Policosanol: A New Treatment for Cardiovascular Disease?

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Abstract

Policosanol is a mixture of alcohols isolated and purified from sugar cane. Recently, Cuban researchers found 5-20 mg daily of policosanol to be effective at improving serum lipid profiles. Policosanol is believed to decrease total cholesterol (TC), low-density lipoprotein (LDL), and increase high-density lipoprotein (HDL) by inhibiting cholesterol synthesis and increasing LDL processing. Lipid profile improvements are seen in healthy volunteers, patients with type II hypercholesterolemia, type 2 diabetics with hypercholesterolemia, postmenopausal women with hypercholesterolemia, and patients with combined hypercholesterolemia and abnormal liver function tests. Additionally, policosanol has performed equal to or better than simvastatin, pravastatin, lovastatin, probucol, or acipimox with fewer side effects in patients with type II hypercholesterolemia. Policosanol also decreases several other risk factors of cardiovascular disease by decreasing LDL oxidation, platelet aggregation, endothelial damage, and smooth muscle cell proliferation. Furthermore, policosanol decreases progression and increases regression of cardiovascular disease assessed by thallium-labeled myocardial perfusion scintigraphy (TL-MPS) and Doppler-ultrasound, and decreases symptoms of cardiovascular disease assessed by the Specific Activity Scale. In post-marketing studies, only 0.31 percent of patients have had adverse events. Furthermore, in animal toxicity studies doses up to 1500 times normal human doses (on the basis of body weight) have shown no negative effects on carcinogenesis, reproduction, growth, and development. However, despite the positive research on policosanol on Cubans, policosanol produced in Cuba is not available in the United States, and only Cuban subjects have been studied. Further research is needed to determine if the same effects will be obtained in U.S. populations with non-Cuban produced policosanol.

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Introduction

Policosanol is a mixture of alcohols isolated and purified from sugar cane (*Saccharum officinarum* L). It consists mainly of 66-percent octacosanol (CH_3-$CH_{2(26)}$-CH_2-OH), 12-percent triacontanol, and 7-percent hexacosanol. Other alcohols (15%), namely tetracosanol, heptacosanol, nonacosanol, dotriacontanol and tetratriacontanol, are minor components.[1]

Recent research, conducted in Cuba, shows policosanol is effective at improving serum lipids by lowering total cholesterol (TC) and low-density lipoprotein (LDL), while raising high-density lipoprotein (HDL).[2-29] Serum lipid benefits are seen in healthy individuals,[2] patients with type II hypercholesterolemia,[3-16] type 2 diabetics,[17-19] postmenopausal women,[20-21] and patients with type II hypercholesterolemia with abnormal liver function tests.[22] Additionally, policosanol performs equal to or better than simvastatin, pravastatin, lovastatin, probucol, or acipimox.[19,23-29]

Besides improving serum lipid profile, policosanol reduces several other cardiovascular disease risk factors, including LDL oxidation,[30,31]

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platelet aggregation,[26,32-36] endothelial cell damage,[26] smooth muscle proliferation,[37,38] signs of cardiovascular disease,[39-41] symptoms of coronary artery disease,[13,15,42,43] and is effective in patients with intermittent claudication.[44,45]

Cholesterol Lowering Effects

Mechanism of Action

Policosanol decreases cholesterol synthesis from acetate but not from mevalonate, suggesting an inhibition of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase.[46-48] However, unlike statin drugs, policosanol does not competitively or non-competitively inhibit HMG-CoA reductase. Although policosanol's exact mechanism of inhibition of HMG-CoA reductase is not known, it is thought to interfere with the synthesis and degradation of the enzyme.[46,47] Furthermore, policosanol significantly increases LDL-binding, uptake, and degradation in a dose-dependent manner in cultured fibroblasts, suggesting it improves LDL metabolism.[48]

Healthy Volunteers

Policosanol was initially studied in healthy volunteers and showed promising results. Thirty-eight subjects with normal cholesterol levels were randomly divided into three groups to receive 10 mg/day policosanol, 20 mg/day policosanol, or placebo in double-blind fashion for four weeks.[2] Both 10 and 20 mg/day significantly reduced TC (10.7% and 11.3%, respectively), but only 20 mg/day showed a significant decrease in LDL (22%) and an increase in HDL (29.93%). There was no difference in the number of adverse effects among the groups or changes in body weight, blood pressure, or liver enzymes.

Type II Hypercholesterolemia

The majority of the research on policosanol is on patients with type II hypercholesterolemia.[3-16] Type II hypercholesterolemia is defined as total cholesterol greater than 6 mmol/L, LDL cholesterol greater than 4 mmol/L, and TG less than 4.52 mmol/L. There have been 14 randomized, placebo-controlled, double-blind studies showing positive results (Table 1). Total cholesterol, LDL, and the ratios of LDL/HDL and TC/HDL were significantly decreased in all 14 trials. Of the 13 trials measuring HDL, seven showed significant increases in HDL and six showed HDL remained unchanged. Doses ranged from 2 mg/day to 40 mg/day with dose-dependent decreases in TC, LDL, LDL/HDL, and TC/HDL and increases in HDL up to 20 mg/day, with no further benefit with 40 mg/day. However, 40 mg/day significantly decreased triglycerides (TG), which was not seen at the lower doses.[16] Table 2 shows the range of serum lipid improvements seen in trials using 5, 10, 20, or 40 mg/day doses. Additionally, side effects were equal to placebo in 12 trials and significantly less than placebo in two trials.

