

A Pharmacological Surveillance Study of the Tolerability of Policosanol in the Elderly Population

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ABSTRACT

Background: Policosanol is a drug derived from sugar cane wax that has cholesterol-lowering and antiplatelet properties. Randomized, controlled studies are the gold standard for demonstrating drug efficacy, safety, and tolerability, but postmarketing surveillance studies are encouraged for corroborating drug effects. A valid proof of the safety of a drug is a well-documented, good tolerability profile in older individuals, since this population is more prone to drug-related adverse events (AEs).

Objective: This study investigated the tolerability of policosanol in the elderly population by monitoring the incidence and nature of AEs occurring in older Cuban patients treated with policosanol in routine clinical practice.

Methods: All patients aged ≥ 60 years treated with policosanol at 7 major medical centers from January 2000 to May 2003 were included. Policosanol (5, 10, or 20 mg/d) was prescribed to patients eligible to receive cholesterol-lowering and/or antiplatelet drugs, with the dosage recommended according to their individual atherosclerotic risk. Patients had follow-up visits approximately every 6 months. Data on AEs and other relevant information, including changes in policosanol treatment, concomitant medications, and discontinuations, were recorded on individual case-report forms.

Results: This study included 2252 patients (1306 women, 946 men): 647 (28.7%), 244 (10.8%), and 173 (7.7%) patients had coronary, cerebrovascular, and peripheral artery disease, respectively. A total of 1485 patients had hypercholesterolemia (65.9%), 1322 (58.7%) had hypertension, and 323 (14.3%) had diabetes mellitus. Of the enrolled patients, 1123 (49.9%), 644 (28.6%), and 485 (21.5%) received policosanol 5, 10, and 20 mg/d, respectively. Treatment duration varied: 2169 (96.3%), 1861 (82.6%), 1116 (49.6%), and 412 (18.3%) patients were treated for 6, 12, 24, and 36 months, respectively. Thirty-one patients (1.4%) experienced serious AEs, 18 of them fatal. Death was most often due to vascular events: myocardial infarction (4 patients), sudden cardiac arrest (1), ventricular arrhythmia (2), ischemic stroke (1), lung thromboembolism (1), cancer (5), pneumonia (1), peritonitis (1), lung edema (1), and dehydration (1). Another 13 patients (0.6%) were hospitalized, and 61 (2.7%) reported moderate or mild AEs. Overall, 21 patients (0.9%) discontinued prematurely from the study, 18 of them due to a fatal serious AE.

Conclusions: Long-term tolerability of policosanol in elderly patients at high vascular risk was very good, as assessed under conditions of routine clinical practice. These results are consistent with those obtained in randomized, double-blind clinical studies of older patients treated with policosanol. (*Am J Geriatr Pharmacother.* 2004;2: 219–229) Copyright © 2004 Excerpta Medica, Inc.

Key words: policosanol, elderly, postmarketing surveillance, adverse events, cholesterol.

INTRODUCTION

Elevated serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are major risk factors for coronary heart disease (CHD).¹ The benefits of lowering LDL-C in CHD prevention at both primary and secondary stages have been proved unequivocally.²⁻⁸

The value of hypercholesterolemia management in the elderly has been questioned because with age, elevated LDL-C levels become less reliable a predictor of relative coronary risk.^{9,10} Nevertheless, evidence obtained from subgroups of older patients included in earlier statin trials showed benefits of lowering LDL-C in this population.²⁻⁴ The Heart Protection Study, which included 5806 adults aged ≥ 70 years, demonstrated the clinical benefits of lowering LDL-C in the elderly population.⁷ PROSPER, the first study examining the cardiovascular benefits of a statin in older subjects, also showed the benefits of lowering LDL-C in older individuals.⁸

Policosanol is a cholesterol-lowering drug with concomitant antiplatelet properties that has been available in Cuba since 1991. It is a specific mixture of higher aliphatic primary alcohols purified from the wax of sugar cane (*Saccharum officinarum* L.) and has been proved to be effective and well tolerated.¹¹ Policosanol lowers cholesterol by inhibiting cholesterol biosynthesis and increasing LDL-receptor-dependent processing.^{12,13}

