Comparative lipid-lowering effects of policosanol and atorvastatin: A randomized, parallel, double-blind, placebo-controlled trial

Luigi X. Cubeddu, MD, PhD, Roberto J. Cubeddu, MD, Todd Heimowitz, DO, Beatriz Restrepo, MD, Gervasio A. Lamas, MD, and Gloria B. Weinberg, MD ***Miami Beach and Fort Lauderdale, FL***

Background Policosanol, commonly derived from purified sugar cane wax, has been reported to exert lipid-lowering effects. Policosanol is available in the United States as a nutritional supplement despite no US research clinical experience. This trial was designed to rigorously establish the lipid-lowering efficacy of policosanol as monotherapy and its potential additive and possibly synergistic effects when added to statin therapy.

Methods A randomized, parallel, double-blind, double-dummy, placebo-controlled design was used. Patients with low-density lipoprotein cholesterol (LDL-C) levels from 140 to 189 mg/dL were assigned into 1 of 4 groups to receive policosanol 20 mg, atorvastatin 10 mg, combination therapy, or placebo for 12 weeks.

Results A total of 99 patients were examined. Baseline characteristics were similar among all treatment groups. Policosanol (20 mg/d for 12 weeks) did not significantly change plasma total cholesterol, LDL-C, high-density lipoprotein cholesterol, or triglyceride levels when compared with baseline values or with values of placebo-treated patients. Atorvastatin (10 mg/d for 12 weeks) reduced total cholesterol by 27% and LDL-C by 35%. Addition of policosanol to atorvastatin failed to produce any further reduction in lipid levels above that of atorvastatin alone. Policosanol was safe and did not affect liver enzyme or creatinine phosphokinase levels.

Conclusions Policosanol did not reduce LDL-C or total cholesterol levels either alone or in combination with atorvastatin. This observation supports the need for systematic evaluation of available products containing policosanol to determine their clinical lipid-lowering efficacy under rigorous experimental conditions. We propose that policosanol should be added to the list of nutritional supplements lacking scientific validity to support their use. (Am Heart J 2006;152:982.e1-982.e5.)

According to the NCEP-ATP III, most patients with dyslipidemia require drug therapy to reach their low-density lipoprotein cholesterol (LDL-C) goal.[1] Although inhibition of hydroxymethylglutaryl coenzyme A reductase with statins is currently the preferred and most effective treatment to reduce LDL-C, the addition of a second or third agent is often needed to achieve NCEP goals.[2,3] It is particularly useful to employ combination therapy with agents that use complimentary mechanisms of action, thereby resulting in incremental reductions of LDL-C with negligible increases in adverse events.[4,5] In addition, the high cost and patient concerns regarding toxicity and adverse side effects often limit the use of statins. Therefore, the search for alternative or complementary lipid-lowering therapy as monotherapy or in combination is necessary.

Policosanol, a mixture of long-chain primary aliphatic alcohols isolated and purified from sugar cane wax (*Saccharum officinarum* L), is used in numerous countries, including the United States, as a nutritional supplement for the treatment of hypercholesterolemia.[6,7] Policosanol in doses ranging from 5 to 20 mg daily, is believed to be effective in lowering levels of total cholesterol and low-density lipoprotein, as well as raising high-density lipoprotein cholesterol (HDL-C) levels.[8,9]

The efficacy and tolerability of policosanol has been reported in animal and human models, including healthy volunteers, postmenopausal women, and patients with type II hypercholesterolemia with or without diabetes mellitus.[10-16] It has been suggested that the total cholesterol– and LDL-C–lowering effects of policosanol are dose dependent and maintained over time with maximal response after 6 to 8 weeks.[17-21] A number of

From the Division of Cardiology and Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL and Department of Pharmaceutical and Administrative Sciences, Nova Southeastern University, Fort Lauderdale, FL.
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Reprint requests: Gloria B. Weinberg, MD, Department of Internal Medicine, 4300 Alton Road, Miami Beach, FL 33140.
E-mail: g-weinberg@msmc.com
0002-8703/$ - see front matter

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Table I. Baseline patient characteristics of study groups