Type 2 Diabetes

Policosanol was effective in three studies on patients with type 2 diabetes mellitus and hypercholesterolemia. The first looked at 19 patients given 5 mg twice daily for 12 weeks in a randomized, double-blind, placebo-controlled trial.[17] Total cholesterol, LDL, TC/HDL, and LDL/HDL all decreased by 28.9, 44.4, 38.3, and 51.6 percent, respectively, while HDL increased by 23.5 percent. There were no adverse effects on glycemic control or glycosylated hemoglobin and policosanol significantly decreased diastolic blood pressure by 5.5 mm Hg. Two patients from the placebo group reported mild reactions of nervousness; however, no patients on policosanol had adverse reactions.

A second study looked at 29 patients with type 2 diabetes and hypercholesterolemia treated with 5 mg policosanol twice daily for 12 weeks.[18] TC and LDL were significantly decreased by 17.5 and 21.8 percent, respectively, although the HDL increase of 11.3 percent was statistically insignificant. Blood biochemical variables remained in the normal range and there was no change in glycemic control. No differences in adverse events were reported between the policosanol and placebo groups.

Table 1 (part a). *Randomized, Placebo-controlled, Double-blind Trials of Policosanol for Patients with Type II Hypercholesterolemia*

Author	Subjects	Dose	Duration	Results	Side Effects
Pons[3] 1992	56 pts with type II hypercholesterolemia	5 mg/day	8 weeks	TC ↓ 13.1%*+ LDL ↓ 17.7%*+ LDL/HDL ↓ 14.1%*+ TC/HDL ↓ 9.1%*+ TG ↓ 13.8%+ HDL ↑ 3.3%	Non-significant difference in adverse events
Aneiros[4] 1993	33 pts with type II hypercholesterolemia	5 mg bid for 6 wks followed by 10 mg bid for 6 more weeks	12 weeks	10 mg policosanol TC ↓ 16.8%*+ LDL ↓ 22%*+ LDL/HDL ↓ 19.1%*+ TC/HDL ↓ 14.4%*+ HDL ↑ 10.8% 20 mg policosanol TC ↓ 20.5%*+ LDL ↓ 29.1%*+ LDL/HDL ↓ 32.8%*+ TC/HDL ↓ 25.1%*+ HDL ↑ 8.6%	7 adverse events: 2 in policosanol and 5 in placebo, however difference was not significant
Pons[5] 1994	59 pts with type II hypercholesterolemia	5 mg/day policosanol	1 yr	TC ↓ 15.3%*+ LDL ↓ 23.7%*+ LDL/HDL ↓ 25.3%*+ TC/HDL ↓ 17.0%*+ HDL ↑ 2.2%	Non-significant differences in adverse events
Pons[6] 1994	22 pts with type II hypercholesterolemia	Successive 5,10,20 mg	8 weeks per dose total of 24 weeks	5 mg: TC ↓ 8.0% LDL ↓ 11.3%* HDL ↑ 7.8% LDL/HDL ↓ 15.3%* TC/HDL ↓ 12.5%* 10 mg: TC ↓ 14.1%* LDL ↓ 21.9%*+ HDL ↑ 7.2% LDL/HDL ↓ 25.6%*+ TC/HDL ↓ 18.4%* 20 mg: TC ↓ 23%*+ LDL ↓ 31.2%*+ HDL ↑ 8.7% LDL/HDL ↓ 34.6%*+ TC/HDL ↓ 27.2%*+	Policsoanol significantly decreased Systolic BP compared to baseline. 10 adverse reactions: 7 in placebo and 3 in policosanol but was non-significant.
Canetti[7] 1995	97 pts with type II hypercholesterolemia	5 mg bid	12 months	TC ↓ 16.3%*+ LDL ↓ 27.5%*+ LDL/HDL ↓ 37.1%*+ TC/HDL ↓ 28%*+ HDL ↑ 28%*	Non-significant difference in adverse events

Table 1 (part b). *Randomized, Placebo-controlled, Double-blind Trials of Policosanol for Patients with Type II Hypercholesterolemia*

