

Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent

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Background Policosanol is a mixture of higher primary aliphatic alcohols isolated from sugar cane wax, whose main component is octacosanol. The mixture has been shown to lower cholesterol in animal models, healthy volunteers, and patients with type II hypercholesterolemia.

Methods We reviewed the literature on placebo-controlled lipid-lowering studies using policosanol published in peer-reviewed journals as well as studies investigating its mechanism of action and its clinical pharmacology.

Results At doses of 10 to 20 mg per day, policosanol lowers total cholesterol by 17% to 21% and low-density lipoprotein (LDL) cholesterol by 21% to 29% and raises high-density lipoprotein cholesterol by 8% to 15%. Because higher doses have not been tested up to now, it cannot be excluded that effectiveness may be even greater. Daily doses of 10 mg of policosanol have been shown to be equally effective in lowering total or LDL cholesterol as the same dose of simvastatin or pravastatin. Triglyceride levels are not influenced by policosanol. At dosages of up to 20 mg per day, policosanol is safe and well tolerated, as studies of >3 years of therapy indicate. There is evidence from in vitro studies that policosanol may inhibit hepatic cholesterol synthesis at a step before mevalonate generation, but direct inhibition of the hydroxy-methylglutaryl-coenzyme A reductase is unlikely. Animal studies suggest that LDL catabolism may be enhanced, possibly through receptor-mediated mechanisms, but the precise mechanism of action is not understood yet. Policosanol has additional beneficial properties such as effects on smooth muscle cell proliferation, platelet aggregation, and LDL peroxidation. Data on efficacy determined by clinical end points such as rates of cardiac events or cardiac mortality are lacking.

Conclusions Policosanol seems to be a very promising phytochemical alternative to classic lipid-lowering agents such as the statins and deserves further evaluation. (*Am Heart J* 2002;143:356-65.)

Data from the Framingham Epidemiological Study indicate that increases in serum cholesterol levels are associated with an increased risk of death from coronary heart disease (CHD)¹ and the 1988 National Cholesterol Education Program (NCEP) has identified elevated low-density lipoprotein cholesterol (LDL-C) as a primary risk factor for CHD.² The 1993 NCEP Adult Treatment Panel II Report has recommended aggressive dietary and drug therapy for patients with known CHD.³ The most potent drugs that are currently used to lower elevated LDL-C levels are the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins). In a meta-analysis it was shown that for every 10 percentage points of cholesterol lowering CHD mortality was decreased by 13% and total mortality by 10%.⁴ Although, according to the most recently published United States National Health

and Nutrition Examination Survey (NHANES III), an estimated 5.5 million Americans with CHD should be treated with lipid-lowering medications under the NCEP guidelines,⁵ only a small proportion of them actually receives treatment.⁶ Because patient reluctance to be treated with chemically derived drugs, especially for primary prevention, may contribute to the above discrepancy, there is a need for effective, safe, and, ideally, naturally derived cholesterol-lowering drugs.

Policosanol is a drug currently in use to reduce elevated LDL-C and total cholesterol levels in combination with dietary therapy in patients with hypercholesterolemia. It was originally developed by Dalmer Laboratories, Havana, Cuba, and was approved for use in Cuba in 1991. Currently it is used in >25 countries throughout the world, mainly in South America and in the Caribbean region, with approval or registration filed or planned in several other countries.

Chemical characteristics

Policosanol is a natural mixture of aliphatic primary alcohols that are isolated from purified sugar cane (*Saccharum officinarum* L) wax by hydrolytic cleavage and subsequent purification. The chemical formula is $\text{CH}_3-(\text{CH}_2)_n-\text{CH}_2\text{OH}$ with chain length varying from 24 to

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Submitted January 22, 2001; accepted August 29, 2001.

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0002-8703/2002/\$35.00 + 0 4/1119997

doi:10.1067/mhj.2002.119997

34 carbon atoms. Octacosanol (62.9%), triacontanol (12.6%), and hexacosanol (6.2%) are the major components of the mixture. Policosanol is supplied as film-coated tablets of 5 and 10 mg.

