A Long-Term Study of Policosanol in the Treatment of Intermittent Claudication

Gladys Castaño, PhD,* Rosa Más Ferreiro, PhD,† Lilia Fernández, PhD,† Rafael Gámez,†
José Illnait, PhD,† and Julio César Fernández,† *Havana City, Cuba*

Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects. This study was undertaken to investigate the long-term effects of policosanol administered to patients with moderately severe intermittent claudication. The study consisted of a 6-week single-blind, placebo-controlled run in phase, followed by a 2-year double-blind, randomized treatment step. Fifty-six patients who met study entry criteria were randomized to receive placebo or policosanol 10 mg twice daily. Walking distances on a treadmill (constant speed 3.2 km/h, slope 10°, temperature 25°C) were assessed before and after 6, 12, 18, and 24 months of treatment. Both groups were similar at randomization. After 6 months of therapy, policosanol significantly increased ($p<0.01$) the initial claudication distance from 125.9 ±8.7 m to 201.1 ±24.8 m and the absolute claudication distance from 219.5 ±14.1 m to 380.7 ±50.2 m. Both variables remained unchanged in the placebo group ($p<0.01$). These effects did not wear off but improved after long-term therapy, so that final values were 333.5 ±28.6 m (initial claudication distance) and 648.9 ±54.1 m (absolute claudication distance); both significantly greater ($p<0.0001$) than those obtained in the placebo group, which showed values of 137.9 ±21.8 m (initial claudication distance) and 237.7 ±28.1 m (absolute claudication distance), respectively. At study completion, 21 policosanol and 5 placebo patients attained increases in claudication distance values >50% ($p<0.001$). Policosanol, but not placebo, significantly increased the ankle/arm pressure index. In addition, from month 6 up to study completion, the frequency of patients reporting improvement of lower limb symptoms was greater in the policosanol group than in the placebo group. The treatment was tolerated well. There were 16 withdrawals (12 placebo, 4 policosanol) from the study. Eight patients in the placebo group experienced a total of 10 serious adverse events, 8 of which were vascular events, compared with none in the policosanol group ($p<0.01$). In addition, 3 patients in the policosanol group and 3 patients in the placebo group reported mild adverse events during the study. The present results demonstrate the long-term usefulness of policosanol therapy to treat patients with intermittent claudication.

Introduction

Peripheral arterial disease (PAD) is a common disease with possible serious clinical consequences with a prevalence increasing with age.[1] Nevertheless, PAD has received generally less attention than coronary and cerebrovascular diseases and is frequently diagnosed when symptomatic.

Intermittent claudication is an occlusive PAD characterized clinically by the severe impairment

Angiology 52:115–<None>, 2001

From the *Medical Surgical Research Center, and †Clinical Studies Group of the Center of Natural Products, National Center for Scientific Research, Havana City, Cuba

Correspondence: Rosa Más Ferreiro, PhD, Center of Natural Products, National Center for Scientific Research, Havana City, Cuba E-mail: dalmer@ip.etecsa.cu

of walking ability and the appearance of lower limb symptoms such as pain, paresthesia, and coldness. This condition causes a high degree of disability among the patients that may adversely affect working, social, and leisure activities in several cases.[2]

The treatment of patients with PAD is addressed to modify atherosclerotic risk factors, taking into account that these patients have a high future risk for coronary morbidity and mortality.[1-3] The risk factors for atherosclerosis development also apply for PAD, although their relative contribution is different from that reported for coronary heart disease (CHD). Thus, cigarette smoking has been recognized as the major risk factor for PAD, compared with other factors such as hypertension, dyslipidemia, diabetes mellitus, increased levels of plasma fibrinogen, hyperhomocystinemia, and high plasma viscosity.[4-6]

There are two main objectives to manage PAD: to prevent ischemic events and to improve the quality of life of the patients, although generally the efficacy of the treatments has been assessed only in terms of the increase on the walking distance.

Considering this background, there is increased interest in the management of intermittent claudication. The basic management strategies include the avoidance of risk factors and the institution of systematic physical training.[7,8] The pharmacologic management of intermittent claudication was restricted to the use of vasodilators, but their efficacy has been highly controversial.[9] The use of antiplatelet drugs in intermittent claudication has been documented.[10,11]

Platelet function is an important factor in the pathogenesis and complications of occlusive arterial disease,[12] and the rationale for using antiplatelet drugs in occlusive PAD is based on the fact that inhibition of platelet adhesion and aggregation should limit thrombus formation and could prevent atherosclerosis development.[13]

Policosanol is a mixture of higher primary aliphatic alcohols purified from sugar cane *(Saccharum officinarum)* wax with cholesterol-lowering effects proven in patients with type II hypercholesterolemia[14-23] and dyslipidemia associated with noninsulin diabetes mellitus.[24,25] Concomitant antiplatelet effects are demonstrated in experimental models and human beings[26-30] that have been mainly related to its ability to reduce thromboxane A_2 serum levels.[26,29]

A previous randomized, double-blind, placebo-controlled study showed that policosanol administered at 20 mg/d for 6 months to patients with intermittent claudication significantly increased pain-free and maximal walking distances compared with baseline and placebo, and improved symptoms of the lower limbs.[31]

Taking into account that PAD is a chronic disease of atherosclerotic etiology, this study was undertaken to investigate the persistence of the efficacy and long-term tolerability of policosanol (20 mg/d) in patients with intermittent claudication.

