Effects of Policosanol on Borderline to Mildly Elevated Serum Total Cholesterol Levels: A Prospective, Double-Blind, Placebo-Controlled, Parallel-Group, Comparative Study

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ABSTRACT

Background: Hypercholesterolemia is a major risk factor for coronary heart disease. Clinical studies have shown that lowering elevated serum cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), is beneficial for patients with borderline to mildly elevated serum total cholesterol (TC) levels (5.0–6.0 mmol/L). Policosanol is a cholesterol-lowering drug made from purified sugar cane wax. The therapeutic range of policosanol is 5 to 20 mg/d.

Objective: This study investigated the efficacy and tolerability of policosanol 5 mg/d in patients with borderline to mildly elevated serum TC levels.

Methods: This 14-week, single-center, prospective, double-blind, placebo-controlled, parallel-group, comparative study was conducted in men and women aged 25 to 75 years with a serum TC level ≥ 4.8 to < 6.0 mmol/L. After a 6-week run-in period in which patients were placed on therapeutic lifestyle changes, in particular a cholesterol-lowering diet, patients were randomly assigned to receive policosanol 5-mg tablets or placebo tablets once daily with the evening meal for 8 weeks, and the diet was continued throughout the study. Lipid profile variables, safety indicators, adverse events (AEs), and compliance with study medications were assessed.

Results: One hundred patients (71 women, 29 men; mean [SD] age, 52 [10] years) entered the study after the dietary run-in period. After 8 weeks of treatment, the mean (SD) serum LDL-C level decreased significantly in the policosanol group ($P < 0.001$ vs baseline and placebo) from 3.57 (0.30) mmol/L to 2.86 (0.41) mmol/L (change, -19.9%). Significantly more patients in the policosanol group

(42 patients [84%]) achieved a $\geq 15\%$ decrease in serum LDL-C than in the placebo group (2 patients [4%]) ($P < 0.001$). Also in the policosanol group, the mean (SD) serum TC level decreased significantly, from 5.20 (0.22) mmol/L to 4.56 (0.44) mmol/L ($P < 0.001$ vs baseline and placebo) (change, -12.3%); the mean (SD) triglyceride (TG) level decreased significantly, from 1.59 (0.57) mmol/L to 1.48 (0.57) mmol/L ($P < 0.01$ vs baseline; $P < 0.05$ vs placebo) (change, -6.9%); and the mean (SD) high-density lipoprotein cholesterol (HDL-C) level increased significantly from 1.05 (0.18) mmol/L to 1.16 (0.21) mmol/L ($P < 0.001$ vs baseline and placebo) (change, $+10.5\%$). The percentage changes were significantly different between the policosanol and placebo groups for serum LDL-C, TC, and HDL-C levels ($P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively), but not for TG. In the placebo group, changes in lipid profile variables from baseline were not significant. Policosanol did not significantly impair any safety indicator and was well tolerated. Three patients (3%) (1 patient [2%] in the policosanol group; 2 patients [4%] in the placebo group) withdrew from the trial, none because of AEs. Two patients (1 patient [2%] each in the policosanol and placebo groups) withdrew from the study because of an unwillingness to return for follow-up; 1 patient (2%) in the placebo group had a change of address and could not be followed up. Overall, 4 patients (4%) (1 patient [2%] in the policosanol group; 3 [6%], placebo) reported AEs; all were mild. Of the patients who received placebo and reported AEs, all 3 (6%) experienced heartburn, and 1 (2%) also experienced dry skin, while the policosanol-treated patient (2%) who reported an AE experienced headache.

Conclusions: In this study of patients with borderline to mildly elevated serum TC levels, based on the criterion that $\geq 70\%$ of policosanol-treated patients reached the LDL-C goal of a decrease $\geq 15\%$ from baseline whenever this proportion was different with respect to placebo, 8 weeks of treatment with policosanol 5 mg/d was effective. The decreased LDL-C, TC, and TG levels, increased HDL-C level, and good tolerability found with this treatment support its use in such patients. (*Curr Ther Res Clin Exp.* 2003;64:522–537) Copyright © 2003 Excerpta Medica, Inc.