	Policosanol	Atorvastatin	Policosanol + atorvastatin	Placebo
n	25	25	25	24
Age (y)	50 ± 2	48.9 ± 2	45.6 ± 2	46 ± 2
F/M	14/11	13/12	13/12	14/10
BMI (kg/m^2)	26.9 ± 0.7	27.2 ± 1	27.6 ± 1	28.2 ± 1
SBP (mm Hg)	121 ± 3.2	121 ± 2.4	121 ± 2.4	117 ± 2.2
DBP (mm Hg)	77 ± 1.3	78 ± 1.4	76 ± 1.7	78 ± 1.9
FSG (mg/dL)	88 ± 2.3	93 ± 3.5	95 ± 3	91 ± 2.2
SrCr (mg/dL)	0.97 ± 0.03	0.96 ± 0.04	0.86 ± 0.04	0.92 ± 0.03
TC (mg/dL)	243 ± 3.2	253 ± 3.5	238 ± 3.9	241 ± 4.2
LDL (mg/dL)	159 ± 2.5	168 ± 2.7	155 ± 2.3	158 ± 2.5
HDL (mg/dL)	52.5 ± 2.4	53.4 ± 2.7	52.8 ± 2.7	50.8 ± 2.6
TG (mg/dL)	165 ± 15	161 ± 13	151 ± 15	160 ± 13
CRP (mg/dL)	0.17 ± 0.03	0.19 ± 0.04	0.28 ± 0.07	0.18 ± 0.03
CK (U/L)	104 ± 8.2	113 ± 7.9	95 ± 8.4	115 ± 15
AST (U/L)	18 ± 0.6	19 ± 1.1	21 ± 2.0	22 ± 2.0
ALT (U/L)	27 ± 4	22 ± 2.3	27 ± 4	27 ± 3

Results are shown as means ± SEM. There were no significant differences between groups. *BMI*, Body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *FSG*, fasting serum glucose; *SrCr*, serum creatine; *TC*, total cholesterol; *TG*, triglyceride; *CRP*, C-reactive protein; *CK*, creatine phosphokinase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase.

small comparative studies including a few of randomized design suggest that policosanol may be equal to or better than statins for the treatment of type II hypercholesterolemia with fewer side effects.[22–28]

The published literature and the ready availability of policosanol, therefore, led us to design and carry out this first US prospective, randomized, placebo-controlled study to evaluate the efficacy of policosanol, given alone and in combination with atorvastatin, in patients with dyslipidemia.

Methods

Study design

Patients were randomly assigned to 4 groups by using a double-dummy design: policosanol 20 mg (Cholesstor, Pharmed Group, Miami, FL) plus placebo-atorvastatin, atorvastatin 10 mg plus placebo-policosanol, policosanol 20 mg and atorvastatin 10 mg, or double placebos for a continuous period of 12 weeks. Placebo atorvastatin and placebo Cholesstor were prepared and provided by the Pharmed Group. Cholesstor and dummy Cholesstor capsules were packed in identical bottles. Similarly, atorvastatin (Lipitor, Pfizer Inc., New York, NY) and dummy atorvastatin tablets were provided in identical bottles, but different from those of Cholesstor. A noninvestigator pharmacist provided to the study coordinator the medications according to the randomization code. Cholesstor was obtained from sugar cane wax. The alcohol composition determined by gas chromatography (GCI Nutrients, DH Hoogvliet, The Netherlands) was as follows (in percent): hexacosanol 3.0 to 8.0, heptacosanol 0.1 to 3.0, octacosanol 62.2, nonacosanol 0.1 to 2.0, triacontanol 10 to 15, dotriacontanol 5 to 10, teriacontanol 01 to 5. An average of 12.6 mg of octacosanol was present in 20 mg of policosanol.

The study was planned so that 25 patients per group would complete the study, assuming a 10% dropout rate. Both patients and study investigators were blinded to study treatment. The American Heart Association step I cholesterol-lowering diet was encouraged in all patients during the 3-month study period. The study was approved by the Institutional Review Board of the Mount Sinai Medical Center, and signed informed consent was obtained before study enrollment.