Author	Subjects	Dose	Duration	Results	Side Effects
Anerios[8] 1995	45 pts with type II hypercholesterolema	5 mg bid	6 weeks	TC ↓ 16.2%*+ LDL ↓ 21.5%*+ HDL ↑ 14% (p=0.07) LDL/HDL ↓ 22.3%*+ TC/HDL ↓ 17.7%*+	Non-significant difference in adverse events
Castano[9] 1995	74 pts with type II hypercholesterolemia	5 mg bid	1 year	TC ↓ 17.2%*+ LDL ↓ 26.4%*+ HDL ↑ 13.6%* LDL/HDL ↓ 33.3%*+ TC/HDL ↓ 25.3%*+	Non-significant difference in adverse events
Canetti[10] 1995	69 pts with type II hypercholesterolemia	5 mg bid	2 years	6 months: TC ↓ 11.7%* LDL ↓ 17.9%*+ HDL ↑ 9.2%* LDL/HDL ↓ 30.4%*+ TC/HDL ↓ 22.5%*+ 12 months: TC ↓ 17.6%* LDL ↓ 26.9%* HDL↑ 21.1%*+ LDL/HDL ↓ 38.3%*+ TC/HDL ↓ 30.5%*+ 18 months: TC ↓ 20.1%*+ LDL ↓ 27.1%*+ HDL ↑ 14%* LDL/HDL ↓ 34.6*+ TC/HDL ↓ 27%*+ 24 months: TC ↓ 18%*+ LDL ↓ 25%*+ HDL ↑ 11.2% LDL/HDL ↓ 32.6%*+ TC/HDL ↓ 27.2%*+	Non-significant difference in adverse events
Castano[11] 1995	62 pts aged 60-75 yo with type II hypercholesterolemia	5 mg bid	12 months	TC ↓ 15.6%*+ LDL ↓ 23.1%*+ HDL ↑ 8% LDL/HDL ↓ 25.2%*+ TC/HDL ↓ 19%*+	Non-significant difference in adverse events
Castano[12] 1996	58 pt with hypertension and type II hypercholesterolemia	10 mg bid	1 yr	2 months: TC ↓ 9.7%* LDL ↓ 13.4%* HDL ↑ 25.4%* LDL/HDL ↓ 23.6%* TC/HDL ↓ 21.4%* 12 months TC ↓13.0%*+ LDL ↓ 19.1%*+ HDL ↑ 17.1%* LDL/HDL ↓ 24.2%*+ TC/HDL ↓ 20%*+	Mild but significant decrease in Systolic BP with policosanol

Table 1 (part c). *Randomized, Placebo-controlled, Double-blind Trials of Policosanol for Patients with Type II Hypercholesterolemia*

Author	Subjects	Dose	Duration	Results	Side Effects
Batista[13] 1996	23 middle-aged pts with Type IIa, IIb, IV and borderline hypercholesterolemia	1 mg bid	14 months	TC ↓ 14.8%*+ LDL ↓ 15.6%*+	Non-significant difference in adverse events
Mas[14] 1999	437 pts with Type II and >2 additional non-lipid risk factors	5 mg/day for 12 wks, increased to 10 mg/day for 12 more wks	24 weeks	5 mg: TC ↓ 13.0%*+ LDL ↓ 18.2%*+ HDL ↑ 15.5%*+ LDL/HDL ↓ 19.1%*+ TC/HDL ↓ 17.3%*+ 79.8% had LDL ↓ >15% 10mg: TC ↓ 17.4%*+ LDL ↓ 25.6%*+ HDL ↑ 28.4%*+ LDL/HDL ↓ 32.5%*+ TC/HDL ↓ 28.8%*+ TG ↓ 5.2%*+ 83.9% had LDL reductions of >15%	Significantly more adverse events in placebo. 10 adverse events in placebo, 7 of which were vascular and 2 pts died. 0 in policsoanol
Castano[15] 2001	179 pts 60-78 yo both sexes	5 mg for 12 weeks, 10 mg for additional 12 weeks	24 weeks	5 mg: TC ↓ 19.8% LDL ↓ 16.9% HDL ↑ 14.6% TC/HDL ↓ 15.6% LDL/HDL ↓ 19% 10mg: TC ↓ 16.2% LDL ↓ 24.4% HDL ↑ 29% LDL/HDL ↓ 28.8% TC/HDL ↓ 27.4% 86.5% poli had ↓ LDL >15% Placebo only 11.2%	Significantly more adverse events in placebo. 7 serious AE in placebo with 0 in policosanol. 14.6% of pts had AE in placebo with only 4.4% in policosanol. Policosanol significantly decreased AST at 5 and 10 mg 10 mg sig ↓ BP comp to baseline and placebo

Castano[16] 2001	77 pts with type II hypercholesterolemia	20 mg or 40 mg	6 months	20 mg: (3 mo, 6 mo)
				TC ↓12.8%*+, ↓15.6%*+
				LDL ↓20.9%*+, ↓27.4%*+
				HDL≠13.4%*+, ↑17.6%*+
				LDL/HDL↓28.4%*+, ↓37.2%*+
				TC/HDL↓21.4%*+, ↓27.1%*+
				TG ↓15.4%*, ↓12.7%
				40 mg: (3 mo, 6 mo)
				TC ↓16.1%*+, ↓17.3%*+
				LDL ↓25.5%*+, ↓28.1%*+
				HDL ≠11.9%*+, ↑17%*+
				LDL/HDL↓31.6%*+, ↓36.5%*+
				TC/HDL↓23.5%*+, ↓27.5%*+
				TG↓15.9%*+, ↓17.4%*
				LDL ↓ >15% in:
				86.2% on 20mg
				86.7% on 40 mg
				6.7% on placebo
				Target LDL level reached
				65.5% on 20 mg
				70% on 40 mg
				0% on placebo
				TG was only sig difference between 20 and 40 mg
					Non-significant difference in adverse events
					
					Total amount of AE trended to be lowest in 40 mg/day but was not significant.