Key words: policosanol, hypercholesterolemia, cholesterol-lowering drugs, borderline dyslipidemia.

INTRODUCTION

Elevated total cholesterol (TC) and particularly, low-density lipoprotein cholesterol (LDL-C) levels are major risk factors for coronary heart disease (CHD).^{1–3} Clinical studies^{2–8} have shown that lowering LDL-C reduces morbidity and mortality in the primary and secondary prevention of CHD.

Reducing serum LDL-C below a specific level (≤ 3.37 mmol/L) is the primary goal in the management of hypercholesterolemia. The use of therapeutic lifestyle changes (TLCs), including adherence to the National Cholesterol Education

Program (NCEP) Step I cholesterol-lowering diet, smoking cessation, and any type of systematic physical exercise, is the first-line therapy for hypercholesterolemia.⁹⁻¹¹ Adherence to TLCs allows many individuals, mainly those with borderline or mildly elevated LDL-C (3.4–4.0 mmol/L) and TC (5.0–6.0 mmol/L) levels, to achieve the desired serum levels of these lipids.⁹ Nonetheless, in many individuals with mildly elevated TC but ≥ 2 nonlipid risk factors (eg, a family history of CHD, postmenopausal status, arterial hypertension) or who are in the secondary prevention stage, the use of TLCs alone usually is not sufficient to achieve the targets because more restricted goals are recommended for these patients. Thus, in both cases, LDL-C is the only lipid with a specific therapeutic goal (< 3.0 mmol/L for diabetic patients and those undergoing secondary prevention; < 3.4 mmol/L in patients with mild or moderate hypercholesterolemia and with ≥ 2 concomitant nonlipid risk factors).^{9,11} Cholesterol-lowering drugs in addition to TLCs may be required to achieve these patients' lipid goals.⁹⁻¹¹ Additional benefits can be obtained by increasing the serum high-density lipoprotein cholesterol (HDL-C) level or reducing the triglyceride (TG) level.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are considered first-line therapy for hypercholesterolemia,^{12,13} with the starting dose dependent on the severity of hypercholesterolemia. In patients with mildly or even moderately increased levels of LDL-C (< 3.4 mmol/L) and TC (5.0– < 7.8 mmol/L), low or standard doses of statins usually are prescribed initially, and higher doses rarely are necessary. With statins, dose adjustment generally is recommended after 6 weeks of therapy. Although statins are generally well tolerated, they are associated with some adverse events (AEs), with gastrointestinal disturbances and increased liver aminotransferase activities being the most common, and muscle-related AEs occurring less frequently but having more serious consequences, such as rhabdomyolysis.^{14,15} Because cholesterol-lowering drug therapy also may be suitable for patients with mildly elevated serum TC levels, especially those at high risk for CHD, the search for lipid-lowering drugs that are as effective as low-dose statins but with a better tolerability profile is justified.

Policosanol is a cholesterol-lowering drug composed of a mixture of high-aliphatic primary alcohols purified from sugar cane (*Saccharum officinarum*, L.) wax.^{16,17} This drug has proven cholesterol-lowering efficacy in type II hypercholesterolemia¹⁸⁻²⁵ and dyslipidemia secondary to type 2 diabetes mellitus.^{26,27} Policosanol inhibits cholesterol biosynthesis between acetate consumption and mevalonate production^{28,29} through the indirect regulation of HMG-CoA reductase activity.³⁰ Policosanol increases LDL receptor-dependent processing,²⁸ enhancing the catabolic rate of LDL.²⁹ Clinical trials¹⁸⁻²⁷ and postmarketing studies^{31,32} have shown that policosanol is well tolerated. The therapeutic range of policosanol is 5 to 20 mg/d.