Patients

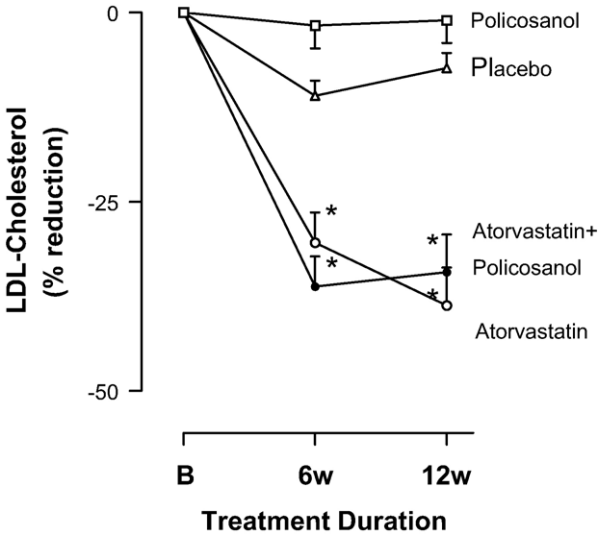
Subjects older than 20 years with serum LDL-C levels ≥140 but <190 mg/dL were eligible for inclusion. Participants were required to be off statin therapy or any lipid-lowering drug for a minimum of 8 weeks before study enrollment. Patients were excluded if there was a history of congestive heart failure, myocardial infarction or coronary revascularization, peripheral vascular disease, angina pectoris, active or chronic liver disease, a history of alcohol or drug abuse, creatinine phosphokinase (CPK) level >2.0 times the upper limit of normal, baseline serum creatinine level >2.5 mg/dL, uncontrolled diabetes (glycosylated hemoglobin A_{1c} >9%), or initiation of oral hypoglycemic therapy within 4 weeks of randomization. Patients were also excluded if thyrotopin was >10 mU/L or malignancy had been diagnosed within 5 years. Women were excluded if they were of childbearing potential and not using a reliable form of contraception, if they were pregnant or breast-feeding, or if they were on hormone replacement therapy. Patients were evaluated at baseline and assessed at 6 and 12 weeks with an interim history, physical examination, laboratory determinations, and assessment of treatment compliance and tolerability.

Study end points and statistics

The study was powered to detect differences in LDL-C between policosanol and placebo (primary end point). Secondary end points included effects on total cholesterol, HDL-C, and triglycerides. We also tested whether policosanol, when added to atorvastatin, produced a greater hypolipidemic effect compared with atorvastatin alone.

Based on the available literature, policosanol was estimated to decrease total cholesterol by 20%. A sample size of 18

Figure 1



Effects of policosanol and atorvastatin on serum LDL-C. Shown are mean values ± SEM of the percentage of reduction in serum LDL-C from baseline induced by placebo (△), policosanol (□), atorvastatin (○), and atorvastatin + policosanol (●) treatments. Asterisk indicates significantly different from baseline at $P < .01$.

Table II. Effects of policosanol and atorvastatin on serum LDL-C (milligrams per deciliter)

	Policosanol	Atorvastatin	Policosanol + atorvastatin	Placebo
n	25	25	25	24
Baseline	159 ± 2.5	168 ± 2.7	152 ± 2.3	158 ± 2.6
6 wk	156 ± 4.9	117 ± 7.0*	97 ± 5.0*	141 ± 5.0
12 wk	158 ± 4.9	103 ± 4.6*	100 ± 6.0*	147 ± 5.2

Results are shown as means ± SEM.
*Significantly different from baseline at $P < .01$.

Table III. Effects of policosanol and atorvastatin on total serum cholesterol (milligrams per deciliter)

	Policosanol	Atorvastatin	Policosanol + atorvastatin	Placebo
n	25	25	25	24
Baseline	234 ± 3.2	253 ± 3.5	238 ± 3.9	241 ± 4.2
6 wk	240 ± 4.9	199 ± 8.0*	170 ± 6*	227 ± 6.1
12 wk	242 ± 4.9	185 ± 7.0*	179 ± 7*	231 ± 6.1

Results are shown as means ± SEM.
*Significantly different from baseline at $P < .01$.

patients per treatment group was calculated to provide 90% power (assuming a SD of 10 mg/dL of LDL-C) to detect a 10 mg/dL difference in LDL-C between placebo and policosanol (primary end point), with a 5% type I error rate for a 1-sided test. Assuming a dropout rate of 10%, enrollment of 25 patients per treatment group would provide an adequate number of evaluated patients.