* - Significant difference compared to baseline
\+ - Significant difference compared to placebo

Table 2. *Summary of Different Doses of Policosanol on Lipid Levels in Patients with Type II Hypercholesterolemia*

Dose/Day	Range of Effect
2 mg[13]	TC ↓14.8% LDL ↓15.6%
5 mg[3,5,6,14,15]	TC ↓ 8-19.8% LDL ↓ 11.3-23.7% HDL ↑ 2.2-15.5% LDL/HDL ↓15.3-25.3% TC/HDL ↓ 9.1-17.3%
10 mg[4,6-11,14,15]	TC ↓14.1-22.1% LDL ↓19.1-27.5% HDL ↑ 7.1-29% LDL/HDL ↓ 19.1-38.3% TC/HDL ↓14.4-30.5%
20 mg[4,6,12,16]	TC ↓ 13-23% LDL ↓ 19.1-31.2% HDL ↑ 8.6-17.6% LDL/HDL ↓ 24.2-37.2% TC/HDL ↓ 20-27.2%
40 mg[16]	TC ↓ 17.3% LDL ↓ 28.1% HDL ↑17% LDL/HDL ↓ 36.5% TC/HDL ↓ 27.5%

Policosanol (10 mg/day) was compared to lovastatin (20 mg/day) in a randomized, double-blind, comparative study on 53 patients with type 2 diabetes and hypercholesterolemia for 12 weeks.[19] Both policosanol and lovastatin significantly decreased TC (14.2% and 14.0%, respectively) and LDL (23.7% and 16.8%, respectively) compared to baseline. While this was not statistically significant, the results are clinically significant. However, policosanol increased HDL (7.5%) while the lovastatin group experienced a decrease in HDL (-2.8%). Policosanol decreased the LDL/HDL ratio significantly more than lovastatin (23.7% with policosanol versus 14.9% with lovastatin). Furthermore, policosanol significantly decreased systolic blood pressure compared to baseline and both systolic and diastolic blood pressure compared to lovastatin; unlike lovastatin, policosanol did not increase the liver enzyme AST or creatinine phosphokinase (CPK). All five patients who withdrew from the study were in the lovastatin group. Three of these had serious adverse effects of unstable angina and hypertension. Mild adverse effects were significantly less with policosanol, with 37 percent of lovastatin patients and 15.4 percent of policosanol patients reporting symptoms.

Postmenopausal Women

Postmenopausal women are at an increased risk for cardiovascular disease and improving serum cholesterol levels is important for decreasing the risk. Two studies showed policosanol to be very effective for improving serum lipid profiles in this population. The first was conducted on 244 postmenopausal women with type II hypercholesterolemia in a randomized, placebo-controlled, double-blind trial.[20] Policosanol (5 mg/day) or placebo was given for 12 weeks, followed by an increased dose of 10 mg/day for an additional 12 weeks. At the end of the first 12 weeks TC, LDL, LDL/HDL and TC/HDL all decreased by 12.6, 17.7, 17, and 16.7 percent, respectively, whereas HDL increased by 16.5 percent. At 24 weeks, 10 mg policosanol resulted in decreased TC, LDL, LDL/HDL, and TC/HDL by 16.8, 25.4, 29.6, and 27.3 percent, respectively, and increased HDL 29.3 percent. There were significantly more side effects in the placebo group (19.7%) compared to policosanol (7.4%), and more patients withdrew from the placebo group.

Another study examined 56 postmenopausal women with hypercholesterolemia given 5 mg/day for eight weeks and then increased to 10 mg/day for another eight weeks compared to placebo.[21] Five mg/day significantly decreased TC, LDL, LDL/HDL, TC/HDL by 12.9, 17.3, 17.2,

and 16.3 percent, respectively, while HDL was unchanged. Ten mg/day decreased TC, LDL, LDL/HDL, and TC/HDL by 19.5, 26.7, 26.5, and 21.0 percent, respectively, and increased HDL by 7.4 percent. Adverse events were again more common in the placebo group (39.3%) compared to the policosanol (21.4%) group.

Comparative Studies: Policosanol versus Conventional Lipid-lowering Drugs

In comparative trials, policosanol improves lipid profiles to a statistically equal or greater extent than simvastatin, pravastatin, lovastatin, probucol, or acipimox (Table 3). Two trials on patients with type II hypercholesterolemia comparing low dose simvastatin (5 or 10 mg/day) and moderate dose policosanol (5 or 10 mg/day) demonstrated that both greatly decrease TC, LDL, LDL/HDL, and TC/HDL with no significant differences between the groups.[23,24] Furthermore, there were no differences in side effects between these groups.

Two trials found policosanol (10 mg/day) compared favorably to low dose pravastatin (10 mg/day) in patients with type II hypercholesterolemia.[25,26] In one trial, policosanol-treated patients had significantly greater decreases in LDL, LDL/HDL, TC/HDL and increases in HDL,[25] while in another trial policosanol-treated patients had significantly greater increases in HDL.[26] Pravastatin had more side effects in both studies.

Comparing policosanol to lovastatin on patients with type 2 diabetes and hypercholesterolemia (type II) found policosanol (10 mg/day) more effective at lowering LDL/HDL and increasing HDL than 10 mg/day lovastatin, with significantly fewer side effects.[19] Additionally, in patients with type II hypercholesterolemia with concomitant coronary risk factors, policosanol (10 mg/day) again decreased LDL/HDL and increased HDL more effectively than 20 mg/day lovastatin with fewer side effects.[27]

Policosanol (5 mg twice daily) also compared favorably to probucol (500 mg twice daily) at reducing TC, LDL, and TG in patients with type II hypercholesterolemia.[28]

Finally, policosanol (10 mg/day) compared favorably to acipimox (750 mg/day), a niacin derivative, in regards to TC, LDL, LDL/HDL, TC/HDL, and HDL with fewer side effects.[29]

Patients with Hypercholesterolemia and Elevated Liver Enzymes

In contrast to statin drugs, policosanol has shown no adverse effects on the liver and may even reduce liver damage. In a trial to determine if policosanol could safely be used on patients with altered liver function tests, 46 patients with primary hypercholesterolemia and elevated liver enzymes were treated with policosanol (5 or 10 mg/day) or placebo for 12 weeks.[22] Both 5 and 10 mg policosanol significantly lowered lipids without having any negative effects on liver enzymes. In fact, GGTP and ALT were significantly lowered with 5 mg, while ALT but not GGTP was significantly lowered with 10 mg, suggesting a decrease in liver damage.