Previous studies of the short- and long-term effects of policosanol have been conducted in populations with hypercholesterolemia ranging from mild (TC 5.0

and <6.1 mmol/L) to severe ($TC \geq 7.8$ mmol/L).^{18–27} Most of the patients included in these studies had moderate hypercholesterolemia ($TC \geq 6.1$ and <7.8 mmol/L), whereas patients with mild hypercholesterolemia have not been included in some studies due to the limits of inclusion criteria ($TC \geq 6.1$ mmol/L).

The present study was undertaken to investigate the efficacy and tolerability of policosanol 5 g/d in patients with borderline to mildly elevated serum TC levels. The primary efficacy variable was the decrease in LDL-C to the individual patient's goal level, with treatment efficacy defined as a decrease in LDL-C $\geq 15\%$ from baseline, whenever this proportion was different with respect to placebo.

PATIENTS AND METHODS

This 14-week, prospective, double-blind, randomized, placebo-controlled, parallel-group, comparative study was conducted at the Medical Surgical Research Center (Havana, Cuba). The patients were enrolled at the Veterans' House of Plaza Zone (Havana, Cuba) on a voluntary basis; they did not receive compensation for their participation in the study. The independent ethics committee of the Medical Surgical Research Center approved the study protocol.

Patients

Men and women aged 25 to 75 years with documented borderline to mildly elevated serum TC levels (5.0–6.0 mmol/L) were eligible for the study. After a 6-week, diet-only run-in period, patients with $TC \geq 4.8$ to <6.0 mmol/L were enrolled. The lower limit (4.8 mmol/L) was chosen to avoid eliminating an excessive number of patients because TC tended to decrease with diet during the run-in period. Patients also were required to have a serum TG level <4.52 mmol/L after the run-in period.

Patients with active renal disease, neoplastic disease, severe hypertension (diastolic blood pressure [DBP] ≥ 120 mm Hg), and uncontrolled diabetes mellitus (serum glucose level >7.5 mmol/L) were excluded from the study. Patients with a history of myocardial infarction, stroke, or coronary surgery within the 3 months prior to the study also were excluded. Pregnant, possibly pregnant, or breastfeeding patients were not included. Female patients of childbearing age were required to use an effective method of birth control throughout the study. All patients provided written consent to participate.

Methods

This study included 4 visits (recruitment, treatment assignment, interim, and final follow-up). At recruitment (visit 1), a complete medical history was taken, and patients entered a 6-week run-in period during which they were to discontinue all existing lipid-lowering therapy and incorporate TLCs (NCEP Step I diet and recommendations to stop smoking and be as physically active as possible [although no formal exercise program was recommended]) into their

lifestyles. This diet consisted of a daily consumption of cholesterol <300 mg/d and a daily intake of total fat (saturated, polyunsaturated, and monounsaturated fatty acids), 8% to 10%; carbohydrates, $\geq 55\%$; and protein, $\sim 15\%$ of total calories (ie, those needed to maintain a desirable body weight).^{9,10} These TLCs were continued throughout the study.

After run-in, laboratory lipid profile (LDL-C, TC, HDL-C, TG) and tolerability indicators (physical: body weight, heart rate, systolic and diastolic BP [SBP and DBP, respectively]; biochemical: alanine and aspartate aminotransferase activities [ALT and AST, respectively], and serum glucose and creatinine levels) were determined. At visit 2 (treatment assignment), eligible patients were randomized, under double-blind conditions, to receive policosanol 5 mg or placebo tablets, once daily with the evening meal for 8 weeks. Study medications were given in identical packages identified by a code number and the treatment number assigned successively. Patients were randomized in balanced groups (1:1) of 6 using an independent computer-determined method.

After therapy, patients returned for interim and final follow-up visits (visits 3 and 4, respectively), the interval between which was 1 week. Patients underwent physical examination at all 4 visits; laboratory analysis was performed at visits 2 and 4. Compliance with treatment and diet, as well as AEs, were assessed at visits 3 and 4.