All numerical values were tested for normality. Parametric variables were expressed as mean values ± SEM. Results were expressed as absolute values (ie, milligrams per deciliter, units, millimeters Hg, beats per minute) or as differences from baseline. The changes from baseline were expressed either in absolute values (ie, milligrams per deciliter of cholesterol reduction) or as percentage of reduction from baseline. The 4 group comparisons were made with the use of analysis of variance with repeated measures, followed by a post hoc analysis (Duncan test). For nonparametric values, the Friedman test for comparison between groups was used. The significance of the difference in proportions of patients experiencing side effects across treatment groups was tested with the χ^2 test. Statistical significance was defined as a P value of <.05.

Results

One hundred ten patients were enrolled, of which 99 (54 women, 45 men, 48 ± 1 years) completed the study. Their body mass index averaged 27.4 ± 0.42 kg/m^2. The systolic blood pressure (119 ± 1.3 mm Hg) and diastolic blood pressure (77 ± 0.8 mm Hg) were within normal limits. The average baseline total cholesterol, LDL-C, and HDL-C levels were 244 ± 1.8, 160 ± 1.3, and 52.5 ± 1.2 mg/dL, respectively. The mean serum triglyceride level was 160 ± 6.4 mg/dL. Baseline characteristics were no different among the 4 groups (Table I). Of the 11 patients who failed to complete the study, 5 moved, 2 were instructed by their primary physician to discontinue the trial, and 4 withdrew because of side effects.

Policosanol, at a dose of 20 mg daily for 12 weeks, did not significantly lower total cholesterol or LDL-C levels (Figure 1). Follow-up total cholesterol and LDL-C levels in patients treated with policosanol were not significantly different from those of patients treated with placebo (Tables II and III).

Daily treatment with 10 mg atorvastatin produced significant reductions in total cholesterol and LDL-C at 6 and 12 weeks (Tables II and III). Atorvastatin resulted in a 27% reduction in total cholesterol and a 35% reduction in LDL-C from baseline to 12 weeks. The percent reduction in total cholesterol and LDL-C observed with the combination of policosanol and atorvastatin was not different from that observed with atorvastatin alone (Figure 1).

Neither atorvastatin, policosanol, nor its combination, had any significant effect on serum HDL-C (Table IV). Policosanol given alone did not significantly reduce serum triglyceride levels ($P = .62$). Serum triglyceride levels were decreased by both atorvastatin alone ($P = .011$) and atorvastatin given in combination with policosanol ($P = .013$). Similar reductions in serum triglyceride levels (13%) were observed in patients

Table IV. Effects of policosanol and atorvastatin on serum HDL-C (milligrams per deciliter)

	Policosanol	Atorvastatin	Policosanol + atorvastatin	Placebo
n	25	25	25	24
Baseline	52.5 ± 2.5	53.4 ± 2.7	52.8 ± 2.7	50.8 ± 2.7
6 wk	53.2 ± 2.7	51.3 ± 2.7	52.6 ± 2.8	50.7 ± 2.8
12 wk	52.3 ± 2.7	53.8 ± 2.8	52.4 ± 3.0	51.7 ± 2.7

Results are shown as means ± SEM. There were no significant differences from baseline or between groups.

Table V. Effects of policosanol and atorvastatin on serum triglycerides

	Policosanol	Atorvastatin	Policosanol + atorvastatin	Placebo
n	25	25	25	24
Baseline	165 ± 15	161 ±13	151 ± 15	158 ± 13
6 wk	151 ± 12	156 ± 24	138 ± 11*	179 ± 13
12 wk	159 ± 13	141 ± 14*	138 ± 9*	169 ± 16

Results are shown as means ± SEM.
*Significantly different from baseline at $P < .01$.

treated with atorvastatin and atorvastatin plus policosanol at week 12 (Table V).

