# Alternative Therapies

## Policosanol

Policosanol is a dietary supplement made of medium-chain alcohols extracted from sugar cane. In both clinical and animal studies, policosanol has been shown to significantly reduce levels of low-density-lipoprotein (LDL) cholesterol and total cholesterol while increasing levels of high-density-lipoprotein (HDL) cholesterol. Moreover, policosanol has favorable effects on intermittent claudication, possibly due to its effects on platelet aggregation and endothelial function.

**Uses.** Clinical trials indicate that policosanol may have applications in the treatment of familial (type II) and diabetes-related hypercholesterolemia, as well as intermittent claudication.

**Pharmacology.** Policosanol contains a mixture of eight primary aliphatic alcohols (24–34 carbons in length) extracted from sugar cane (*Saccharum officinarum*) wax. Octacosanol is the predominant moiety, comprising approximately 63% of the mixture. Other important constituents include triacontanol (13%) and hexacosanol (6%). Minor components include tetracosanol, heptacocosanol, nonacosanol, dotriacontanol, and tetratriacontanol.

The exact lipid-lowering mechanisms of policosanol have not been adequately elucidated. Policosanol appears to lower LDL and total cholesterol by inhibiting hepatic cholesterol synthesis prior to the formation of mevalonate.[1-3] In addition, policosanol enhances the binding, uptake, and degradation of the LDL cholesterol in the endoplasmic reticulum, independent of its effect on cholesterol synthesis. It is unclear whether policosanol affects hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase.[3,4] The oral absorption and bioavailability of policosanol are limited, and a lipid-lowering effect in the intestine cannot be ruled out.[5] Pharmacokinetic data in humans are lacking.

Policosanol has significant antiplatelet effects in both humans and animal models. Policosanol decreases levels of thromboxane $A_2$ and may increase levels of prostacycline.[6-8] In addition, large doses can inhibit platelet aggregation induced by arachidonic acid and collagen but not by adenosine diphosphate.[9] Policosanol's antiplatelet mechanism of action differs from that of aspirin, and potentiates the antithrombotic effects of aspirin.[10] In humans, 20 mg of policosanol taken daily has a similar effect to 100 mg of aspirin daily on platelet adhesiveness; however, policosanol does not significantly affect coagulation time.[10]

**Clinical studies.** A number of reasonably well-designed, short- and long-term trials found that policosanol significantly lowered both LDL and total cholesterol levels in patients with familial hypercholesterolemia, patients with type 2 diabetes mellitus, postmenopausal women, and elderly patients. Some longer-term studies have shown that policosanol significantly raises HDL cholesterol levels. In addition, policosanol has shown promise in treating patients with intermittent claudication.

*Placebo-controlled trials for treating hypercholesterolemia.* Short-term (eight and six weeks), small randomized clinical trials in patients with familial hypercholesterolemia found that doses of 5 mg/day and 5 mg twice daily, respectively, lowered LDL cholesterol by 17.7% and 21.5% and total cholesterol by 13.1% and 16.2%, respectively ($p < 0.05$ for all).[11,12] Long-term studies (52 and 104 weeks) with type 2 hypercholesterolemic patients showed that 5 mg twice daily lowered LDL cholesterol by 27.5% and 24.8%, lowered total cholesterol by 16.3% and 18.3%, and raised HDL cholesterol by 25.9% and 11.2%, respectively ($p < 0.05$ for all the above).[13,14] These four studies demonstrated that maximum LDL and total cholesterol reductions occur after six to eight weeks of policosanol use, whereas increases in HDL cholesterol require several months of therapy.

A 12-week randomized clinical trial involving 29 patients with hypercholesterolemia and type 2 diabetes mellitus who were taking 5 mg of policosanol twice

*Continued on page 1114*

*The* Alternative Therapies *column features short reviews of herbals and other "nutraceuticals" for which there is some scientific evidence of effectiveness. The contributing editor for* Alternative Therapies *is Joseph Pepping, Pharm.D., Codirector, Integrative Medicine Service, Kaiser Permanente, Honolulu, HI 96814. Readers are invited to send ideas for the column to* AJHP *at 7272 Wisconsin Avenue, Bethesda, MD 20814 (301-657-3000) or ajhp@ashp.org.*