The placebo group was included as a parallel control to detect any systematic bias due to adherence to lifestyle in both groups, any change in concomitant medications, or any other factor that could induce a systematic change in any study variable. The placebo group also was included because few data regarding the efficacy of policosanol in mild hypercholesterolemia are available, and no study had previously been conducted in such a specific subset of patients (ie, patients with borderline to mildly elevated TC levels), according to a MEDLINE search of studies published from 1991 to 2002 and including the key term *policosanol*. Because all patients were following the TLC regimen and treatment duration was short, patients receiving placebo were not at increased risk for complications, including myocardial infarction, angina pectoris, stroke or transient ischemic attacks, compared with run-in, when they were following the lipid-lowering dietary regimen.

Efficacy Analysis

Change in serum LDL-C level was the primary efficacy variable. Treatment was considered effective only if $\geq 70\%$ of patients treated with policosanol achieved LDL-C reductions $\geq 15\%$ from baseline, whenever this percentage was different with respect to placebo.³³ In addition, this criterion was corroborated if $\geq 70\%$ of treated patients reached LDL-C goals defined by expert guidelines⁹⁻¹¹ according to their overall risk for CHD, which depends not only on serum TC and LDL-C levels, but also on the presence of other concomitant nonlipid risk factors, such as a history of CHD, cerebrovascular or peripheral atherosclerotic diseases, arterial hypertension, diabetes mellitus, smoking, male sex and age

>45 years, postmenopausal status, obesity (body mass index ≥ 30 kg/m²), and a family history of early onset CHD. Changes in other lipid profile values were secondary efficacy variables.

Tolerability Analysis

Data from the physical examinations, laboratory tests, and interviews to assess AEs were used in the analysis of drug tolerability. Physical tolerability indicators included body weight, heart rate, and blood pressure. Biochemical tolerability indicators included measurements of serum ALT and AST activities and serum glucose and creatinine levels.

AEs were recorded on case-report forms, and information from spontaneous reports of AEs between visits was added. We recorded both AEs that developed during the study and those that reflected worsening of symptoms that had existed before the study. Death and disabling events that led to or prolonged hospitalization were defined as *serious*. Events requiring discontinuation of therapy (based on the judgment of the physician) and/or specific treatment were considered *moderate*. Events that did not require discontinuation of the study drug and/or specific treatment were classified as *mild*. AEs also were classified as *unlikely*, *doubtfully*, *possibly*, or *probably drug related*.

Laboratory Analysis

Blood samples were drawn between 8:00 AM and 8:30 AM after a 12-hour fast, and aliquots were taken for laboratory assessment. Serum TC and TG levels were determined by enzymatic methods using reagent kits (F. Hoffmann-La Roche Ltd., Basel, Switzerland). Serum HDL-C levels were determined according to the cholesterol content present in the supernatant obtained after beta-lipoprotein precipitation.³⁴ LDL-C values were calculated using the Friedewald equation.³⁵ Blood sampling and analysis were performed by laboratory technicians at the study center.

Laboratory tolerability indicators were determined using routine enzymatic laboratory tests and reagent kits. All laboratory tests were performed using the Hitachi 719 autoanalyzer (Hitachi, Tokyo, Japan) located at the laboratory of the Medical Surgical Research Center.

Systematic quality control was performed by quality-assurance personnel throughout the study. Precision was assessed according to repeatability (*r*) (within-day variations) and reproducibility (*R*) (between-day variations); accuracy was assessed against standard references. The coefficients of variations were as follows: TC, *r* = 2.5 and *R* = 2.9; HDL-C, *r* = 3.0 and *R* = 3.5; and TG, *r* = 3.7 and *R* = 4.0. The variations from the standard reference were <4% for TC and <5% for TG. The assay bias was constant throughout the trial.

Compliance Assessment

Compliance with study medications was assessed using tablet count, patient interviews, and a chart on which patients were instructed to record their

medication consumption each day. Compliance was considered as *good* or *very good* if the patient consumed at least 90% or 95%, respectively, of the tablets that were to have been taken since the previous visit. Compliance with dietary recommendations was assessed using patient menus, patient interviews, and body weight measurement; compliance with exercise and smoking cessation was assessed using patient interviews.