Effects on cholesterol and lipoprotein metabolism

Lipid-lowering effects of policosanol have been shown in a variety of animal species, including rabbits and other rodents, beagle dogs, monkeys, swine, and chickens. Because policosanol exerts its main effect on LDL-C, a mechanism of action through cholesterol synthesis inhibition or enhanced LDL catabolism would be conceivable. In cultured human fibroblasts policosanol decreased carbon 14-labeled acetate incorporation into cholesterol, whereas incorporation of ¹⁴C-labeled mevalonate was not affected, suggesting inhibition of cholesterol synthesis *in vitro* at a step before mevalonate formation.⁷ LDL binding, uptake, and degradation were enhanced at concentrations that did not significantly decrease cholesterol synthesis.⁷ Unfortunately, these studies lack adequate controls, the completion of full dose-response curves, or an adequate number of repeats to secure sound statistics. Moreover, a decrease in cholesterol synthesis *in vivo* in rats by use of tritiated water could not be demonstrated beyond doubt.⁸ There was also no competitive or noncompetitive inhibition of HMG-CoA reductase in liver homogenates.⁸ In rabbits with hypercholesterolemia (induced by wheat starch-casein diet), policosanol decreased tritiated water incorporation into hepatic sterols.⁹ In addition, the rate of removal of iodine 125-labeled LDL from blood and the hepatic LDL binding capacity were enhanced, suggesting that, at least in part, increased receptor-mediated uptake by the liver is involved in the policosanol-induced LDL-C decrease. On the basis of the studies mentioned, the precise mechanism leading to LDL reduction remains unclear, but inhibition of cholesterol synthesis, increased hepatic LDL uptake, and increased serum LDL catabolic rates may play a role. Other mechanisms for lowering cholesterol such as inhibition of cholesterol or bile acid absorption from the intestine, effects on lipoprotein production/secretion, or increased fecal excretion of bile acids have not been investigated. It should be pointed out that *in vitro* work with policosanol is hampered by the fact that the aliphatic alcohol mixture is very difficult to dissolve.

In summary, little is known about the mechanisms of the lipid-lowering actions of policosanol. Because the overall absorption of policosanol is low but its effects are substantial, a lipid-lowering effect on the level of the intestine should be considered, which would distinguish policosanol from other known lipid-lowering principles. It is assumed that its major constituent, octacosanol, is mainly responsible for its effects, but in

some experimental models the specific mixture of the policosanol aliphatic alcohols is slightly superior to octacosanol alone. On the basis of the demonstration that fatty alcohol oxidation can be achieved in cell cultures and in intestinal mucosa through a reversible fatty alcohol cycle^{10,11} and that β -oxidation chain shortening of very long chain fatty acids (VLCFA) occurs in rat liver peroxisomes,^{12,13} Menendez et al⁹ speculated that policosanol-induced changes in hepatic cholesterol metabolism may be caused by the presence not only of aliphatic alcohols but also of VLCFA and chain-shortened secondary metabolites.

Clinical pharmacology

Pharmacokinetics

Pharmacokinetic data in humans are unpublished except for one study that used tritiated octacosanol where only total radioactivity was measured.¹⁴ Studies with unlabeled octacosanol could not be evaluated because of the detection limit of the analytic methods used. A gas chromatographic method for determining the fatty alcohols composing policosanol in the film-coated tablets has been published,¹⁵ and a method exists for determination of 1-octacosanol in plasma of animals after intravenous dosing,¹⁶ but there is no validated method to determine these compounds or their metabolites in serum or tissues *ex vivo* after administration of therapeutic doses to humans. Thus there is no final proof that significant amounts of the intact aliphatic alcohols are absorbed from the intestinal tract and are systemically available.