LDL Oxidation

LDL oxidation is thought to be a necessary step in the development of atherosclerosis. Studies on humans and rats show policosanol decreases LDL oxidation. Rats given 250-500 mg/kg/day policosanol for four weeks had a significant increase in the LDL oxidation lag time, decreased LDL oxidation propagation rate, and decreased maximum generation of LDL conjugated diene formation induced by copper ion.[30] Policosanol also significantly reduced macrophage-mediated-oxidation-produced thiobarbituric-acid-reactive-substances (TBARS) and reduction of lysine amino groups of LDL.

Consistent with the animal work, 69 healthy human volunteers given 5 or 10 mg/day policosanol had significantly decreased lag time and propagation rate of conjugated diene formation in LDL induced by copper ion.[31] Additionally, policosanol at both doses significantly decreased macrophage-mediated oxidation measured by TBARS production. Effects were dose dependent in both oxidizing systems.

Table 3 (part a). *Comparative Trials of Policosanol and Cholesterol-lowering Drugs*

Author	Subjects	Dose	Duration	Results	Side Effects
Ortensi 1997[23]	53 elderly patients (60-77 yo) with Primary Hypercholesterolemia	10 mg/day policosanol vs. 10 mg/day simvastatin	8 weeks in a randomized, double-blind, comparative trial.	Policosanol TC ↓ 14.7%* LDL ↓ 17.9%* HDL NS LDL/HDL ↓ 15.4%* TC/HDL ↓ 12.4%* TG ↓ 13.8%* Simvastatin TC ↓ 15.2%* LDL ↓ 19.8%* HDL NS LDL/HDL ↓ 16.6%* TC/HDL ↓ 11.8%* TG ↓ 8.7%* Chol ↓ < 200 25% policosanol 26.1% simvastatin LDL <160 40.7% policosanol 34.8% simvastatin	No significant difference in adverse events.
Illnait 1997[24]	50 patients with type II hypercholesterolemia	5 mg policosanol vs. 5 mg simvastatin	6 weeks randomized, double-blind, comparative trial	Policosanol TC ↓ 13%* LDL ↓ 21.1%* LDL/HDL ↓ 26.4%* TC/HDL ↓ 20.9%* HDL ↑ 10.9%* Simvastatin TC ↓ 20.3%* LDL ↓ 26.2%* LDL/HDL ↓ 22.3%* TC/HDL ↓ 16.3%* HDL NS	No significant differences in adverse events.
Benitez 1997[25]	24 pts with type II hypercholesterolemia	10 mg/day policosanol vs. 10 mg/day pravostatin	6 weeks in a randomized, double-blind, comparative study	Policosanol TC ↓ 15.7%* LDL ↓ 24.2%*+ HDL ↑ 13.6%*+ LDL/HDL ↓ 33%*+ TC/HDL ↓ 25.7%*+ TG ↓ 8.7%* Pravostatin TC ↓ 15.3%* LDL ↓ 19.6%* HDL↑ 4.7% LDL/HDL ↓ 22.8%* TC/HDL ↓ 18.7%* TG ↓ 13.6%*	4 moderate adverse effects of nausea, dizziness, abdominal pain and pruritus were reported in pravostatin with none in policosanol 10 Mild adverse events were reported with 5 in each group Body weight, ALT, and AST ↑ in pravostatin comp to baseline
Castano 1999[26]	68 elderly patients 60-80 yo with Type II hypercholesterolemia and high coronary risk	10 mg/day policosanol vs. 10 mg/day pravastatin	8 weeks in a randomized, double-blind, comparative trial.	Policosanol TC ↓ 13.9%* LDL ↓ 19.3%* HDL ↑ 18.4%*+ LDL/HDL ↓ 28.3%* TC/HDL ↓ 24.4%* TG ↓ 14.1%* Pravostatin TC ↓ 11.8%* LDL ↓ 15.6%* HDL ↑ 5.6% LDL/HDL ↓ 18.9%* TC/HDL ↓ 15.7%* TG ↓ 3.4%	ALT significantly ↑ in prav ALT significantly ↓ in poli 2 dropped in pravastatin, one with MI and one with jaundice. None in policosanol 3 AE all in pravostatin (HA, polyphagia, myalgia), none in policosanol

Table 3 (part b). *Comparative Trials of Policosanol and Cholesterol-lowering Drugs*

