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 after 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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Elevated serum concentrations of cholesterol, particularly low-density lipoprotein (LDL) cholesterol, constitute a risk factor for the development of coronary heart disease (CHD). A direct correlation exists between hypercholesterolemia and cardiovascular disease mortality and morbidity. Clinical trials have demonstrated that aggressive reduction of lipid levels reduces this risk in patients with and without CHD. In fact, each 1% reduction of LDL cholesterol lowers the risk of CHD by 2%. Diet and lifestyle interventions are generally the first steps taken toward reducing lipid levels but often have small and inconsistent effects. Therefore, pharmacological measures are necessary for those patients who continue to have elevated lipid levels following diet and lifestyle changes. Bile acid sequestrants interrupt the enterohepatic circulation of bile acids by binding with them in the intestine to form an insoluble complex that is excreted in the feces. The depletion of the bile acid pool alters hepatic cholesterol homeostasis, producing an increase in surface-active LDL receptors and decreased serum cholesterol levels. The safety and lipid-lowering efficacy of cholestyramine resin and colestipol hydrochloride, 2 of the most commonly prescribed bile acid sequestrants, which have been in use for over 20 years, have been demonstrated repeatedly. Bile acid sequestrants alone reduce LDL cholesterol concentrations by 10% to 30%. Combination therapy of bile acid sequestrants with niacin or lovastatin produces even larger LDL cholesterol reductions of up to 60%.
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 Cholesterol* and *The 2D Food Portion Visual*. 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. Despite their proven efficacy and the lack of systemic effects caused by nonabsorption in the gastrointestinal tract, the bile acid sequestrants that are currently available have a high drug discontinuance rate caused, in part, by gastrointestinal side effects. Constipation occurs in up to 39% of patients taking currently available bile acid sequestrants; in severe cases, it may lead to fecal impaction. Other gastrointestinal side effects, such as gas, bloating, flatulence, and cramping, also occur in a large percentage of patients who are treated with currently available bile acid sequestrants. Therefore, an effective cholesterol-lowering agent with a non-systemic mechanism of action and greater tolerability than currently available bile acid sequestrants would be a useful option for hypercholesterolemia treatment. Each 400-mg capsule of Cholestagel (GelTex Pharmaceuticals Inc, Waltham, Mass) contains 375 mg of anhydrous colesevelam hydrochloride and 1% magnesium stearate. Colesevelam hydrochloride is a nonabsorbed polymer (water-absorbing hydrogel) that has been specifically engineered to bind to bile acids. It is a polyallylamine cross-linked with epichlorohydrin and alkylated with 1-bromodecane and 6-bromohexyltrimethylammonium bromide (Figure 1). Colesevelam has been found to have a high affinity 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 nonsweetened 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 SmithKline 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 (adverse event [n = 2], withdrawal of consent after randomization [n = 2], and non-compliance [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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**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>
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<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>
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<td></td>
<td></td>
</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>
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<td>Black</td>
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<td>3 (10)</td>
<td>6 (21)</td>
<td>4 (13)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hispanic</td>
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<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 covariation, 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 high 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, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels from baseline (week 0) to the end of treatment (week 6) in patients who received placebo or colesevelam hydrochloride therapy. Cholesterol values are means; TG values are medians. Mean percentage changes in LDL cholesterol levels were significantly different among treatment groups (P<.001). Significant change from baseline (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>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>
</tbody>
</table>

**Note:** 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).

**Figure 2.** Percentage change in total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride (TG) levels from baseline (week 0) to the end of treatment (week 6) in patients who received placebo or colesevelam hydrochloride therapy. Cholesterol values are means; TG values are medians. Mean percentage changes in LDL cholesterol levels were significantly different among treatment groups (P<.001).
High-density lipoprotein cholesterol levels did not differ across treatment groups at the end of treatment (Table 2). However, HDL cholesterol levels significantly increased by approximately 0.10 mmol/L (4 mg/dL) in the 3.0-g/d and 3.75-g/d colesevelam groups (11.2%, P = .006, and 8.1%, P = .02, respectively). Median TG concentrations did not differ significantly across treatment groups, nor was there any significant change from baseline in TG levels within any group (Table 2).

SAFETY

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) and 4.92 ± 6.44 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 6.81 ± 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.

COMMENT

In this randomized, double-blind, placebo-controlled trial, colesevelam treatment administered at dosages of 1.5 g/d, 2.25 g/d, 3.0 g/d, and 3.75 g/d resulted in a decrease in low-density lipoprotein cholesterol levels without a significant increase in high-density lipoprotein cholesterol levels.
data further suggests that compliance with bile acid sequestrants is likely to be even lower in nonresearch settings. In the present study, overall compliance with colesevelam treatment was very high (93%), which reflects its low incidence of intolerable side effects. Although this study period was shorter (6 weeks) than in some previous reports, side effects have typically been found to be more severe in the early stages of trials, when the gastrointestinal tract attempts to adjust to a nonabsorbable bile acid sequester. Thus, long-term compliance with colesevelam therapy would be expected to remain high.

Laboratory parameters were largely unchanged except for statistically but not clinically significant increases in alkaline phosphatase levels in the 1.5- and 3.0-g/d colesevelam groups and increases in aspartate aminotransferase and alanine aminotransferase levels in the 3.75-g/d colesevelam group. These alterations have been reported with use of other bile acid sequestrants and 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. 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 sequester therapy, smaller doses 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%. 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. Proportionally less additional LDL cholesterol level lowering is realized with the increased dosage of a single drug. Combination therapy is an important strategy for optimizing the effectiveness of drug therapy to achieve LDL cholesterol level goals. In fact, unpublished data from a study comparing combination therapy of low-dose Cholestegel 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-CPTT results, and more recently the Cholesterol Lowering Atherosclerosis Study and the Familial Atherosclerosis Treatment Study, it is clear that bile acid sequester 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 cholesterol level reductions of 8% and 12%, respectively, 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.

Colesevlam therapy may offer an alternative to other bile acid sequestrants and systemic lipid-lowering drugs for individuals requiring moderate (≤20%) LDL cholesterol level reduction and has the potential for use in combination therapy. There is a large population of persons with mild to moderate hypercholesterolemia for whom NCEP guidelines recommend bile acid sequestrants as first-line therapy. However, primarily because of gastrointestinal side effects, treatment is frequently discontinued, and the hypercholesterolemia either goes untreated or is treated with a systemic drug. Colesevlam therapy may achieve beneficial lipid reductions with very few of the unpleasant gastrointestinal side effects associated with other bile acid sequestrants or the possible systemic toxic effects experienced with absorbed lipid-altering agents.

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