The pharmacokinetic data in animals are sparse: kinetic studies were performed with oral administration of tritiated octacosanol in various doses. Almost exclusively, total radioactivity was measured, thus not allowing a pharmacokinetic characterization of the parent drug. Absorption in rodents after oral administration is assumed to range between 10% and 35% and bioavailability between 5% and 12%. Studies after oral administration of ¹⁴C-labeled octacosanol in rats show that the absorbed fraction is distributed between several tissues and may be partially degraded to fatty acids.¹⁷ According to unpublished data of Menendez et al (cited in reference 9), tritiated octacosanol is present mainly in the liver within 24 hours after oral administration and octacosanoic acid, presumably an active metabolite, can also be found there. Quantitative evaluation of these kinetic data is missing. Studies in different animal species with an intravenously administered emulsion of octacosanol revealed a terminal half-life of the compound between 1 and 2 hours.

Drug interactions

Data from long-term studies in humans indicate that coadministration of nifedipine and other calcium antago-

Table I. Randomized double-blind placebo-controlled trials with the primary outcome parameter of cholesterol lowering

Reference	Study population (No. of participants)	Policosanol dosage regimen (mg/d)	Treatment duration (wk)	Baseline LDL-C (mg/dL [mmol/L]) of treatment group	LDL-C change (%)
27	HV (38)	2 × 5 2 × 10	4	114 ± 28 (2.9 ± 0.7) 114 ± 23 (2.9 ± 0.6)	-10.0 (NS) -22.0*
28	HC (56)	1 × 5	8	197 ± 26 (5.1 ± 0.7)	-17.7*
29	HC (45)	2 × 5	6	214 ± 47 (5.5 ± 1.2)	-21.5*
30	HC (33)	2 × 5 2 × 10	6 6	195 ± 32 (5.0 ± 0.8)	-21.2* -30.0*
23	HC (22)	1 × 5 2 × 5 2 × 10	8 8 8	221 ± 54 (5.7 ± 1.4)	-11.3* -21.9* -32.2*
31	HC (59)	1 × 5	52	188 ± 26 (4.9 ± 0.7)	-23.7*
32	HC (97)	2 × 5	52	210 ± 36 (5.4 ± 0.9)	-27.5*
33	HC (69)	2 × 5	104	207 ± 37 (5.4 ± 1.0)	-24.8*

Only English language original publications are referenced. All studies are single-center trials. TC, Total cholesterol; HDL-C, high-density lipoprotein cholesterol; HV, healthy volunteers; NS, not significant; HC, patients with hypercholesterolemia type II.

* $P < .05$ between values at baseline and end of treatment.

Table II. Randomized double-blind placebo-controlled trials with the primary outcome parameter of cholesterol lowering in special patient populations

Reference	Study population (No. of participants)	Policosanol dosage regimen (mg/d)	Treatment duration (wk)	Baseline LDL-C (mg/dL [mmol/L]) of treatment group	LDL-C change (%)	TC change (%)
36	HC and NIDDM (29)	2 × 5	12	212 ± 47 (5.5 ± 1.2)	-21.7*	-16.9*
37	HC and NIDDM (19)	2 × 5	12	204 ± 41 (5.3 ± 1.1)	-44.4*	-28.9*
38	HC and hypertension (58)	2 × 5	52	203 ± 32 (5.2 ± 0.8)	-19.1*	-13.0*
39	HC elderly patients (62)	2 × 5	52	209 ± 39 (5.4 ± 1.0)	-23.1*	-15.6*
35	HC postmenopausal women (244)	1 × 5 1 × 10	12 12	195 ± 44 (5.0 ± 1.1)	-17.7* -25.2*	-12.6* -16.7*
40	HC and >2 risk factors (437)	1 × 5 2 × 5	12 12	197 ± 29 (5.1 ± 0.7)	-18.2* -25.6*	-13.0* -17.4*
21	HC and hepatic dysfunction (46)	1 × 5 2 × 5	12 12	200 ± 20 (5.2 ± 0.5) 209 ± 48 (5.4 ± 1.2)	-19.1* -22.3*	-13.6* -15.4*

Only English language original publications are referenced. All studies except for references 38 and 40 are single-center trials. TC, Total cholesterol; HC, patients with hypercholesterolemia type II; NIDDM, non-insulin-dependent diabetes mellitus; NS, not significant.