Author	Subjects	Dose	Duration	Results		Side Effects
Crespo 1999[19]	53 pts with NIDDM and hypercholesterolemia	10 mg/day policosanol vs 20 mg/day lovastatin	12 weeks in a randomized, double-blind, comparative trial.	Policosanol TC ↓ 14.2%* LDL ↓ 20.4%* HDL ↓ 7.5%*+ LDL/HDL ↓ 23.7%*+ TG ↓ 18.4%	Lovastatin TC ↓ 14.0%* LDL ↓ 16.8%* HDL ↑ 2.8%* LDL/HDL ↓ 14.9%* TG ↓ 0.5%	5 patients withdrew, all from lovastatin, 3 because of adverse reactions (unstable angina, hypertension). Mild Adverse reactions were significantly greater in lovastatin at 37.0% compared to 15.4% in policosanol. Policosanol significantly ↓ BP, AST, and ALT compared to lovastatin. Lovastatin ↑ Creatine kinase
Castano 2000[27]	59 patients with type II hypercholesterolemia	10 mg/day policosanol or 20 mg/day lovastatin	12 week randomized double-blind, comparative trial	Policosanol TC ↓ 22.4%* LDL ↓ 32.4%* LDL/HDL ↓ 39.3%*+ TC/HDL ↓ 32.0%* HDL ↑ 14.3%*+	Lovastatin TC ↓ 19.8%* LDL ↓ 27.6%* LDL/HDL ↓ 32.8%* TC/HDL ↓ 25.2%* HDL ↑ 3.7%	Lovastatin ↑ Creatine kinase Policosanol ↓ Creatine kinase 2 lovastatin patients discontinued because of adverse events (rash, GI disturbance) Adverse events were significantly higher in lovastatin. 9/30 in lovastatin 2/29 in policosanol
Pons 1997[28]	27 pts with type II primary hypercholesterolemia	5 mg policosanol bid or 500 mg probucol bid.	8 week, randomized, double-blind, comparative trial	Policosanol TC ↓ 18%*+ LDL ↓ 22.7%*+ HDL ↑ 3% LDL/HDL ↓ 25.5%* TC/HDL ↓ 20.8%* TG ↓ 16.2%*+	Probucol TC ↓ 7.8%* LDL ↓ 11.8%* HDL ↓ 0.05% LDL/HDL ↓ 15.0%* TC/HDL ↓ 11.4%*	Probucol treated patients reported more adverse events than policosanol but it did not reach significance.
Alcocer 1999[29]	63 patients with type II hypercholesterolemia	10 mg/day policosanol or 750 mg/day acipimox	8 wk, randomized, double-blind, comparative trial	Policosanol TC ↓ 15.8%*+ LDL ↓ 21%*+ LDL/HDL ↓ 15.8%*+ TC/HDL ↓ 11.5%*+ HDL ↑ 1.3%+	Acipimox TC ↓ 7.5%* LDL ↓ 7.5%* LDL/HDL ↑ 11.6% TC/HDL ↑ 11% HDL ↓ 11%	15.6% of patients taking acipimox has adverse events with none in patients taking policosanol.

* - significant difference compared to baseline
\+ - significant difference compared to cholesterol lowering drug

Platelet Aggregation

Policosanol decreased platelet aggregation in healthy volunteers and in patients with type II hypercholesterolemia. While the mechanism is not totally clear, in humans it appears there is a decrease in platelet aggregating thromboxane B2 (TXB_2) with no effect on platelet inhibiting prostacyclin (PGI_2).[32] In a single-dose study on 87 healthy volunteers, 5, 10, 25, and 50 mg were given and platelet aggregation induced by ADP, epinephrine, and collagen was studied.[33] Doses of 10, 25, and 50 mg significantly decreased aggregation induced by ADP and epinephrine, but not collagen. Repeated doses given for seven days showed 20 mg/day significantly inhibited platelet aggregation by ADP and epinephrine, with insignificant trends toward decreased aggregation induced by collagen. At a dose of 10 mg/day there were insignificant trends for ADP, epinephrine, and collagen.

In healthy volunteers given 10 mg/day policosanol for 15 days, platelet aggregation caused by arachidonic acid (AA) and collagen, but not ADP, was significantly decreased.[32] TXB_2 was significantly decreased but 6-keto-$PGF_1\alpha$ (a metabolite and estimate of PGI_2) was not decreased.

The effects of policosanol proved to be dose dependent in a trial using 10 mg policosanol for seven days, 20 mg for seven more days, followed by 40 mg for seven days on 37 healthy individuals.[34] Policosanol decreased platelet aggregation induced by ADP, epinephrine, and collagen in a dose-dependent fashion, with significant values being seen at 20 mg for ADP and epinephrine, and 40 mg for ADP, epinephrine, and collagen. No change in bleeding time was observed.

Policosanol may have advantages over aspirin (ASA) because it decreases platelet aggregating TXB_2 without affecting platelet anti-aggregating PGI_2. In a study to compare policosanol to ASA, healthy volunteers were given placebo, 20 mg policosanol, 100 mg ASA, or 20 mg policosanol plus 100 mg ASA for seven days.[35] Both policosanol and ASA were more effective than placebo at decreasing aggregation induced by epinephrine and collagen; however, policosanol and not ASA significantly decreased ADP-induced platelet aggregation. The combination of policosanol and ASA was significantly better than ASA for epinephrine- and ADP-induced platelet aggregation, with an insignificant trend toward better anti-aggregation when compared to policosanol. Coagulation time was not affected by either mono-therapy, but combined therapy increased coagulation time; adverse events were greater in the ASA group.