The cholesterol-lowering efficacy of policosanol has been clinically proven in healthy volunteers,¹⁴ patients with type 2 hypercholesterolemia,¹⁵⁻²³ and dyslipidemia due to type 2 diabetes mellitus.²⁴⁻²⁶ In addition, the antiplatelet effects of policosanol have been demonstrated in preclinical and clinical studies.²⁷⁻³⁰ Results of toxicity³¹⁻³⁵ and clinical data,^{15-25,28-30} including some previous postmarketing surveillance studies,^{36,37} support the fact that policosanol is well tolerated. The adverse events (AEs) more frequently reported ($>1\%$) by policosanol patients in placebo-controlled studies (but at rates not significantly different from placebo) were headache (1.3%), nervousness/anxiety (1.6%), and insomnia (1.3%). The AE most frequently reported in previous postmarketing surveillance studies was weight loss (100/31,481 [0.3%]),^{36,37} with 29 patients discontinuing treatment. Comparisons of the reports of weight loss between policosanol and control patients followed over 5 years, however, did not show significant differences.³⁸ The other AEs most frequently reported (0.05%–0.1%) by policosanol patients in postmarketing surveillance studies were headache, dizziness, somnolence, polyuria, and polyphagia. Despite

the antiplatelet effects of policosanol, bleeding reactions have been almost absent, with only 2 epistaxis episodes reported. Several randomized, double- and single-blind studies have investigated specifically the effects of policosanol on individuals ≥ 60 years of age,¹⁸⁻²³ including a long-term study that demonstrated the benefits of policosanol on clinical end points in this population.²³ Although randomized, controlled studies are the gold standard for demonstration of efficacy, safety, and tolerability of a drug, the conduction of postmarketing surveillance studies under conditions of routine clinical practice is encouraged for corroborating drug effects. This type of study is particularly important in the elderly population, since older individuals are more sensitive to drug-related AEs and have the highest rates of concomitant drug consumption, morbidity, and mortality.^{9,10} The utility of postmarketing surveillance studies lies not only in their large sample size, but also their lack of patient selection criteria, which renders their results more generalizable to patients in routine clinical practice. The purpose of this study was to evaluate the tolerability of policosanol in the elderly population through collected data on AEs occurring in patients aged ≥ 60 years who were treated with policosanol.

PATIENTS AND METHODS

Study Design

This study was conducted in 7 major medical centers in Havana that were selected specifically because they served a large population of older individuals. The surveillance started in January 2000 and the present report includes data available up to May 2003. Study patients were followed systematically, and policosanol prescriptions were reviewed. In addition to the normal system surveillance of these patients, individual case-report forms (CRFs) were filed for each patient. Data on AEs were specifically requested and not based only on spontaneous declarations. Other relevant data were also recorded. CRFs were filed and signed by each physician. At recruitment, the clinical history of each patient was recorded, including history of CHD (myocardial infarction, angina, congestive heart failure, coronary atherosclerosis), cerebrovascular disease (stroke, transient ischemic attack, evidence of cerebral or carotid atherosclerosis), peripheral artery disease (intermittent claudication, severe limb ischemia, peripheral thrombosis or insufficiency), any vascular surgery, or any other relevant health condition. Any AE requiring medical attention during the follow-up period was carefully recorded, including the hospitalizations and their

causes. Changes in policosanol treatment, concomitant medications, duration of treatments, and study discontinuations were also entered. Adherence to follow-up protocol and uniformity in the procedures followed at each center were controlled via monitoring visits.

No special risks or conditions were introduced to study patients, since the decision to initiate or discontinue treatment with policosanol was based entirely on physicians' opinions and patient characteristics, similar to what would occur in routine clinical practice. Patients provided informed written consent. In accordance with Cuban regulations, physicians and patients did not receive any additional payment for participation in the study. Information from all patients receiving policosanol treatment was included in this report.

Study Population

The present study included all patients aged ≥ 60 years who were treated with policosanol at the 7 aforementioned sites. At recruitment, patients were new users of policosanol. Policosanol was prescribed at the physician's discretion based on the product indications and patient characteristics. Consistent with the cholesterol-lowering and antiplatelet effects of policosanol, the study population included patients with primary hypercholesterolemia and/or atherosclerotic disease.

Patients in whom policosanol was contraindicated or for whom package insert warnings were applicable were excluded. Therefore, patients known to be hypersensitive to any component of the medication were excluded from this study.

Patients could be withdrawn prematurely from the trial if an AE occurred that justified such a decision, if they were unwilling to follow up, or if they were lost to follow-up. However, if a patient experienced a serious AE that was not likely related to treatment, he or she could continue in the study after hospital discharge, provided the physician and patient approved the decision.

Treatment

Physicians were advised to prescribe 20 mg/d for patients at the secondary prevention stage, including all patients with a history of CHD, cerebrovascular disease, or peripheral artery disease. Patients with diabetes were considered to be in the same risk status as secondary prevention patients. A dose of 10 mg/d was recommended for patients at the primary prevention stage who had hypercholesterolemia (total cholesterol >5.2 mmol/L) and ≥ 2 concomitant nonlipid atherosclerotic risk factors. A dosage of 5 mg/d was recommended for patients at the primary prevention stage who had hypercholes-

terolemia and ≤ 1 nonlipid atherosclerotic risk factor. Nonlipid risk factors included hypertension (diastolic blood pressure ≥ 90 mm Hg or documented family history), smoking, age (applicable for all patients), obesity (body mass index ≥ 30 kg/m²), and family history of CHD. The aforementioned recommendations were only guidelines; the final dosage for each patient was decided by the physician based on these guidelines as well as specific patient characteristics.