* $P < .05$ between values at baseline and end of treatment.

† $P = .06$.

nists, angiotensin-converting enzyme inhibitors, β -blockers, diuretics, nitrates, nonsteroidal anti-inflammatory drugs, anxiolytics, antidepressants, neuroleptics, oral hypoglycemic drugs, digoxin, thyroid hormones, and antiulcer drugs is safe; however, formal drug interaction studies in humans have not been performed until now.

Dosing and use in special patient populations

The recommended starting dose of policosanol is 5 mg once a day, taken with the evening meal, which can

be increased up to 10 and 20 mg per day. Higher dosages, up to 80 mg per day, are currently being studied. The drug is contraindicated during pregnancy, although no teratogenic effects have been found in animal models.¹⁸⁻²⁰ It is unknown whether the drug or its metabolites pass into human milk; therefore therapy must be discontinued during lactation. Treatment of children is not recommended because of lack of experience in this particular population. The drug seems to be safe in elderly subjects. In patients with impaired

TC change (%)	HDL-C change (%)	LDL/HDL change (%)	TC/HDL change (%)	Triglycerides change (%)	Remarks
-10.7 *	+2.6 (NS)	-22.4 (NS)	-19.7*	-33.6*	3-Group study design (2 dosages vs placebo)
-11.3*	+23.9*	-42.4*	-32.6*	-36.5 (NS)	
-13.1*	-3.3 (NS)	-14.1*	-9.1*	-13.7 (NS)	
-16.2*	+14.0 (NS)	-23.0*	-17.7*	-4.3 (NS)	
-16.7*	+2.9 (NS)	-24.9*	-21.0*	-23.3 (NS)	Successive dose increases, 6 wk each period (total 12 wk)
-20.9*	+7.7 (NS)	-33.8*	-26.0*	-12.1 (NS)	
-8.0*	+7.8 (NS)	-15.3*	-12.5*	-2.7 (NS)	Successive dose increases, 8 wk each period (total 24 wk)
-14.1*	+7.2 (NS)	-25.6*	-18.4*	+7.8 (NS)	
-23.0*	+7.7 (NS)	-34.6*	-27.2*	-10.5 (NS)	
-15.3*	+2.2 (NS)	-25.3*	-17.0*	±0.0 (NS)	
-16.3*	+25.9*	-37.1*	-28.0*	+17.5 (NS)	HDL +21% after 52 wk, +14% after 78 wk, and +11.2% after 104 wk
-18.3*	+11.2*	-32.6*	-26.6*	+13.0 (NS)	

HDL-C change (%)	LDL/HDL change (%)	TC/HDL change (%)	Triglycerides change (%)	Remarks
+6.5 (NS)	-26.5*	-22.0*	-6.6 (NS)	See Table III for another study in NIDDM patients ⁴⁴
+23.5*	-51.6*	-38.3*	-2.4 (NS)	
+17.1*	-24.2*	-20.0*	-8.0 (NS)	Patients aged 60-80 y Successive dose increases, 12 wk each period (total of 24 wk)
+6.3 (NS)	-25.2*	-19.0*	-3.5 (NS)	
+16.5*	-17.0*	-16.7*	+3.5 (NS)	Successive dose increases, 12 wk each period (total of 24 wk) (See Table III for another study of patients with multiple CHD risk factors. ⁴⁵)
+29.3*	-29.3*	-27.2*	-4.6 (NS)	
+15.5*	-19.1*	-17.3*	+1.5 (NS)	4-Group study design (2 dosages vs 2 placebo groups); high dropout rate (10/46)
+28.4*	-32.5*	-28.8*	-5.2*	
+11.5*	-25.5*	-21.1*	-11.9 (NS)	
+17.9†	-32.2*	-26.1*	-10.2 (NS)	

liver function, no dose reduction is recommended.²¹ Studies in patients with impaired kidney function have not been published.