*Continued from page 1112*

daily yielded similar results: LDL and total cholesterol were lowered 21.7% and 16.9%, respectively ($p < 0.05$ for both).[15]

A larger randomized clinical trial involving 244 postmenopausal women with familial hypercholesterolemia found that, in successive groups receiving 12-week regimens of 5 and 10 mg/day, policosanol lowered LDL cholesterol by 17.7% and 25.2% and total cholesterol by 12.6% and 16.7%, respectively ($p < 0.05$ for all).[16] In addition, their HDL cholesterol levels increased by 16.5% and 29.3%, respectively ($p < 0.05$ for both).

A randomized clinical trial of 437 patients with familial hypercholesterolemia and more than two additional risk factors for coronary artery disease (CAD) received 5 mg/day of policosanol or placebo for 12 weeks, then 5 mg twice daily for an additional 12 weeks. The 5- and 10-mg policosanol regimens reduced LDL cholesterol by 18.2% and 25.6% and total cholesterol by 13.0% and 17.4%, respectively ($p < 0.001$ for all).[17] Patients' HDL cholesterol levels increased by 15.5% and 28.4%, respectively ($p < 0.01$ for both), respectively.[17]

A subsequent, 24-week randomized clinical trial by the same authors, involving 179 elderly patients (ages 60–78 years) with familial hypercholesterolemia and at high risk for CAD, found that successive 12-week daily doses of 5 mg, then 10 mg, significantly reduced patients' LDL cholesterol by 16.9% and 24.4% and total cholesterol by 12.8% and 16.2%, respectively ($p < 0.001$ for all).[18] HDL cholesterol levels increased by 14.6% ($p < 0.01$) and 29.1% ($p < 0.001$).

*Comparative trials for treating hypercholesterolemia.* Fifty-three patients with hypercholesterolemia and type 2 diabetes mellitus were randomized to receive either 10 mg of policosanol or 20 mg of lovastatin daily for 12 weeks.[19] Similar results were obtained with each group; policosanol lowered LDL and total cholesterol by 20.4% ($p < 0.0001$) and 14.2% ($p < 0.0001$), respectively, from base line, while lovastatin lowered LDL and total cholesterol by 16.8% ($p < 0.01$) and 14.0% ($p < 0.001$), respectively, from base line. Policosanol increased HDL cholesterol levels by 7.5% ($p < 0.01$), and lovastatin lowered HDL cholesterol by 2.8% (not significant).

Sixty-eight elderly (60–80 years old) patients with familial hypercholesterolemia and multiple risk factors for CAD were randomized to take policosanol or pravastatin 10 mg daily for eight weeks.[20] Again, similar results were obtained with each group; policosanol lowered LDL and total cholesterol by 19.3% ($p < 0.05$) and 13.9% ($p < 0.05$) from base line, respectively, while pravastatin lowered LDL and total cholesterol by 15.6% ($p < 0.05$) and 11.8% ($p \geq 0.05$) from base line, respectively.

Another eight-week trial of 53 elderly patients with hypercholesterolemia compared the effectiveness of 5 mg of policosanol twice daily with 5 mg of simvastatin twice daily.[21] In the policosanol group, LDL and total cholesterol were lowered by 17.9% and 14.7%, respectively, whereas LDL and total cholesterol were lowered by 19.8% and 15.2%, respectively, in the simvastatin group ($p < 0.05$ for all groups).

*Placebo-controlled trials for treating intermittent claudication.* Sixty-two patients with intermittent claudication were randomized to receive policosanol 10 mg twice daily or placebo for six months.[22] Compared with placebo, policosanol significantly increased both the mean ± S.D. initial claudication distance (measured using a treadmill) from 132.5 ± 13.5 to 205.7 ± 36.3 m ($p < 0.05$) and the absolute claudication distance increased from 229.5 ± 22.0 to 365.4 ± 46.9 m ($p < 0.05$), while no changes were noted from base line in the placebo group.