Statistical Analysis

All data were analyzed by the intent-to-treat approach (ie, analyses included all patients as randomized). For the primary efficacy variable, we assumed that policosanol 5 mg/d would show a difference in LDL-C reduction of $\geq 15\%$ compared with placebo. Based on an 80% power and a 5% significance level, a sample size of 90 patients was considered sufficient. Allowing for an estimated withdrawal rate of 10%, at least 100 patients had to be recruited.

Comparisons of continuous variables were performed using nonparametric methods because the normal distribution of lipid variables had not been proved. For within-group comparisons of continuous variables, we used the Wilcoxon signed rank test for paired samples, and for between-group comparisons, we used the Mann-Whitney *U* test. After determining significance using these tests, we corroborated the results with dependent (within-group comparison) and independent (between-group comparison) *t* tests. For the lipid profile variables, we compared absolute actual values (in mmol/L) and mean percentage changes obtained after determining the percentage change for each patient. Comparisons of categorical variables were performed using the Fisher exact test. All tests were 2-tailed. A value of $\alpha = 0.05$ was considered significant. Statistical analyses were performed using Statistica® version 4.2 (StatSoft®, Inc., Tulsa, Oklahoma).

RESULTS

Baseline Characteristics

One hundred patients were enrolled in the study (71 women, 29 men; mean [SD] age, 52 [10] years), and 97 (97%) completed it. The 2 treatment groups were similar with respect to baseline characteristics (Table I). The patients showed a high frequency of nonlipid risk factors for CHD, including a family history of CHD (40 patients [40%]), postmenopausal status (38 patients [38%]), arterial hypertension (37 patients [37%]), and, for men, age >45 years (16 patients [16%]). Although all patients' TC levels were only borderline to mildly elevated, the prevalence of CHD among the study population was relatively high (18 patients [18%]). Use of concomitant therapy was relatively high (52 patients [52%]) and was consistent with the patients' concomitant nonlipid risk factors. Hence, diuretics, calcium antagonists, and antiplatelet agents were the 3 drug classes most frequently used during the study (15 [15%], 14 [14%], and 12 patients [12%], respectively).

Table I. Baseline characteristics of study patients (N = 100).^{*} (Values are expressed as no. [%] of patients unless otherwise noted.)

Characteristic	Placebo (n = 50)	Policosanol (n = 50)
Age, y		
Mean (SD)	52 (11)	52 (9)
Range	32–75	30–75
Sex		
Women	34 (68)	37 (74)
Men	16 (32)	13 (26)
BMI, mean (SD), kg/m ²	25.4 (3.5)	25.9 (4.7)
Nonlipid risk factors		
Family history of CHD	22 (44)	18 (36)
Postmenopausal women	18 (36)	20 (40)
Arterial hypertension	18 (36)	19 (38)
History of CHD	9 (18)	9 (18)
Men aged >45 years	9 (18)	7 (14)
Smokers	6 (12)	5 (10)
Diabetes mellitus	5 (10)	4 (8)
Stroke	1 (2)	2 (4)
Concomitant medications [†]	25 (50)	27 (54)
Diuretic drug	7 (14)	8 (16)
Calcium channel blocker	7 (14)	7 (14)
Antiplatelet drug	6 (12)	6 (12)
Muscle relaxant drug	5 (10)	3 (6)
ACE inhibitor	3 (6)	4 (8)
Anxiolytic drug	3 (6)	4 (8)
Nitrate vasodilator	3 (6)	2 (4)
Beta-blocker	2 (4)	3 (6)
Oral hypoglycemic drug	2 (4)	2 (4)
Neuroleptic drug	2 (4)	0 (0)
Digitalis	1 (2)	1 (2)

BMI = body mass index; CHD = coronary heart disease; ACE = angiotensin-converting enzyme.

^{*}No statistically significant between-group differences were found.

[†]Includes only those drugs consumed by ≥ 2 patients.