Compliance with policosanol therapy was assessed through patient reports and monitoring of tablets prescribed and purchased for each period.

The use of any concomitant drugs was recorded; any change in the medication regimen that occurred during the study period was registered on individual forms.

Patients had follow-up visits approximately every 6 months. At each follow-up visit, a physical examination was conducted and vital signs (body weight, pulse rate, arterial pressure) were recorded. Laboratory analyses were indicated as required.

Adverse Events

AEs occurring during the follow-up period were recorded, whether or not they were related to treatment. AEs not present at baseline and those that worsened during the follow-up period were included.

Information on AEs was collected from both spontaneous reports and responses to an AE questionnaire that enabled appropriate classification; the information was recorded on CRFs by study investigators. Data on the onset, duration, specific treatment, and evolution of the AEs were also recorded. AEs were classified according to intensity as mild, moderate, or serious. Mild AEs were those that did not require study medication withdrawal or treatment of the specific AE. Moderate AEs were those that required medication withdrawal (because of intensity, duration, and patient perception) and/or specific treatment of the AE, with the exception of asthma attacks requiring albuterol or other short-acting beta-agonists in patients with asthma at baseline. Serious AEs were those that were disabling or life-threatening, or that placed patients at serious risk. All AEs leading to patient hospitalization and/or death were considered serious. In cases of sudden death, the cause of death was ascertained through certificates and records of family physicians. The possible relationship of the AE to policosanol treatment was assessed and classified as unlikely, doubtful, possible, probable, or definite. Unlikely drug-related AEs were those that were not expected based on the cumulative AE profile of policosanol and that could be convincingly attributed to external factors. Any AE with some degree

of drug-related causality was considered an adverse drug reaction (ADR). The relationship of the AE to treatment was classified as doubtful if the AE was generally not considered to conform to the AE profile of policosanol or if it was most likely to be caused by other factors. An AE was considered possibly drug related if it demonstrated a time course consistent with drug administration and/or the expected pattern of AEs of policosanol, but could be attributed to other factors. An AE was classified as probably drug related if it followed a time course consistent with drug administration and/or the expected pattern of policosanol-related AEs, but could not be explained by other factors. An AE was classified as definitely drug related if it stopped with treatment discontinuation and reappeared during rechallenge with policosanol therapy. All ADRs experienced during the follow-up period were reassessed using the Naranjo ADR algorithm, using the following scoring system: doubtful, <1; possible, 1–4; probable, 5–8; definite, ≥ 9 .³⁹ Causes of AE were classified as vascular or nonvascular based on the most probable cause of hospitalization or death.

Data Analysis

Because the time of occurrence of some events was uncertain, cumulative incidence of AEs is reported. Descriptive statistics are shown using continuous or categorical variables. For the continuous variables, mean (SD) values were used, whereas for categorical variables, exact proportions (numerator/denominator) and percentages were used. Comparisons of continuous data among study groups were done using the *t* test for independent samples, whereas comparisons of categorical data were done using chi-square and Fisher exact tests.

RESULTS

Table I summarizes the baseline characteristics of the study population. This study followed 2252 patients at high coronary risk (1306 women, 946 men) (mean age, 68 years), including 647 patients (28.7%) with CHD, 244 (10.8%) with cerebrovascular disease, and 173 (7.7%) with peripheral artery disease. A majority of patients had primary hypercholesterolemia (1485, 65.9%) and hypertension (1322, 58.7%). Of the 2252 enrolled subjects, 1123 (49.9%), 644 (28.6%), and 485 (21.5%) were treated with policosanol 5, 10, and 20 mg/d, respectively. Only 32 (2.8%) and 14 (2.1%) subjects initially treated with 5 and 10 mg/d, respectively, required upward dose titration during the study. Study groups were not comparable at baseline because their risk factors increased across the strength of the prescribed doses, indicating that

prescription recommendations were followed. Thus, the group treated with 20 mg/d had a higher prevalence of CHD and cerebrovascular, peripheral artery, and vascular disease than the other groups. The 10 mg/d and 20 mg/d groups had greater numbers of men and obese individuals compared with the 5 mg/d group.

Treatment duration ranged from 6 to 36 months, so that 2169 (96.3%), 1861 (82.6%), and 1116 (49.6%) had 6, 12, and 24 months of follow-up after enrollment. A total of 412 (18.3%) patients who were enrolled early had 36 months of follow-up data; 83 patients had no data corresponding to the first 6 months on treatment since they were enrolled later. Overall, 21 patients (0.9%) were discontinued prematurely, 18 (0.8%) of them due to a fatal AE. One patient discontinued the study because of financial reasons and 2 due to change of address.

