.01 ± 0.21 (−0.5 ± 8.3)</td>
<td>0.01 ± 0.21 (0.5 ± 8.1)</td>
<td>0.01 ± 0.16 (0.5 ± 6.3)</td>
<td>0.11 ± 0.19 (4.4 ± 7.2)</td>
<td>0.11 ± 0.24 (4.3 ± 9.1)</td>
</tr>
</tbody>
</table>

*All treatment groups had similar lipid levels at baseline. Values for low-density lipoprotein (LDL) cholesterol, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels are mean ± SD; for triglyceride levels, median ± SD.
†Values for the placebo group did not change significantly from baseline for any lipid parameter.
‡Mean change from baseline was significantly different among treatment groups (P < .001).
§Significant change from baseline (P < .05).
¶Significant change from baseline (P < .001).
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All dosages of colesevelam were generally well tolerated. There was no statistically significant difference across treatment groups in the number of patients who experienced adverse events caused by colesevelam treatment (placebo, 41% [12/29]; 1.5-g/d colesevelam, 40% [12/30]; 2.25-g/d colesevelam, 53% [16/30]; 3.0-g/d colesevelam, 52% [16/31], and 3.75-g/d colesevelam, 55% [16/29]). The most common side effects were those that occurred in the body as a whole (ie, infection). The digestive system was the area with the second most frequent reports of adverse events; flatulence and constipation were the most common complaints (Table 3). There were no statistically significant differences among treatment groups for the incidence of gastrointestinal adverse events, with the exception of diarrhea, which was reported by 3 patients in the 2.25-g/d colesevelam group only. Four (2.7%) of 149 patients left the study because of digestive system adverse events (1 from the 2.25-g/d colesevelam group because of diarrhea and gas, 2 from the 3.0-g/d colesevelam group because of constipation, and 1 from the 3.75-g/d colesevelam group because of stomach burning).

There were no clinically significant changes from baseline to the end of treatment in serum chemistry parameters. In general, the change from baseline for indicators of kidney and liver function did not differ among treatment groups, with the exception of a non–dose-related alkaline phosphatase response. Mean ± SD alkaline phosphatase levels increased by 6.81 ± 11.06 U/L (P < .001) from baseline levels of 67.37 ± 22.07 U/L and 70.35 ± 22.20 U/L for the 1.5- and 3.0-g/d colesevelam groups, respectively. In the group receiving the highest dosage of colesevelam (3.75 g/d), alanine aminotransferase and aspartate aminotransferase levels were elevated by 8.61 ± 11.06 U/L (P < .001) and 3.41 ± 6.84 U/L (P = .02) from baseline levels of 18.52 ± 7.79 U/L and 18.14 ± 4.71 U/L, respectively, but remained within the normal range. There were no clinically significant changes noted for hematologic parameters, serum levels of vitamins A and E, prothrombin time, partial thromboplastin time, estradiol levels, body weight, pulse, and systolic and diastolic blood pressure throughout the course of the trial. Physical examination following treatment revealed little change from baseline assessment.

In this randomized, double-blind, placebo-controlled trial, colesevelam treatment administered at dosages of 1.5 g/d,

### Table 3. Gastrointestinal Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 29)</th>
<th>1.5 g/d (n = 30)</th>
<th>2.25 g/d (n = 30)</th>
<th>3.0 g/d (n = 31)</th>
<th>3.75 g/d (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>6 (20)</td>
<td>7 (23)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Anorexia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Eructation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>0 (0)</td>
<td>1 (3)</td>
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<td>Tooth disorder</td>
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*Values are No. (%).
†Significantly different between treatment groups (P = .03).

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2.25 g/d, 3.0 g/d, and 3.75 g/d produced dosage-related reductions of total and LDL cholesterol concentrations in patients with moderate hypercholesterolemia. Colesevelam treatment at 3.75 g/d resulted in a 19% decrease in LDL cholesterol levels, which is similar to the responses produced by standard dosages of other bile acid sequestrants.19–24 The currently available bile acid sequestrants, cholestyramine and colestipol hydrochloride, are generally administered as packets to reach dosages of 24 or 30 g/d, respectively. Thus, colesevelam treatment appears to have greater potency than these other bile acid sequestrants.

Although the LDL cholesterol response was dosage-dependent (ie, LDL cholesterol levels were reduced with each increase in the dosage of colesevelam), there seemed to be increased efficacy per gram of colesevelam at the highest dosage. This increased efficacy differs from the type of nonlinear response that is seen with most other bile acid sequestrants. Typically, there is proportionally less additional LDL cholesterol lowering with increased dosages.25 This may be a chance finding owing to the relatively small sample size in the study, or it may be indicative of the recruitment of additional cholesterol-lowering mechanisms at the highest dosage. Alternatively, the dosages used in the present study may not have all fallen in a linear portion of the dosing curve.

The response of other lipoprotein fractions to colesevelam treatment was similar to that observed with other bile acid sequestrants. Effects on HDL cholesterol levels have varied among studies but generally exhibit a slight increase of 3% to 8%.20,21,23,29 This is consistent with other bile acid sequestrants.19–24 The currently available bile acid sequestrants, cholestyramine and colestipol hydrochloride, are believed not to represent toxic effects but rather to be secondary to changes in lipid metabolism, such as increased bile acid synthesis and excretion.30 Surprisingly, levels of vitamin E, which is carried in the LDL fraction, were not reduced along with LDL cholesterol levels. Results from longer studies of colesevelam therapy will likely provide additional information regarding this apparent anomaly.

In order to avoid the adverse events that lead to poor compliance with bile acid sequestrant therapy, smaller dosages are often used in combination with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, probucol, fibrates, or nicotinic acid, resulting in LDL cholesterol level reductions as large as 60%.6,7,13,22,31,37,38 Although the increased complexity of the dosage regimen may also reduce compliance, it is particularly effective because bile acid sequestrants and HMG CoA reductase inhibitors have nonlinear dosage response curves.25 Proportionally less additional LDL cholesterol level lowering is realized with the increased dosage of a single drug.25–28 Combination therapy is an important strategy for optimizing the effectiveness of drug therapy to achieve LDL cholesterol level goals.25 In fact, unpublished data from a study comparing combination therapy of low-dose Cholestal gel and lovastatin with either drug therapy alone showed an additive effect on LDL cholesterol level reduction with the combination regimen.

Since publication of the LRC-CPPT results, and more recently the Cholesterol Lowering Atherosclerosis Study6,37 and the Familial Atherosclerosis Treatment Study,7 it is clear that bile acid sequestrant therapy, alone and in combination with other agents, is effective for reducing cholesterol levels as well as cardiac morbidity and mortality. Although the lipid-lowering effects of colesevelam therapy were relatively modest and less than those expected with HMG CoA reductase inhibitor therapy, they represent a beneficial response in terms of CHD risk reduction. It is estimated that approximately 52 million people have at least mild hypercholesterolemia and would benefit from lipid-lowering therapy. For the vast majority of persons with hypercholesterolemia, LDL cholesterol level reductions of 15% to 25% with diet and bile acid sequestrant therapy would be adequate to reach their NCEP LDL cho-
olesterol level goal. In
the LRC-CPPT, total and LDL cho-
esterol level reductions of 8% and 12%, respec-
tively, beyond the effects of diet restrictions and relative to placebo produced a 19% decrease in risk for CHD death and/or non-
fatal myocardial infarction.

Colestevam therapy may offer an alternative to other bile acid sequestrants and systemic lipid-lowering drugs for individuals requiring moderate (≤20%) LDL cho-

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