Efficacy

The values of the lipid profile variables at baseline and after 8 weeks of treatment are shown in [Table II](#). The 2 groups had similar profiles at baseline. In the policosanol group, the mean (SD) serum LDL-C level was decreased significantly from 3.57 (0.30) mmol/L to 2.86 (0.41) mmol/L ($P < 0.001$ vs baseline and placebo) (change, -19.9%). Also in the policosanol group, the mean (SD) serum TC level decreased significantly from 5.20 (0.22) mmol/L to 4.56 (0.44) mmol/L ($P < 0.001$ vs baseline and placebo) (change, -12.3%), and the mean (SD) TG level decreased significantly, from 1.59 (0.57) mmol/L to 1.48 (0.57) mmol/L ($P < 0.05$ vs placebo and $P < 0.01$ vs baseline) (change, -6.9%). In addition,

Table II. Lipid profile of patients with type II hypercholesterolemia at baseline and after 8 weeks of treatment with policosanol 5 mg/d (n = 39) or placebo (n = 38).

Component/Treatment	Normal Value	Baseline	Week 8	% Change
LDL-C, mmol/L	1.55–3.37			
Policosanol				
Mean (SD)		3.57 (0.30)	2.86 (0.41)*†	–19.9‡
95% CI		3.49–3.64	2.74–2.98	–
Placebo				
Mean (SD)		3.51 (0.31)	3.55 (0.40)	+1.1
95% CI		3.42–3.60	3.43–3.67	–
TC, mmol/L	<5.17			
Policosanol				
Mean (SD)		5.20 (0.22)	4.56 (0.44)*†	–12.3‡
95% CI		5.14–5.27	4.43–4.69	–
Placebo				
Mean (SD)		5.16 (0.24)	5.22 (0.35)	+1.1
95% CI		5.09–5.23	5.11–5.32	–
HDL-C, mmol/L	Men, 0.91–1.68; women, 0.91–2.07			
Policosanol				
Mean (SD)		1.05 (0.18)	1.16 (0.21)*†	+10.5‡
95% CI		1.00–1.10	1.10–1.22	–
Placebo				
Mean (SD)		1.07 (0.17)	1.07 (0.15)	0.0
95% CI		1.02–1.12	1.02–1.11	–
TG, mmol/L	0.11–2.15			
Policosanol				
Mean (SD)		1.59 (0.57)	1.48 (0.57)‡§	–6.9
95% CI		1.43–1.76	1.31–1.64	–
Placebo				
Mean (SD)		1.57 (0.49)	1.62 (0.47)	+3.2
95% CI		1.43–1.71	1.49–1.76	–

LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

* $P < 0.001$ versus baseline (Wilcoxon test for paired samples).

† $P < 0.001$ versus placebo (Mann Whitney *U* test).

‡ $P < 0.05$ versus placebo (Mann Whitney *U* test).

§ $P < 0.01$ versus baseline (Wilcoxon test for paired samples).

mean (SD) HDL-C increased significantly from 1.05 (0.18) mmol/L to 1.16 (0.21) mmol/L ($P < 0.001$ vs baseline and placebo) (change, +10.5%). Changes in lipid variables in the placebo group were small and nonsignificant. Percentage changes in serum LDL-C, TC, and HDL-C levels were significantly different between groups ($P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively), but not for TG.

The frequency with which patients in the policosanol group achieved a decrease in serum LDL-C $\geq 15\%$ compared with baseline (42/50, 84%) was significantly greater than that in the placebo group (2/50, 4%) ($P < 0.001$). In addition, 45 of 50 policosanol-treated patients (90%) reached the LDL-C goals according to their risk status, a frequency significantly greater than that of the patients in the placebo group (16/50, 32%) ($P < 0.01$).

Tolerability

Policosanol was well tolerated; none of the physical or biochemical indicators of tolerability were negatively affected (Table III). SBP and DBP were not significantly different between the 2 groups, including the values in the subgroup of

Table III. Tolerability indicators at baseline and after 8 weeks of treatment with policosanol 5 mg/d (n = 50) or placebo (n = 50).