Table II shows the serious AEs that occurred during the study. Based on the Naranjo ADR criteria,³⁹ none of these serious AEs was classified as possibly, probably, or definitely related to policosanol treatment. The serious AEs that occurred were those normally expected in this age group and related primarily to the underlying atherosclerotic condition. Thus, 31 (1.4%) patients had serious AEs of scores ≤ 1 according to the Naranjo ADR algorithm. A total of 18 deaths occurred due to various causes: myocardial infarction (4), sudden cardiac arrest (1), ventricular arrhythmia (2), stroke (1), lung thromboembolism (1), cancer (5), pneumonia (1), peritonitis (1), lung edema (1), and dehydration (1). The frequency of deaths was similar in all study groups. Another 13 patients (0.6%) experienced nonfatal serious AEs (7 vascular and 6 nonvascular) that required hospitalization. The serious nonfatal vascular AEs were heart murmur (1) in the 5 mg/d group, myocardial infarction (1) in the 10 mg/d group, and unstable angina (2), peripheral thrombosis (2), and lower-limb edema (1) in the 20 mg/d group. The 6 serious nonfatal, nonvascular AEs all occurred in the 20 mg/d group: cancer (2), asthenia (2), pneumonia (1), and loss of vision (1). The 2 cases of cancer had been diagnosed at the time of recruitment. The frequency of serious AEs, both vascular and nonvascular, in the group treated with policosanol 20 mg/d was higher than in the other groups, as expected from baseline differences.

Sixty-one patients (2.7%) reported moderate or mild AEs (**Table III**). According to the Naranjo ADR algorithm,³⁹ 7 reports were considered possibly drug related (score of 1–4), including heartburn (1), muscle cramps (1), lower-limb contractions (2), arthralgia (2), and asthenia (1). Of these, the case of heartburn and the

Table 1. Baseline characteristics of study population.

	Policosanol Dosage			Total (N = 2252)
	5 mg/d (n = 1123)	10 mg/d (n = 644)	20 mg/d (n = 485)	
Age, mean (SD), y	68 (6)	67 (8)	67 (8)	68 (7)
Sex, no. (%)				
Female	741 (66.0)	329 (51.1)*	236 (48.7)*	1306 (58.0)
Male	382 (34.0)	315 (48.9)*	249 (51.3)*	946 (42.0)
CHD, no. (%)				
Myocardial infarction [†]	94 (8.4)	69 (10.7)	83 (17.1)*	246 (10.9)
Unstable angina pectoris	97 (8.6)	75 (11.7) [‡]	99 (20.4)* [§]	271 (12.0)
Congestive heart failure	29 (2.6)	16 (2.5)	18 (3.7)	63 (2.8)
Other	7 (0.6)	20 (3.1)*	40 (8.2)* [§]	67 (3.0)
Total	227 (20.2) [¶]	180 (28.0)* [¶]	240 (49.5)* ^{§¶}	647 (28.7) [¶]
Cerebrovascular disease, no. (%)				
Stroke	26 (2.3)	27 (4.2) [‡]	64 (13.2)* [§]	117 (5.2)
Transient ischemic attacks	22 (2.0)	40 (6.2)*	53 (10.9)*	115 (5.1)
Others [#]	1 (0.1)	6 (0.9)**	5 (1.0)**	12 (0.5)
Total	49 (4.4)	73 (11.3)*	122 (25.2)* [§]	244 (10.8)
Peripheral artery disease, no. (%)				
Intermittent claudication	7 (0.6)	13 (2.0)*	59 (12.2)*	79 (3.5)
Severe ischemia	6 (0.5)	7 (1.1)	15 (3.1)* ^{¶††}	28 (1.2)
Peripheral thrombosis	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.1)
Arterial insufficiency	11 (1.0)	7 (1.1)	20 (4.1)* [§]	38 (1.7)
Venous insufficiency	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Others ^{‡‡}	1 (0.1)	9 (1.4)	14 (2.9)	24 (1.1)
Total	27 (2.4)	37 (5.8)*	109 (22.5)* [§]	173 (7.7)
Family history of CHD	462 (41.1)	253 (39.3)	275 (56.7)* [§]	990 (44.0)
Primary HC	840 (74.8)	417 (64.8)*	228 (47.0)* [§]	1485 (65.9)
Hypertension	574 (51.1)	422 (65.5)*	326 (67.2)*	1322 (58.7)
Diabetes mellitus	128 (11.4)	85 (13.2)	110 (22.7)* [§]	323 (14.3)
Obesity	84 (7.5)	127 (19.7)*	112 (23.1)*	323 (14.3)
Concomitant medications ^{§§}				
Diuretics	272 (24.2)	209 (32.5) [‡]	122 (25.2)	603 (26.8)
Antiplatelet drugs	215 (19.1)	130 (20.2)	164 (33.8) ^{‡‡}	509 (22.6)
Calcium channel blockers	100 (8.9)	95 (14.8)	60 (12.4)	255 (11.3)
Oral hypoglycemic drugs	80 (7.1)	55 (8.5)	93 (19.2)* ^{‡‡}	228 (10.1)

CHD = coronary heart disease; HC = hypercholesterolemia.