In addition to decreasing platelet aggregation in healthy volunteers, policosanol decreased platelet aggregation in patients with type II hypercholesterolemia.[36] Policosanol at 10 mg for 30 days significantly decreased aggregation induced by arachidonic acid, high and low concentration collagen, and high and low concentration ADP. There were no adverse events.

In a comparison trial between pravastatin (10 mg/day) and policosanol (10 mg/day), policosanol significantly decreased platelet aggregation induced by low AA, high AA, collagen, and adenosine, compared to baseline and pravastatin.[26] Additionally, policosanol significantly decreased circulating endothelial cells more than pravastatin, suggesting improvement in vascular wall function.

Smooth Muscle Cell Proliferation

Neointimal formation related to smooth muscle cell proliferation is a crucial step in the progression of atherosclerotic plaque. In experimental rabbit models, policosanol at 5 or 25 mg/kg/day for 15 days decreased neointimal formation of cuffed carotid arteries, indicating a decrease in smooth muscle cell proliferation.[37] In a comparative study on rabbits both lovastatin and policosanol significantly decreased neointimal formation, but policosanol decreased formation significantly more than lovastatin.[38] The extent that decreasing smooth muscle cell proliferation reduces atherosclerotic disease is unknown but should be explored.

Assessment of Cardiovascular Disease

Unlike statin drugs that have been demonstrated to reduce cardiovascular events, there are no studies on cardiovascular disease events or mortality using policosanol, but there are trials

looking at coronary artery health. Forty-five patients with documented ischemic heart disease were placed on 5 mg policosanol twice daily, 5 mg policosanol twice daily plus 125 mg ASA, or 125 mg ASA for 20 months.[39] Ischemia was assessed using thallium-labeled myocardial perfusion scintigraphy (TL-MPS), exercise capacity by exercise electrocardiography, and left ventricular ejection fraction by bidimensional echocardiography. Lipid levels were significantly improved in the policosanol groups at levels expected from other trials. The policosanol groups showed an insignificantly lower percentage of patients with functional progression of ischemia and a significantly greater partial regression of ischemia assessed by TL-MPS. Furthermore, both exercise capacity and left ventricular function were improved significantly in the policosanol groups compared to the ASA group. Both policosanol groups were more effective than ASA alone, but policosanol plus aspirin was more effective than policosanol alone. There were four vascular events in ASA alone (1 fatal myocardial infarction (MI), 2 unstable angina, 1 cardiac failure), one in the group taking policosanol alone (nonfatal MI), and none in the combined group.

A follow-up study on the same patients examined treadmill exercise EKG testing performance.[40] Those taking policosanol demonstrated decreases in cardiovascular functional class, rest- and exercise-induced angina, cardiac events, and ischemic ST-segment response. These benefits were greatest in the policosanol plus aspirin group. Additionally, policosanol showed an increase in maximum oxygen uptake, a decline in double product (peak heart rate times peak systolic blood pressure), and an increase in aerobic functional capacity compared to placebo.

Atherosclerotic lesions in patients with carotid-vertebral atherosclerosis improved when given policosanol. Twenty-two patients with mild carotid-vertebral atherosclerosis were given 10 mg/day policosanol in a one-year, randomized, placebo-controlled, double-blind trial.[41] Carotid-vertebral atherosclerosis was assessed using Doppler-ultrasound. Progression of disease was seen in three of 11 patients on placebo and no patients on policosanol. Disease regression occurred in six of 11 on policosanol and one of 11 on placebo. Neither of these values reached statistical significance; however, when a progression/regression ratio was calculated it reached statistical significance for improvement with policosanol.

Policosanol improves cardiovascular function assessed by the specific activity scale (SAS). The SAS uses a set of questions to assess a patient's ability to perform a number of normal daily activities.[42] Each activity is given a numerical value called a metabolic equivalent (MES) that is then added up to categorize patients into four functional classes. Sixty-eight patients with type II hypercholesterolemia and high global coronary risk were given 20 mg/day policosanol for one year in a randomized, placebo-controlled, double-blind trial.[43] Lipid levels improved similar to expected values from other trials. Physical capacity, assessed as maximal metabolic equivalents, increased significantly with policosanol but not placebo. The improvement in MES correlated with an improvement in cardiovascular capacity functional class with policosanol but not with placebo.

In another study of 179 elderly patients with type II hypercholesterolemia, policosanol was given at 5 mg/day for 12 weeks, followed by 10 mg/day for 12 more weeks in a randomized, placebo-controlled, double-blind trial.[15] Lipid values declined as expected from other trials. Cardiovascular capacity assessed by MES significantly increased and improvements were seen in cardiovascular functional class frequency with policosanol but not placebo.

Policosanol also decreased symptoms of angina and abnormal rest stress EKG patterns. Policosanol (2 mg/day) was given in a single-blind, placebo-controlled trial for 14 months to 23 middle-aged patients with primary or marginal hypercholesterolemia. Total cholesterol and LDL cholesterol decreased by 14.8 and 15.6 percent despite the low dose.[13] No patient had a new coronary event but significantly more patients (5/12) in the policosanol group with stable angina or silent ischemia had improved coronary symptoms and/or rest stress EKG patterns compared to placebo (0/11). Policosanol-treated patients also had no deterioration in symptoms or rest stress EKG patterns, while three of 11 placebo-treated patients did.