Toxicity and clinical safety profile

Experiments of single- and repeated-dose toxicity in several animal species, reproductive toxicity, mutagenic potential in vitro and in vivo as well as carcinogenicity tests of policosanol did not reveal any safety concerns. For example, a 1-year study in rats receiving

oral administration of up to 500 mg/kg per day did not cause any drug-related toxicity.²² Single oral doses of 1000 mg administered to healthy volunteers were tolerated without adverse drug reactions. During long-term administration, policosanol is generally well tolerated and safe, causing no serious adverse clinical or biochemical effects.²³⁻²⁵ The most frequently reported adverse events are weight loss (1.8%), polyuria (0.7%), and headache (0.6%).²⁶ Other side effects are insomnia, polyphagia, nervousness, somnolence, dizziness,

Table III. Randomized double-blind comparative trials with the primary outcome parameter of cholesterol lowering

Reference	Study population (No. of participants)	Treatment and dosage regimen (mg/d)	Treatment duration (wk)	Baseline LDL-C (mg/dL [mmol/L]) of treatment groups	LDL-C change (%)
41	HC elderly patients (53)	Policosanol 2 × 5 Simvastatin 2 × 5	8	194 ± 32 (5.0 ± 0.8) 196 ± 18 (5.1 ± 0.5)	-17.9* -19.8*
42	HC (24)	Policosanol 2 × 5 Pravastatin 1 × 10	6	193 ± 19 (5.0 ± 0.5) 195 ± 8 (5.0 ± 0.2)	-24.2* -19.6*
43	HC in elderly patients with multiple CHD risk factors (68)	Policosanol 1 × 10 Pravastatin 1 × 10	8	179 ± 23 (4.6 ± 0.6) 173 ± 25 (4.6 ± 0.6)	-19.3* -15.6*
44	NIDDM (53)	Policosanol 1 × 10 Lovastatin 1 × 20	12	206 ± 46 (5.3 ± 1.2) 204 ± 40 (5.3 ± 1.0)	-20.4* -16.8*
45	HC and >2 CHD risk factors (59)	Policosanol 1 × 10 Lovastatin 1 × 20	12	181 ± 35 (4.7 ± 0.9) 176 ± 31 (4.6 ± 0.8)	-32.4* -27.6*
46	CD (29)	Bezafibrate 1 × 400 Bezafibrate 1 × 400 plus policosanol 1 × 10	8	185 ± 29 (4.8 ± 0.8) 205 ± 38 (5.3 ± 1.0)	-10.7* -27.7*

Only English language original publications are referenced. All studies are single-center trials. TC, Total cholesterol; HC, patients with hypercholesterolemia type II; NS, not significant; CD, combined dyslipidemia.

* $P < .05$ between values at baseline and end of treatment.

excitability, hypotension, hypertension, pruritus, skin rash, nausea, epigastric pain, diarrhea and constipation.

Efficacy

Clinical trials overview

The efficacy and tolerability of policosanol have been documented in >3000 patients in >60 clinical trials. Sufficient data on white and other ethnic populations are still lacking and are necessary to comply with International Conferences on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data" regulations.

Lipid-lowering clinical trials (Table I)

A substantial number of clinical studies have been carried out during short- and long-term administration of policosanol in randomized placebo-controlled study designs that were published in the English language. Publications in Spanish and unpublished studies are not considered in this review. In normocholesterolemic volunteers without dietary restrictions, 10 or 20 mg of policosanol per day given for 4 weeks decreased total and LDL cholesterol significantly and dose dependently.²⁷ Short-term studies over a 6- or 8-week period in patients with type II hypercholesterolemia indicated that 5 or 10 mg per day would lower total cholesterol by about 13% or 16% and LDL-C by about 18% or 22%, respectively.^{28,29} Two further short-term studies over 6 to 8 weeks that used incre-

mental dose increases confirmed that the cholesterol-lowering effects are dose dependent and that, with 20 mg per day, LDL-C can be lowered by about 30%.^{23,30} In addition, the ratios of total and LDL cholesterol to high-density lipoprotein cholesterol (HDL-C) can be substantially lowered in the order of magnitude of 30%. HDL-C increased only slightly but not significantly and triglyceride levels showed a variable response.