* $P < 0.001$ versus 5 mg/d group.

[†]Confirmed or suspected.

[‡] $P < 0.05$ versus 5 mg/d group.

[§] $P < 0.001$ versus 10 mg/d group (chi-square test).

^{||}Coronary atherosclerosis.

[¶]Some patients had >1 condition.

[#]Cerebral or carotid atherosclerosis, multi-infarct dementia, cerebrovascular insufficiency.

** $P < 0.01$ versus 5 mg/d group.

^{††} $P < 0.05$ versus 10 mg/d group.

^{‡‡}Lymphangitis, peripheral atherosclerosis. Atherosclerosis reports were based on an imaging method.

^{§§}Concomitant drugs consumed by >10% of study patients.

Table II. Serious adverse events (AEs) that occurred during the study period.

	Policosanol Dosage			Total (N = 2252)
	5 mg/d (n = 1123)	10 mg/d (n = 644)	20 mg/d (n = 485)	
Fatal events, no. (%)				
Cardiovascular	4 (0.4)	1 (0.2)	2 (0.4)	7 (0.3)
Myocardial infarction	1 (0.1)	1 (0.2)	2 (0.4)	4 (0.2)
Sudden cardiac arrest	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Ventricular arrhythmia	2 (0.2)	0 (0)	0 (0)	2 (0.1)
Stroke (hemorrhagic)	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Lung thromboembolism (hemorrhagic)	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Total due to vascular causes	5 (0.5)	1 (0.2)	3 (0.6)	9 (0.4)
Cancer	3 (0.3)	1 (0.2)	1 (0.2)	5 (0.2)
Lung	1 (0.1)	0 (0)	1 (0.2)	2 (0.1)
Colon	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Gastric	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Prostate	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Other nonvascular	1 (0.1)	1 (0.2)	2 (0.4)	4 (0.2)
Peritonitis	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Dehydration	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Pneumonia	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Lung edema	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Total due to nonvascular causes	4 (0.4)	2 (0.3)	3 (0.6)	9 (0.4)
Total fatal	9 (0.8)	3 (0.5)	6 (1.2)	18 (0.8)
Nonfatal events, no. (%)				
Cardiovascular	1 (0.1)	1 (0.2)	2 (0.4)	4 (0.2)
Myocardial infarction	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Unstable angina	0 (0)	0 (0)	2 (0.4)	2 (0.1)
Heart murmur	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Other vascular	0 (0)	0 (0)	3 (0.6)*†	3 (0.1)
Peripheral thrombosis	0 (0)	0 (0)	2 (0.4)	2 (0.1)
Severe lower-limb edema	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Total due to vascular causes	1 (0.1)	1 (0.2)	5 (1.0)*	7 (0.3)
Cancer	0 (0)	0 (0)	2 (0.4)‡	2 (0.1)
Lung	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Prostate	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Other nonvascular	0 (0)	0 (0)	4 (0.8)§†	4 (0.2)
Asthenia	0 (0)	0 (0)	2 (0.4)	2 (0.1)
Pneumonia	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Loss of vision	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Total due to nonvascular causes	0 (0)	0 (0)	6 (1.2)*	6 (0.3)
Total nonfatal	1 (0.1)	1 (0.2)	11 (2.3)*¶	13 (0.6)
Total serious AEs	10 (0.9)	4 (0.6)	17 (3.5)*¶	31 (1.4)

* $P < 0.001$ versus 5 mg/d group.† $P < 0.05$ versus 10 mg/d group.‡ $P < 0.05$ versus 5 mg/d group.§ $P < 0.01$ versus 5 mg/d group.|| $P < 0.01$ versus 10 mg/d group.¶ $P < 0.001$ versus 10 mg/d group.

Table III. Moderate and mild adverse events (AEs) reported by study patients.