Intermittent Claudication

Two studies show positive results using policosanol on patients with intermittent claudication. Sixty-two patients treated with 10 mg policosanol twice daily for six months[44] were tested on a treadmill at 3.2 km/hr at a 10-percent uphill grade and were asked to note when they first had symptoms (initial claudication) and then when they absolutely could not walk any further (absolute claudication). After six months, initial claudication distances increased from 132.5 meters to 205.7 meters, a 63.1-percent improvement. Absolute claudication distances increased from 229.5 meters to 367.4 meters, a 65.1-percent improvement; placebo had no effect on distances. Policosanol also improved lower extremity symptoms of coldness and pain compared to placebo, but failed to improve arm/ankle pressures. There were significantly more adverse events in the placebo (38.7%) compared to the policosanol group (9.7%).

A two-year follow-up study with 56 patients using the same design was conducted to see if arm/ankle pressures would increase.[45] Improvements were progressive throughout the study with initial claudication improving from 125.9 to 201.1 meters (60.1% improvement) after six months and to 333.5 meters (187.8% improvement) after 24 months. Absolute claudication distances improved from 219.5 to 380.7 meters (81% improvement) after six months and to 648.9 meters (249.5% improvement) after 24 months. Significantly more patients on policosanol (21/27) increased claudication distances greater than 50 percent compared to placebo (5/29). Policosanol also significantly decreased symptoms of claudication and increased arm/ankle pressure at 12 and 24 months. Even more impressive, significantly more patients in the placebo group (8 patients with 10 events) had serious vascular events, while there were none in the policosanol group.

Side Effects

One of the best ways to test a substance for side effects is to look at a very large number of patients for a long duration. Post-marketing studies do this by keeping records on thousands of patients using a product over several years. In post-marketing studies policosanol has been shown to be very safe.

A study monitoring 27,879 patients for an average duration of 2.7 years yielded only 86 patients (0.31%) having adverse effects.[49] The most common adverse effects were weight loss (0.08%), polyuria (0.07%), insomnia (0.05%), and polyphagia (0.05%). Only 22 patients (0.14%) had to discontinue because of adverse effects.

In a five-year study, 3,602 patients with type II hypercholesterolemia and at least one concomitant non-lipid risk factor for cardiovascular disease were compared to 3,009 patients with normal serum lipids and at least one non-lipid risk factor not given policosanol.[50] Patients were started on 5 mg/day policosanol and could be increased up to 20 mg/day. There were significantly more patients hospitalized (10.3% placebo, 7.5% policosanol) and hospitalized with special care (1.6% placebo and 0.97% policosanol) in the placebo-treated patients compared to the policosanol-treated patients. Five patients died; three in the control group (one MI and two strokes) and two in the policosanol group (one due to intoxication and one due to respiratory arrest). At baseline, a history of serious vascular events had been more common in the policosanol group (34 events) compared to placebo (14 events). However, at follow-up there was a significant change to 23 events in the policosanol group and 34 in the placebo group. Twenty-six patients (0.72%) discontinued policosanol because of adverse events, including weight loss, asthenia, and somnolence. Adverse events that did not result in discontinuation were similar between policosanol and control with the most frequent adverse events with policosanol being weight loss (1.75%), polyuria (0.68%), headache (0.61%), dizziness (0.44%), and polyphagia (0.36%).

Toxicity Studies

Toxicological studies on animals indicate policosanol is safe up to 500 mg/kg/day, a dose that is 1500 times the normal human dose of 20 mg/day. In rats, 500 mg/kg/day for 12 or 24 months showed no signs of toxicity or carcinogenicity.[51,52]

Up to 180 mg/kg/day given to beagle dogs for one year showed no adverse effects.[53] Monkeys given 25 mg/kg/day for 54 months had no signs of adverse effects.[54] Finally, mice given up to 500 mg/kg/day for 18 months showed no adverse effects or evidence of carcinogenicity.[55]

Reproductive and fertility studies also show no adverse effects on fertility, reproduction, teratogenesis, or development. In rats, policosanol feeding up to 500 mg/kg/day from the 15th day of pregnancy to 21 days post-parturition resulted in no signs of toxicity for the mother or offspring.[56] In rats, given 500 mg/kg/day for two weeks before mating, throughout pregnancy, and 21 days into lactation, there were no adverse effects on fertility, reproduction, teratology, or postnatal growth and behavior.[57] Male rats given 500 mg/kg/day for 60 days prior to mating showed no signs of decreased fertility.[57] Rats given 500 mg/kg/day for three successive generations showed no adverse effects on fertility, reproduction, or development.[58] Finally, in rabbits, 1000 mg/kg/day during pregnancy showed no evidence of teratogenic effects or embryonic toxicity.[57]

Conclusion

Policosanol appears to be a safe and effective supplement that can be used to lower several cardiovascular disease risk factors. Doses of 5-20 mg/day policosanol have resulted in decreased TC, LDL, TC/HDL and LDL/HDL ratios, and increased HDL in several human populations. Additionally, policosanol has beneficial effects on platelet aggregation, LDL oxidation, intermittent claudication, liver function, and symptoms of cardiovascular disease, while displaying virtually no side effects. Since anecdotal reports by health practitioners using other than policosanol from Cuba have not been as glowing, further research on populations other than Cubans and on policosanol that is currently available in the United States is needed. In addition, research is needed to determine whether these favorable findings will translate into decreased cardiovascular events.

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