Long-term studies performed over a 1-year period with use of 5 mg per day³¹ or 10 mg per day³² and over 2 years with use of 10 mg per day³³ showed that the total and LDL cholesterol-lowering effects are maintained throughout this time period and that the maximal effects are reached after 6 to 8 weeks of treatment. On the other hand, the increase in HDL-C seems to develop much more slowly than the decrease in apolipoprotein B-containing lipoproteins. Furthermore, the cholesterol-lowering effects do not differ substantially between the 5- and the 10-mg doses. Until now there has been no double-blind placebo-controlled long-term study with 20 mg per day or higher doses.

Of specific interest is the ability of policosanol to increase HDL-C, which has been observed consistently in several studies in patients with type II hypercholesterolemia.^{23,28,29,34,35} Accordingly, the ratios of total or LDL cholesterol to HDL-C, which are considered important parameters to characterize beneficial effects on lipid profiles in terms of cardiovascular risk, were improved substantially. In this respect, policosanol seems to be superior to both statins and fibrates. Triglycerides are also reduced to some extent in

TC change (%)	HDL-C change (%)	LDL/HDL change (%)	TC/HDL change (%)	Triglycerides change (%)	Remarks
-14.7*	-1.7 (NS)	-15.4*	-12.4*	-13.8*	Patient age 60-77 y (Baseline triglyceride concentrations were significantly higher in policosanol group.) HC type IIb
-15.2*	-2.9 (NS)	-16.6*	-11.8*	-8.7*	
-15.7*	+13.6*	-33.0*	-25.7*	-8.7*	
-15.3*	+4.7 (NS)	-22.8*	-18.7*	-13.7*	Patients' age 60-80 y (Additional outcome parameters were effects on platelet aggregation.)
-13.9*	+18.4*	-28.3*	-24.4*	-14.1*	
-11.8	+5.6*	-18.9*	-15.7*	-3.4 (NS)	
-14.2*	+7.5*	-23.7*		-18.4 (NS)	
-14.0*	-2.8 (NS)	-14.9*		-0.5 (NS)	
-22.4*	+14.3*	-39.3*	-32.0*	-22.5*	
-19.8*	+3.7 (NS)	-32.8*	-25.2*	-24.0*	Baseline triglyceride levels: 295 ± 80 (3.3 ± 0.9) 277 ± 65 (3.1 ± 0.7)
-9.2*	+8.0*	-13.3*	-13.8*	-29.2*	
-20.8*	+14.5*	-36.8*	-29.8*	-30.2*	

patients with type II hypercholesterolemia but mostly not significantly. Policosanol does not induce a rebound effect after treatment cessation.^{24,32,33}

Studies in special patient populations (Table II)

Because CHD is the main cause of death in patients with diabetes mellitus, with its characteristic dyslipidemia being a major risk factor, the efficacy of new lipid-lowering agents must be comprehensively investigated in this patient group. A double-blind placebo-controlled study using 10 mg per day in patients with controlled non-insulin-dependent diabetes mellitus (NIDDM) and hypercholesterolemia showed significant reductions in total cholesterol of 16.9%, in LDL-C of 21.7%, and a nonsignificant increase in HDL-C of 6.5%.³⁶ Triglyceride concentrations, glucose levels, and hemoglobin (Hb) A₁ values remained unchanged. In another study in diabetic patients, LDL-C levels decreased by 44% and HDL-C increased by 23.5%.³⁷ The ratios of total and LDL-C to HDL-C were significantly improved. It remains unclear why the effects on cholesterol were so large in this latter study, but because of its pronounced effect on the ratio of LDL-C to HDL-C policosanol seems to be very promising for the treatment of diabetic dyslipidemia.