	Policosanol Dosage			Total (N = 2252)
	5 mg/d (n = 1123)	10 mg/d (n = 644)	20 mg/d (n = 485)	
Moderate AEs, no. (%)				
Peripheral and central nervous system				
Loss of coordination	0 (0)	2 (0.3)	0 (0)	2 (0.1)
Diabetic neuropathy	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Vision and hearing				
Cataracts	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Glaucoma	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Skeletal muscle/bone system				
Arthralgia	2 (0.2)	0 (0)	5 (1.0)*†	7 (0.3)
Cardiovascular system				
Peripheral edema	0 (0)	2 (0.3)	1 (0.2)	3 (0.1)
Bradycardia	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Chest pain	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Heart murmur	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Gastrointestinal system				
Cholelithiasis	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Gastroduodenal ulcer	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Heartburn	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Hemorrhoids	2 (0.2)	0 (0)	1 (0.2)	3 (0.1)
Urinary system				
Renal cyst	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Renal sepsis	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Metabolic and nutritional				
Hypoglycemia	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Mild AEs, no. (%)				
Vision and hearing				
Cataracts	1 (0.1)	0 (0)	1 (0.2)	2 (0.1)
Hypoacusia	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Impairment of equilibrium	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Skeletal muscle/bone system				
Arthralgia	8 (0.7)	6 (0.9)	7 (1.4)	21 (0.9)
Lower-limb contracture	2 (0.2)	0 (0)	0 (0)	2 (0.1)
Muscle cramps	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Gastrointestinal system				
Rectal pressure and discomfort	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Urinary system				
Cystitis	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
Respiratory system				
Bronchitis	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Flu	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Reproductive system				
Testis pain	0 (0)	1 (0.2)	0 (0)	1 (<0.1)
Metabolic and nutritional				
Asthenia	0 (0)	0 (0)	1 (0.2)	1 (<0.1)
Total moderate and mild AEs	18 (1.6)	15 (2.3)	28 (5.8)‡	61 (2.7)

*P < 0.05 versus 5 mg/d group.

†P < 0.01 versus 10 mg/d group.

‡P < 0.001 versus 5 mg/d group.

2 cases of arthralgia were classified as moderate AEs; the remainder were classified as mild. For the other mild and moderate AEs, the relationship to drug treatment was doubtful (ie, score of <1). In the present study, 10 patients (4, 3, and 3 patients treated with 5, 10, and 20 mg/d, respectively) were receiving levodopa, a drug thought to interact with policosanol, but none experienced an AE. Policosanol treatment did not induce significant changes in safety measures obtained during physical examination and laboratory analyses (data not shown).

DISCUSSION

Policosanol is a cholesterol-lowering drug purified from sugar cane wax that reduces TC and LDL-C levels and generally increases high-density lipoprotein cholesterol (HDL-C) levels; its effects on triglycerides have not been consistent.^{15–25} In head-to-head comparative studies, policosanol (10 mg/d) has been shown to be as effective as pravastatin 10 mg/d,¹⁹ fluvastatin 20 mg/d,²⁰ and lovastatin 20 mg/d in lowering LDL-C,²⁶ but less effective than atorvastatin 10 mg/d.^{23,27} The effects of policosanol on HDL-C, however, have been better than those obtained with these statins, including atorvastatin.^{19,20,23,26,27} The present postmarketing surveillance study demonstrates that in routine clinical practice, policosanol therapy is well tolerated in elderly patients. The low cumulative frequency of serious, moderate, and mild AEs reported here supports the low risk associated with its use, even in a population particularly sensitive to AEs and with a high morbidity and mortality rate. The results presented herein are consistent with safety and tolerability data obtained in randomized, single- and double-blind, short- and long-term studies conducted in the adult population, including older individuals.^{15–26,28–30} In contrast with other lipid-lowering drugs,^{39–41} policosanol does not appear to induce increases in serum transaminases or creatine phosphokinase, nor does it appear to alter liver or muscle function. Indeed, in several clinical studies,^{16,20,21} including a double-blind, placebo-controlled study of patients with increased transaminase levels, policosanol significantly reduced these values compared with baseline values and with placebo.⁴² Policosanol has also shown good tolerability in 2 previous postmarketing surveillance studies conducted in >30,000 middle-aged patients treated with policosanol for up to 4 or 5 years, with a very low cumulative incidence of AEs.^{36,37} The characteristics of the study population are consistent with the indicated population for policosanol therapy and with the patient samples in previous randomized, placebo-controlled studies conducted in older patients,^{18–23} with the excep-

tion of the gender distribution. The male:female ratio in the present study was more balanced than in previous trials perhaps due to the inclusion of patients from 3 veterans' medical centers. Another reason for the increased participation by men could be that they were more motivated to participate in a real-world study with less strict follow-up requirements than in a controlled study with the possibility of taking a placebo.

As expected from the prescription recommendations, study arms were not comparable. Therefore, the proportion of patients with vascular disease and risk factors was highest in the 20 mg/d group and lowest in the 5 mg/d group, suggesting that physicians adhered to the dosage recommendations outlined in the study protocol. Nevertheless, there were deviations from these recommendations, as might occur in actual clinical practice—some patients at the secondary prevention stage were treated with 5 mg/d and some individuals at the primary prevention stage received 20 mg/d. Few patients required upward titration of policosanol doses. The frequency of withdrawals was low, considering the sample size, age of patients, and duration of follow-up. Most of the withdrawals were due to a fatal serious AE, an expected finding given the age and risk status of enrolled patients. However, the incidence of serious AEs in the study (31/2252 [1.4%]) was low despite the mean age and high-risk status of the study population. Most of the serious AEs were related to the risk status of the patients at enrollment and were consistent with those expected in this age group. Although the incidence of serious AEs increased with dose, most of the AEs reported in the 20 mg/d group were related to the multiple risk factors present at baseline rather than to the tolerability of this dose. Thus, at enrollment, 49.5%, 25.2%, and 22.5% of patients included in the 20 mg/d group had CHD, cerebrovascular disease, and peripheral artery disease, respectively, compared with 20.2%, 4.4%, and 3.5% of patients in the 5 mg/d group; these differences were statistically significant. The use of policosanol in older individuals at high risk for developing vascular disease is supported by the low incidence of serious AEs in this study (0.9% in the 5 mg/d group, 0.6% in 10 mg/d group, and 3.5% in the 20 mg/d group). The use of 20 mg/d, in particular, for older patients at highest risk appears to be highly favorable in terms of risk-to-benefit ratio. The good tolerability of policosanol is also supported by the low incidence of mild and moderate AEs; only 61 were reported during the follow-up period and none of them led to withdrawal from therapy. With respect to mild and