A two-year study of 56 patients by the same research group found similar results.[23] Again, the treatment group received 10 mg of policosanol twice daily or placebo. Treadmill walking distances were measured at 6, 12, 18, and 24 months. After 6 months of therapy, policosanol significantly increased both the mean ± S.D. initial claudication distance from 125.9 ± 8.7 to 201.1 ± 24.8 m ($p < 0.01$) and the absolute claudication distance from 219.5 ± 14.1 to 380.7 ± 50.2 m ($p < 0.01$), compared with placebo. These beneficial effects seemed to improve as the study progressed, with the mean ± S.D. 24-month initial claudication distance increasing from a base line of 125.9 ± 8.7 to 333.5 ± 28.6 m ($p < 0.0001$) and the absolute claudication distance increasing from 219.5 ± 14.1 to 648.9 ± 54.1 m ($p < 0.0001$), compared to placebo.

**Dosage.** The suggested starting dosage of policosanol for treatment of hypercholesterolemia is 5–10 mg daily, taken with the evening meal. Hepatic synthesis of cholesterol is thought to occur primarily at night; therefore, once-daily doses of policosanol should be taken in the evening. Dosages exceeding 10 mg/day are usually given in divided doses with meals. Daily doses as high as 40 mg have been studied; however, maximum clinical benefits appear to be obtained with 20 mg/day.[24] The recommended dosage for intermittent claudication is 10 mg twice daily with meals.

No dosage reduction is necessary in patients with compromised hepatic function. No studies have been conducted with patients with compromised renal function.[5]

**Adverse effects.** Several animal studies using doses up to 500 mg/kg (rat model) did not reveal any significant drug, reproductive, or mutagenic toxicity.[25] Policosanol appears to be well tolerated and safe when given long-term (clinical trials up to three years).[26] Quantifiable adverse effects include weight loss (1.8% of patients), polyuria (0.7%), and headache (0.6%). Other reported adverse effects include insomnia, polyphagia, nervousness, somnolence, dizziness, erythema, excitability, hypotension, hypertension, pruritis, skin rash, nausea, epigastric pain, diarrhea, constipation, and bleeding from the nose and gums.[5] Increases in hepatic enzymes and creatine kinase have not been reported with policosanol.

**Drug interactions.** Because of its effects on platelet adhesiveness, policosanol can have additive effects with all anticoagulant and antiplatelet medications. Cumulative data from long-term clinical trials have not indicated drug inter-

actions or additive toxicity with calcium-channel blockers, angiotensin-converting-enzyme inhibitors, β-blockers, diuretics, nitrates, nonsteroidal antiinflammatory agents, anxiolytics, antidepressants, neuroleptics, oral hypoglycemic agents, digoxin, thyroid hormones, and antiulcer medications.[5] However, formal drug interaction studies in humans have not been performed.

**Contraindications and precautions.** Policosanol should be avoided in pregnant and lactating women until further research can be performed to assure its safety in this population.

Since the mechanism of action has not been clearly defined, policosanol should not be given concurrently with HMG-CoA reductase inhibitors until further research can prove the safety of using both medications concurrently.

**Conclusion.** Policosanol is a relatively nontoxic and useful agent for reducing LDL and total cholesterol in patients with type 2 or diabetes-related hypercholesterolemia. Long-term use may increase levels of HDL cholesterol. While the lack of numerous independent clinical trials precludes the use of policosanol as a first-line agent for treating hypercholesterolemia or intermittent claudication, available safety and efficacy data indicate that it may be useful as a second-line agent in patients who cannot use HMG-CoA reductase inhibitors and other lipid-lowering medications.