In a study in patients with type II hypercholesterolemia and concomitant hypertension, it was shown that policosanol significantly lowered systolic blood pressure by a mean of 10 mm Hg.³⁸ Beneficial effects on blood pressure have not been confirmed in other studies.

The safety and efficacy of policosanol was documented in elderly hypercholesterolemic patients in a

long-term study.³⁹ No increase in drug-related adverse events was observed in this special population, where impairment in renal and hepatic function, multiple medication intake, and concomitant diseases are usually present. A recent study in postmenopausal women with type II hypercholesterolemia demonstrated effective lowering of total and LDL-C and an increase of HDL-C (by 29%) and good tolerability.³⁵

A study in patients with type II hypercholesterolemia and 2 or more additional CHD risk factors confirmed the good safety profile and efficacy of the drug.⁴⁰ An open-label study over 1 year using 20 mg per day in patients with a high CHD risk (88% family history of premature CHD, 71% hypertension, 60% previous coronary events, 60% severe hypercholesterolemia >300 mg/dL [7.8 mmol/L]) demonstrated an impressive decrease in LDL-C of 44.8% and an increase in HDL-C of 68.5%.³⁴

Studies comparing policosanol with other lipid-lowering drugs

Of special interest in judging the efficacy of policosanol are trials in which the effects of established lipid-lowering medications, such as statins or fibrates, are compared with those of policosanol. Unfortunately, most of these studies are published in Spanish and are thus not accessible to the general scientific community, published only in abstract form, or exist as "data on file" in the manufacturer's laboratories. Additional studies comparing policosanol directly with statins are planned.

Table III shows the available trials. Comparison of

simvastatin (10 mg per day) with policosanol (10 mg per day) in elderly patients with moderate primary hypercholesterolemia showed that both drugs have at these dosages similar efficacy in lowering total cholesterol and LDL-C.⁴¹ In another short-term study (6 weeks) comparing the efficacy of policosanol (10 mg per day) versus pravastatin (10 mg per day), the reduction in total cholesterol was similar with both drugs, whereas the decrease in LDL-C and the increase in HDL-C were more pronounced during policosanol treatment.⁴² This finding could be confirmed in a recent study in elderly patients treated for 8 weeks.⁴³ A study in patients with NIDDM comparing policosanol (10 mg per day) with lovastatin (20 mg per day) also showed that policosanol was slightly superior in lowering total and LDL cholesterol and increasing HDL-C.⁴⁴ This finding was confirmed in a study using the same dosages in patients with multiple CHD risk factors.⁴⁵

Comparative studies with policosanol versus gemfibrozil, bezafibrate, probucol, and acipimox have been performed but are not published in referenced English language journals. In short, policosanol (10 mg per day) was slightly more effective in lowering LDL-C than gemfibrozil (1200 mg per day), bezafibrate (400 mg per day), probucol (1000 mg per day), or acipimox (750 mg per day). A pilot study comparing the effects of bezafibrate alone (400 mg per day) versus bezafibrate plus policosanol (10 mg per day) showed that the coadministration is safe and that policosanol is able to augment the HDL-C-raising and LDL-C-lowering effects of fibrate monotherapy, whereas the triglyceride-lowering effects could not be augmented.⁴⁶

Studies in patients with CHD and other atherosclerotic manifestations

Several studies have been performed in patients with CHD.⁴⁷⁻⁵⁰ The ultimate goal of lipid-lowering medications is to prove significant efficacy on clinical end points. Up to now, there has been no study that demonstrates such beneficial effects of policosanol. A study in 23 middle-aged patients with CHD receiving 2 mg per day for 14 months was certainly not long enough and not adequately powered to demonstrate such effects.⁴⁷ The same holds true for a study investigating regression of carotid-vertebral atherosclerosis by Doppler ultrasonography after 1 year of treatment⁵¹ and another study in secondary prevention patients investigating functional improvement of CHD by thallium myocardial perfusion scintigraphy, maximum oxygen uptake during exercise electrocardiography, and bidimensional echocardiography.^{48,49} However, because of improved maximum oxygen uptake, increased aerobic functional capacity and a lower double product (peak heart rate multiplied by peak sys-

toxic blood pressure),⁴⁸ there is evidence for some "ergogenic" (exercise performance promoting) effect of policosanol (or octacosanol) that had been discussed previously.⁵²