moderate AEs, the incidence was highest in the 20 mg/d group (28 [5.8%]); arthralgia was most commonly reported. This result is consistent with the baseline characteristics of this group since a relatively high percentage of this group (64/485 [13.2%]) reported having arthrosis or arthritis at baseline. Although some authors have documented interactions between levodopa and octacosanol,^{43,44} the most abundant aliphatic alcohol within policosanol, we did not find evidence of such drug interactions. In the present study, no patient reported or had evidence of weight loss, a result different from that found in a previous postmarketing study conducted in middle-aged adults, but consistent with all randomized studies conducted in older patients. This study demonstrates that policosanol is very well tolerated in patients ≥ 60 years of age, a population particularly prone to serious AEs and drug-related AEs.

To date, policosanol has not been registered or submitted for drug approval in the United States. Although there are reports of “policosanols” being available in the United States as dietary supplements, such products do not have the same identity or source of the policosanol discussed here, a drug whose efficacy, safety, and tolerability has been well documented in controlled clinical trials. Proof of efficacy, safety, and tolerability of policosanol cannot be extrapolated to other mixtures of higher aliphatic alcohols. To date there are no published data from large-scale studies that suggest that policosanol reduces morbidity (eg, cerebrovascular accident) or mortality in older patients with high cholesterol levels. Although the currently available cholesterol-lowering drugs are highly effective, policosanol therapy could be an alternative for elderly patients and other subgroups with increased susceptibility to statin-related hepatic and muscular side effects.

CONCLUSIONS

Long-term tolerability of policosanol in elderly patients at high vascular risk was very good, as assessed under conditions of routine clinical practice. These results are consistent with those obtained in randomized, double-blind clinical studies conducted in older subjects treated with policosanol.

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REFERENCES

1. Lipid Research Clinics Program: The Lipid Research Clinics coronary primary prevention trial results. II. The relationship on reduction in the incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365–374.
2. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
3. Sacks FM, Pfeffer MA, Moyé LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
4. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and deaths with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
5. Shepherd S, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301–1307.
6. Downs JR, Clearfield M, Weiss S, et al, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615–1622.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomized placebo-controlled trial. *Lancet*. 2002;360:7–22.
8. Shepherd J, Blauw GJ, Murphy MB, et al, on behalf of the PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomized controlled study. *Lancet*. 2002;360:1623–1630.
9. Manolio TA, Pearson TA, Wenger NK, et al. Cholesterol and heart disease in older persons and women: Review of an NHLBI workshop. *Ann Epidemiol*. 1992;2:161–176.
10. Bilheimer DW. Clinical considerations regarding treatment of hypercholesterolemia in the elderly. *Atherosclerosis*. 1991;91(Suppl):S35–S57.
11. Más R. Policosanol. *Drugs Future*. 2000;25:569–586.
12. Menéndez R, Fernández I, Del Río A, et al. Policosanol inhibits cholesterol biosynthesis and enhances LDL processing in cultured human fibroblasts. *Biol Res*. 1994;27:199–203.