1. Menendez R, Fernandez SI, Del Rio A et al. Policosanol inhibits cholesterol biosynthesis and enhances low density lipoprotein processing in cultured human fibroblasts. *Biol Res.* 1994; 27:199-203.
2. Menendez R, Amor AM, Gonzales RM et al. Effect of policosanol on the hepatic cholesterol biosynthesis of normocholesterolemic rats. *Biol Res.* 1996; 29: 253-7.
3. Menendez R, Arruzazabala L, Mas R et al. Cholesterol-lowering effect of policosanol on rabbits with hypercholesterolaemia induced by a wheat starch-casein diet. *Br J Nutr.* 1997; 77:923-32.
4. Menendez R, Amor AM, Rodeiro I et al. Policosanol modulates HMG-CoA reductase activity in cultured fibroblasts. *Arch Med Res.* 2001; 32(1):8-12.
5. Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J.* 2002; 143:356-65.
6. Arruzazabala ML, Valdez S, Mas R et al. Effect of policosanol successive dose increases on platelet aggregation in healthy volunteers. *Pharmacol Res.* 1996; 34:181-5.
7. Valdes S, Arruzazabala ML, Fernandez L et al. Effect of policosanol on platelet aggregation in healthy volunteers. *Int J Clin Pharmacol Res.* 1996; 16:67-72.
8. Arruzazabala ML, Molina V, Carbajal D et al. Effect of policosanol on cerebral ischemia in Mongolian gerbils: role of prostacyclin and thromboxane A2. *Prostaglandins Leukot Essent Fatty Acids.* 1993; 49:695-7.
9. Carbajal D, Arruzazabala ML, Valdes S et al. Effect of policosanol on platelet aggregation and serum levels of arachidonic acid metabolites in healthy volunteers. *Prostaglandins Leukot Essent Fatty Acids.* 1998; 58:61-4.
10. Arruzazabala ML, Valdez S, Mas R et al. Comparative study of policosanol, aspirin and the combination therapy policosanol–aspirin on platelet aggregation in healthy volunteers. *Pharmacol Res.* 1997; 36:293-7.
11. Pons P, Mas R, Illnait J et al. Efficacy and safety of policosanol in patients with primary hypercholesterolemia. *Curr Ther Res.* 1992; 51:568-75.
12. Aneiros E, Mas R, Calderon B et al. Effect of policosanol in lowering cholesterol levels in patients with type II hypercholesterolemia. *Curr Ther Res.* 1995; 56:176-82.
13. Canetti M, Moreiro M, Illnait J et al. One-year study of the effect of policosanol on lipid profile in patients with type II hypercholesterolemia. *Adv Ther.* 1995; 12:245-54.
14. Canetti M, Moreiro M, Mas R et al. A two-year study on the efficacy and tolerability of policosanol in patients with type II hyperlipoproteinaemia. *Int J Clin Pharmacol Res.* 1995; 15:159-65.
15. Torres O, Agreamonte AJ, Illnait J et al. Treatment of hypercholesterolemia in NIDDM with policosanol. *Diabetes Care.* 1995; 18:393-6.
16. Castano G, Mas R, Fernandez L et al. Effects of policosanol on postmenopausal women with type II hypercholesterolemia. *Gynecol Endocrinol.* 2000; 14:187-95.
17. Mas R, Castano G, Illnait J et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther.* 1999; 65:439-47.
18. Castano G, Mas R, Fernandez J et al. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J Gerontol.* 2001; 56A: M186-92.
19. Crespo N, Illnait J, Mas R et al. Comparative study of the efficacy and tolerability of policosanol and lovastatin in patients with hypercholesterolemia and noninsulin dependent diabetes mellitus. *Int J Clin Pharmacol Res.* 1999; 19:117-27.
20. Castano G, Mas R, Arruzazabala M et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelemia in older hypercholesterolemic patients. *Int J Clin Pharmacol Res.* 1999; 19:105-16.
21. Ortensi G, Gladstein J, Valli H et al. A comparative study of policosanol versus simvastatin in elderly patients with hypercholesterolemia. *Curr Ther Res.* 1997; 58: 390-401.
22. Castano G, Mas R, Roca J et al. A double-blind, placebo-controlled study of the effects of policosanol in patients with intermittent claudication. *Angiology.* 1999; 50: 123-30.
23. Castano G, Mas R, Fernandez L et al. A long-term study of policosanol in the treatment of intermittent claudication. *Angiology.* 2001; 52:115-25.
24. Castano G, Mas R, Fernandez L et al. Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: a 6-month double-blind study. *Int J Clin Pharmacol Res.* 2001; 21:43-57.
25. Aleman CL, Mas R, Hernandez C et al. A 12-month study of policosanol oral toxicity in Sprague Dawley rats. *Toxicol Lett.* 1994; 70:77-87.
26. Fernandez L, Mas R, Illnait J et al. Policosanol: results of a postmarketing surveillance of 27,879 patients. *Curr Ther Res.* 1998; 59:717-22.


**Joseph Pepping, Pharm.D.**