Tolerability Indicator/Treatment	Normal Value	Baseline	Week 8
Physical			
Body weight, mean (SD), kg	–		
Policosanol		68.95 (14.18)	68.84 (14.00)
Placebo		68.55 (9.39)	68.78 (9.60)
HR, mean (SD), beats/min	70–100		
Policosanol		72.32 (5.91)	72.52 (5.52)
Placebo		71.40 (5.62)	71.71 (4.67)
SBP, mean (SD), mm Hg	≤ 130		
Policosanol		126.20 (12.60)	123.65 (11.19)
Placebo		126.20 (9.23)	124.69 (11.01)
DBP, mean (SD), mm Hg	≤ 90		
Policosanol		80.20 (6.54)	78.54 (6.52)
Placebo		81.50 (5.91)	81.12 (6.71)
Biochemical			
ALT, mean (SD), U/L	10.00–40.00		
Policosanol		21.36 (7.13)	19.60 (8.75)*
Placebo		22.56 (6.42)	21.39 (6.10)
AST, mean (SD), U/L	20.00–48.00		
Policosanol		21.34 (8.25)	19.77 (7.99)
Placebo		22.02 (8.21)	20.35 (5.91)
Glucose, mean (SD), mmol/L	3.90–6.10		
Policosanol		4.98 (0.83)	5.04 (0.83)
Placebo		4.71 (0.81)	4.89 (0.83)
Creatinine, mean (SD), $\mu\text{mol/L}$	53.00–106.00		
Policosanol		87.76 (14.23)	87.81 (12.96)
Placebo		91.74 (12.61)	90.20 (13.80)

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

* $P < 0.05$ versus placebo (Mann Whitney *U* test).

37 hypertensive patients (19 patients [38%] in the policosanol group; 18 [36%], placebo). The final mean ALT value in the policosanol group was significantly lower than in the placebo group ($P < 0.05$) but was not significantly different from baseline. None of the other tolerability indicators differed significantly either between groups or compared with baseline.

Three patients (1 patient [2%] in the policosanol group; 2 [4%], placebo) withdrew from the trial, but none due to AEs. Two patients (1 patient [2%] each in the policosanol and placebo groups) withdrew from the study because of an unwillingness to return for follow-up; 1 patient (2%) in the placebo group had a change of address and could not be followed up. Overall, 4 patients (4%) (1 patient [2%] in the policosanol group; 3 [6%], placebo) reported at least 1 AE; all were classified as mild. The 3 patients in the placebo group who experienced AEs reported heartburn, and 1 of them [2%] also reported dry skin, whereas the policosanol-treated patient who experienced an AE reported headache that was classified as treatment related.

Compliance

Overall, compliance with study medications was considered very good because all patients (except those who withdrew from the study) showed $\geq 95\%$ compliance with the treatment regimen since the previous visit, as documented by tablet counts, patient interviews, and control charts. However, overall compliance with diet was considered only fair because many patients (28 [56%] in the policosanol group and 25 [50%] in the placebo group) declared some dietary violations during the weekends.

DISCUSSION

On the basis of the primary efficacy variable (ie, the change in LDL-C), treatment with policosanol was effective. This study shows that policosanol (5 mg/d) administered for 8 weeks was effective in decreasing LDL-C in patients with borderline to mildly elevated serum TC values. Also, policosanol produced additional beneficial changes in the lipid profile of the patients, as the reductions in serum levels of TC and TG were accompanied by an increase in HDL-C. The effects of policosanol on LDL-C and TC levels in this study are consistent with those reported for this dose and treatment duration in populations with broad ranges of TC indicating mild to severe hypercholesterolemia.^{22,23,25,27}