A double-blind placebo-controlled study in 62 patients with claudication with use of policosanol 20 mg per day over 6 months demonstrated a significant improvement of initial and absolute claudication distance with no significant change in the ankle/arm pressure ratio.⁵³ These data were confirmed recently in a long-term study⁵⁴ and may be attributed to the antiplatelet effects of the drug (see below).

Other pharmacodynamic effects in animal models and humans

There is evidence from various animal studies that policosanol prevents the onset of spontaneously and experimentally induced atherosclerotic lesions. It seems to have, in addition to reducing cholesterol, effects on smooth muscle cell proliferation, LDL oxidation, and platelet aggregation. In rabbits and rats it reduces the development of atherosclerotic lesions, including foam cell formation^{55,56} and neointimal formation (smooth muscle cell proliferation).⁵⁷ Policosanol decreased the susceptibility of lipoproteins to peroxidation in rats⁵⁸ and in humans *in vivo*.⁵⁹

Policosanol has pronounced antiplatelet effects in animal models and there is evidence that a decrease in thromboxane B₂ and an increase in prostacyclin levels is involved.⁶⁰⁻⁶² These effects have also been discussed as the mechanisms responsible for the anti-ischemic action of policosanol demonstrated in animal models of cerebral ischemia.⁶³ Antiplatelet effects were also shown in healthy volunteers during single or continuous dosing^{64,65} and in patients with hypercholesterolemia.^{43,66} A comparative study showed that the antiplatelet effects of policosanol are equal to those of aspirin and that the combination of the 2 drugs has some advantages over the respective monotherapies.⁶⁷ A study using 10 mg of policosanol per day showed that platelet aggregation induced by arachidonic acid and collagen, but not by adenosine diphosphate, was significantly inhibited, whereas there was no significant increase in 6-keto-prostaglandin F_{1α} levels.⁶⁸ The fact that policosanol potentiates the antithrombotic effects of aspirin together with the latter observation suggests that policosanol has a different mechanism of action than aspirin. Because a relationship between serum cholesterol and thromboxane A₂ formation in human platelets has been shown, suggesting that thromboxane formation and platelet hyperreactivity may be associated with hypercholesterolemia, the antiplatelet properties of policosanol seem to be the most promising additional feature of this new lipid-lowering drug.

Conclusions and future perspectives

Policosanol has been proved to possess potent cholesterol-lowering properties that, at the dosages evaluated clinically up to now, are comparable to the effects of the low to medium dosage levels of the older statins. In addition, policosanol has antiplatelet effects, prevents lipoprotein peroxidation, and beneficially affects atherosclerosis development in a variety of experimental models. Other potential advantages of the drug are its good tolerability and a low rate of clinical and laboratory adverse events, which may obviate the need for frequent monitoring of specific laboratory parameters. A major shortcoming in evaluating the in vitro work investigating the mechanism of action of policosanol is the fact that the majority of the experiments have been performed in one center only. The clinical studies were also performed in very few centers exclusively in Middle and South America. Independent confirmation of the findings is necessary. It should also be pointed out that until now no clinical outcomes studies have been done. Further pharmacokinetic studies of the complex metabolism of this mixture of naturally occurring compounds and efforts to elucidate the precise lipid-lowering mechanism of action are currently under way.

An intriguing characteristic of policosanol is its natural source. It makes policosanol an attractive alternative for a large number of patients who, although in dire need of lipid-lowering treatment, are reluctant to use chemically derived drugs and would gladly welcome a natural and efficient alternative. In general, policosanol is in our opinion a fascinating new agent for the prevention and treatment of atherosclerotic disease.

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