13. Menéndez R, Arruzazabala ML, Más R, et al. Cholesterol-lowering effect of policosanol on rabbits with hypercholesterolemia induced by a wheat starch-casein diet. *Brit J Nutr.* 1996;77:923–932.
14. Menéndez R, Amor A, Rodeiro I, et al. Policosanol modulates HMGCoA reductase activity in cultured fibroblasts. *Arch Med Res.* 2001;32:8–12.
15. Hernández F, Illnait J, Más R, et al. Effects of policosanol on serum lipids and lipoproteins in healthy volunteers. *Curr Ther Res Clin Exp.* 1992;51:568–575.
16. Pons P, Rodríguez M, Robaina C, et al. Effects of successive dose increases of policosanol on the lipid profile of patients with type II hypercholesterolemia and tolerability to treatment. *Int J Clin Pharmacol Res.* 1994;14:27–33.
17. Más R, Castaño G, Illnait J, et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther.* 1999;65:439–447.
18. Castaño G, Más R, Fernández L, et al. Effect of policosanol on postmenopausal women with type II hypercholesterolemia. *Gynecol Endocrinol.* 2000;13:1–9.
19. Castaño G, Más R, Arruzazabala ML, et al. Effects of policosanol, pravastatin on lipid profile, platelet aggregation, endothelium in older hypercholesterolemic patients. *Int J Clin Pharm Res.* 1999;19:105–116.
20. Fernández JC, Más R, Castaño G, et al. Comparison of the efficacy, safety and tolerability of policosanol versus fluvastatin in elderly hypercholesterolemic women. *Clin Invest.* 2001;21:103–113.
21. Castaño G, Más R, Fernández JC, et al. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J Gerontol A.* 2001;56:M186–M192.
22. Más R, Castaño G, Fernández L, et al. Effects of policosanol in older hypercholesterolemic patients with coronary disease. *Clin Drug Invest.* 2001;21:485–497.
23. Castaño G, Más R, Fernández L, et al. Comparison of the efficacy, safety and tolerability of policosanol versus atorvastatin in elderly patients with type II hypercholesterolemia. *Drugs Aging.* 2002;20:153–163.
24. Más R, Castaño G, Fernández J, et al. Effects of policosanol on morbidity and mortality in older hypercholesterolemic patients. *J Am Coll Cardiol.* 2002;39(Suppl B):429B. Abstract.
25. Torres O, Agramonte AJ, Illnait J, et al. Treatment of hypercholesterolemia in NIDDM with policosanol. *Diabetes Care.* 1995;18:393–397.
26. Crespo N, Illnait J, Más 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;19:117–127.
27. Castaño G, Fernández L, Más R, et al. Comparison of the effects of policosanol and atorvastatin on lipid profile and platelet aggregation in patients with dyslipidemia and type 2 diabetes mellitus. *Clin Drug Invest.* 2003;23:639–650.
28. Arruzazabala ML, Carbajal D, Molina V, et al. Effect of policosanol on cerebral ischemia in mongolian gerbils: Role of prostacyclin and thromboxane A2. *Prostaglandins Leukot Essent Fatty Acids.* 1993;49:695–697.
29. Arruzazabala ML, Valdés S, Más R, et al. Effect of policosanol successive dose increases on platelet aggregation in healthy volunteers. *Pharmacol Res.* 1996;34:181–185.
30. Carbajal D, Arruzazabala ML, Valdés S, Más R. Effect of policosanol on platelet aggregation and serum levels of arachidonic acid metabolites in healthy volunteers. *Prostaglandins Leukot Essent Fatty Acids.* 1998;58:61–64.
31. Arruzazabala ML, Más R, Molina V, et al. Effect of policosanol on platelet aggregation in type II hypercholesterolemic patients. *Int J Tissue React.* 1998;10:119–124.
32. Alemán C, Más R, Rodeiro I, et al. Acute, subchronic and chronic toxicology of policosanol in rats. *Toxicol Lett.* 1992(Suppl):248. Abstract of the 6th International Congress of Toxicology, Rome, Italy.
33. Mesa A del R, Más R, Noa M, et al. Toxicity of policosanol in beagle dogs: One year study. *Toxicol Lett.* 1994;73:81–90.
34. Alemán C, Más R, Hernández C, et al. A 12-month study of policosanol oral toxicity in Sprague-Dawley rats. *Toxicol Lett.* 1994;70:77–87.
35. Alemán CL, Más R, Noa M, et al. Carcinogenicity of policosanol in Sprague Dawley rats: A 24 month study. *Teratog Carcinog Mutagen.* 1994;14:239–249.
36. Rodríguez MD, García H. Teratogenic and reproductive studies of policosanol in the rat and rabbit. *Teratog Carcinog Mutagen.* 1994;14:107–113.
37. Fernández L, Más R, Illnait J, Fernández JC. Policosanol: Results of a postmarketing surveillance control on 27 879 cases. *Curr Ther Res Clin Exp.* 1998;59:717–722.
38. Más R, Rivas P, Izquierdo JE, et al. Pharmacoeconomic study of policosanol. *Curr Ther Res Clin Exp.* 1999;60:458–467.
39. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239–245.
40. Baker SK, Tarnopolsky MA. Statin myopathies: Pathophysiologic and clinical perspectives. *Clin Invest Med.* 2001;24:258–272.

41. Gaist D, García A, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: A population-based followup study. *Epidemiology*. 2001;12:565–569.
42. Pasternak RC, Smith SC Jr, Bairey Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;40:567–572.
43. Zardoya R, Tula L, Castaño G, et al. Effects of policosanol on hypercholesterolemic patients with disturbances on serum biochemical indicators of hepatic function. *Curr Ther Res Clin Exp*. 1996;57:568–577.
44. Snider SR. Octacosanol in parkinsonism [letter]. *Ann Neurol*. 1984;16:723.

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