Because 84% of policosanol-treated patients achieved reductions $\geq 15\%$ in serum LDL-C level and 90% achieved LDL-C goals as defined by expert guidelines,⁹⁻¹¹ the primary efficacy goal of these changes being achieved in $\geq 70\%$ of patients was met. The frequency of study patients achieving goal reductions of LDL-C was high and was comparable to that reported for highly effective statins.^{13,36} In this study, the response was greater than that found in other short-term studies^{19,21} using the same dose of policosanol. This result was probably due in part to the fact that only patients with borderline to moderate

hypercholesterolemia were included in the present study, so although policosanol induced a decrease in LDL-C similar to that in patients with higher LDL-C levels, the patients in our study needed smaller reductions to reach the goal. Also, although we included patients at secondary prevention for CHD and with other conditions indicating high risk for CHD, many of these patients had ≥ 1 concomitant nonlipid risk factor in addition to an increased serum TC level. Hence, the global CHD risk of the study population was lower than in previous studies in which most patients had multiple risk factors or were at the secondary prevention stage in addition to having hypercholesterolemia. Furthermore, in the present study 36% of patients in the placebo group reached these goals; this frequency was significantly lower than in the policosanol-treated patients but was higher than that achieved in patients with more severe hypercholesterolemia using only TLCs.

The increase in serum HDL-C level in the policosanol group was also within the expected range, although the extent of the change varied from that found in a previous study.²² This change is an additional benefit of policosanol treatment that may contribute to reducing the risk for CHD after long-term therapy. Likewise, although the effects of policosanol on TG have not been consistent in all studies, modest but significant reductions have been obtained in some,^{20,21,27} and those findings are consistent with the present results. The reduction in TG observed in this study falls within the expected range in people with normal or moderately increased TG levels.

The changes in the lipid profile in our study are similar to those reported in previous studies^{22,23,25,27} and support the use of policosanol in patients with borderline to mildly elevated serum TC levels. Studies in animals and humans have shown that policosanol has pleiotropic properties that offer additional benefits in preventing atherosclerosis and complications, such as the inhibition of platelet aggregation³⁷⁻⁴⁵ and lipid peroxidation.^{24,46} There is some concern about the use of antiplatelet agents for primary CHD prevention. Nevertheless, although policosanol dose dependently inhibits platelet aggregation, it does not affect bleeding time or coagulation parameters, which is consistent with the lack of hemorrhagic disorders associated with this therapy, even after long-term use. Furthermore, preliminary results of a recently concluded 3-year prevention study in older patients with type II hypercholesterolemia and high CHD risk conducted with policosanol 5 mg/d demonstrated the clinical benefits of the treatment.⁴⁷

In this study, the treatment groups were sufficiently similar in terms of all variables (ie, demographic, efficacy, and tolerability variables, including concomitant drug use), so that the effects described were considered drug related. Animal studies have shown that among concomitant drug therapies, policosanol exhibits interactions only with aspirin^{38,42} and beta-blockers.⁴⁸ Thus, policosanol enhances the antiplatelet and antithrombotic effects of aspirin while increasing the antihypertensive effects of beta-blockers, without modifying the decrease in heart rate induced by such drugs.⁴⁸ Because 10 of the 12 patients

taking antiplatelet agents consumed aspirin (10%; 5 patients [10%] in the policosanol group; 5 patients [10%] in the placebo group) and only 5 patients consumed dipyridamole (5%; 3 patients [6%] in the policosanol group; 2 patients [4%] in the placebo group), such conditions were well matched too, so that the influence of such interaction on the present results is negligible. Finally, because of the cholesterol-raising effects of these drugs, the negative influence of beta-blockers and diuretics on lipid-lowering drugs cannot be ignored. Nevertheless, in addition to the balanced distribution of beta-blocker use in the 2 study groups, consumption of diuretics also was similar, so that the influence of this factor also was similar in the 2 groups.

Policosanol was well tolerated, as reflected by the lack of withdrawals due to AEs. The present results also are consistent with the documented tolerability profile of policosanol.^{16–27,31,32}

CONCLUSIONS

In this study of patients with borderline to mildly elevated serum TC levels, based on the criterion that $\geq 70\%$ of policosanol-treated patients reached the LDL-C goal of a decrease $\geq 15\%$ from baseline whenever this proportion was different with respect to placebo, 8 weeks of treatment with policosanol 5 mg/d was effective. The decreased LDL-C, TC, and TG levels, increased HDL-C level, and good tolerability found with this treatment support its use in such patients. However, longer-term studies are needed.

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