Serum C-reactive protein levels were not significantly affected by either drug given alone or in combination. Policosanol, atorvastatin, or combined treatment did not affect fasting serum glucose, serum creatinine, CPK, aspartate aminotransferase, or alanine aminotransferase levels. One patient (1/25) treated with atorvastatin experienced a transient asymptomatic increase in serum CPK levels (756 U/L). Of the 4 patients who self-withdrew from the study, 2 patients randomized to placebo developed rash and fatigue, respectively, and 2 patients randomized to combination therapy complained of transient myalgias, although they had normal CPK levels.

Discussion

Policosanol, a mixture of primary alcohols derived from purified sugar cane wax, has been reported to have lipid-lowering properties.[6–8] Important lipid profile improvements have been reported in healthy volunteers, patients with type II hypercholesterolemia, patients with type 2 diabetes mellitus with hypercholesterolemia, postmenopausal women with hypercholesterolemia, and patients with combined hypercholesterolemia and abnormal liver function test findings.[12–16] Although a number of policosanol formulations are marketed in the United States as nutritional supplements, until now there has been no US clinical research experience demonstrating their efficacy or safety. In this study, we investigated the lipid-lowering effects of policosanol by using a randomized, placebo-controlled, parallel, double-dummy, and double-blind design. The trial was designed to rigorously establish the lipid-lowering efficacy of policosanol as monotherapy and to test for the potential additive and possible synergistic efficacy when policosanol was added to low-dose statin treatment. In this trial, daily administration of 20 mg policosanol (Cholestor) did not lower serum total cholesterol, LDL-C, or triglyceride levels, nor did it increase serum HDL-C. Furthermore, when given in combination with atorvastatin, policosanol did not produce any additional lipid lowering above that induced by atorvastatin alone.

Several factors may account for the lack of lipid-lowering efficacy of policosanol in our study. Insufficient dosing and treatment duration are common causes of treatment failure for any therapy. Based on the current literature, doses of 10 to 20 mg/d of policosanol have been documented to induce significant cholesterol lowering.[8] Furthermore, peak LDL-C lowering with policosanol has been reported to occur at 6 to 8 weeks after initiation of treatment.[19–21] In our study, policosanol was dosed at 20 mg/d and patients were treated for 12 weeks. Therefore, it is unlikely that the lack of LDL-C reduction observed in this trial was due to inadequate dosing or insufficient length of therapy. The baseline levels of serum cholesterol could also determine the lipid-lowering efficacy of policosanol. In our study, LDL-C levels ranged from 140 to 189 mg/dL and averaged 159 ± 2.5 mg/dL in the policosanol group. Previous studies have shown that policosanol lowers serum LDL-C in both normo- and hyperlipidemic subjects.[8] Therefore; it is also unlikely that the LDL-C levels of our study patients limited the lipid-lowering efficacy of policosanol.

The alcohol composition of the policosanols may be another important factor accounting for the discrepancies in the lipid-lowering efficacy of policosanols. However, the composition of the policosanol used in this study is quite comparable to that of the policosanols used in studies with both positive[6–28] and negative[29–31] results. Octacosanol, triacontanol, and hexacosanol are the major alcohols proposed to be responsible for the policosanol lipid-lowering efficacy and were found in largest concentrations in the brand of policosanol investigated.

In conclusion, this study refutes prior findings that policosanol has potent lipid-lowering effects. Our results are supported by a recent study conducted in the Netherlands where policosanol was found ineffective in lowering serum LDL-C in human patients.[29] Similarly, 2 additional studies in animals revealed that sugar cane, rice wax, or sunflower oil cake policosanol did not lower plasma total cholesterol or LDL-C.[30,31] Because most positive findings derive from studies conducted by one research group, our study supports the need for systematic evaluation of available products containing policosanol to determine their clinical lipid-lowering efficacy under rigorous experimental conditions. We

propose that policosanol should be added to the list of nutritional supplements that lack appropriate scientific validity to support their use.

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