Materials and Methods

Study Design

This study followed a randomized, double-blind, placebo-controlled design and was conducted at the Medical Surgical Research Center (Havana City, Cuba). Claudicant patients submitted to repetitive testing on a treadmill with an increase in walking distances,[32] which may represent a learning curve of a typical placebo effect; that is why the study design included a control placebo group to avoid overestimation of treatment efficacy.[33] The duration of therapy was 2 years, considered a reasonable time to evaluate the persistence of the therapeutic response in this disease. The trial was conducted in according with the Declaration of Helsinki and the study protocol approved by the Institutional Ethical Committee. All patients gave informed written consent at enrollment.

Sixty-two outpatients of both sexes, aged between 35 to 80 years old with stable, symptomatic, moderate-to-severe intermittent claudication were enrolled in the study. Claudication was considered to be stable if no significant variation in the severity of symptoms had occurred in the 6 months prior to the study.

At recruitment (visit 1), a complete clinical history and physical examination were done and the patients were instructed to follow lifestyle recommendations during a 6-week baseline period. Although the patients were not included on any regular exercise program, during the entire study duration they were encouraged to stop smoking and keep walking. In addition, those patients with a history of dyslipidemia were advised to start or continue on a step one cholesterol-lowering diet.[34] These lifestyle measures were recommended and followed for the whole study.

After the 6-week baseline period, walking distances on a treadmill at a constant speed (3.2 km/h), slope (10%) and room temperature (25°C) were assessed. To be included in the study, the patients had to walk at least 50 m before complaining of leg pain, but had to feel the pain before a distance of 300 m in the treadmill test; that is, an initial claudication distance (ICD) between 50 m and 300 m. The absolute claudication distance (ACD) was restricted as less than 500 m measured under the same conditions as ICD. Baseline values of claudication distances were determined as the mean of 2 consecutive values determined within 15 days.

At this time, ankle/arm systolic pressure index values at rest were from 0.5 to 0.9 as determined with Doppler studies. In addition, lipid profile determinations were obtained in claudicant patients with hypercholesterolemia.

Exclusion criteria were age > 80 years; myocardial infarction, vascular surgery, unstable angina or stroke 3 months before the study; severe hypertension (diastolic pressure ≥ 120 mm Hg); occlusive thromboangiitis; and congenital or acquired hemorrhagic diseases. Pregnant or nursing women were also excluded from the trial.

Patients who qualified for the double-blind active treatment period were randomly allocated (visit 2) to receive either placebo or policosanol (10 mg) that was taken twice daily.[31] After 6 months of therapy, claudication distances and ankle/arm indexes were measured again and at visit 3, a complete physical examination, evaluations of symptoms, and a request for adverse events (AE) were done. All these control examinations were repeated after 12, 18, and 24 months of therapy (visits 4 to 6). After 12 and 24 months of treatment (visits 4 and 6), lipid profile determinations were repeated for hypercholesterolemic patients.

Compliance to treatment was assessed by tablet count from visits 3 to 6 and at each visit, the patients received the tablets required for the next 6 months up to study completion.

Efficacy Variables

The main efficacy variables established were the effects of the treatments on ICD and ACD values. Thus, the treatment was considered as effective only if an increase on both treadmill walking distances ≥ 50% compared with baseline was reached. Treatment was not taken 12 hours before the treadmill test; the morning dose on the day of the test was omitted.

The effects of the treatment on the lower limb symptoms (pain, paresthesia, and coldness) were considered as secondary variables. These effects were assessed through an specific interview to evaluate if the symptoms improved, worsened, or remained unchanged.

Lipid Profile Determination

In those patients with concomitant hypercholesterolemia, blood samples were obtained after an evening fast of 12 hours and aliquots were obtained for laboratory determinations. Total cholesterol and triglycerides were determined with colorimetric enzymatic methods using reagent kits from Böerhinger Mannheim (Germany). Levels of HDL-C were determined according to the cholesterol content present in the supernatant obtained after β-lipoprotein precipitation,[35] LDL-C values were calculated using the Friedewald equation.[36]

Concomitant medications for the management of coexisting diseases were generally allowed, except for drugs with a recognized effect on platelet aggregation, such as aspirin, dipyridamole, indubofen, ticlopidine, or clopidogrel. Analgesic and antiinflammatory drugs different from paracetamol were used only if strictly necessary.

Tolerability

A complete physical examination was performed at each visit and a detailed record of any AE was kept. The AE predefined to be serious were fatal events and disabling events, leading to or prolonging hospitalization.

Statistical Analysis

Two-tailed tests were used for statistical analysis. For within-group comparisons, the Wilcoxon test for matched samples was used, and comparisons between groups were done with the Mann Whitney U test. A Bonferroni's adjustment for multiple comparisons in a single test was applied.[37] An *a priori* $\alpha = 0.05$ was assumed for statistical significance. Comparisons between groups of categoric variables were done using the Fisher's exact test. All statistical tests were performed using the CSS package (Stat Soft, Tulsa, OK).

Table I. Baseline characteristics of study patients.

	Policosanol (n = 27)	Placebo (n = 29)		Total (n = 56)
Age (years) ($\bar{X}$ ±SD)	59 ±11	59 ±11	NS†	59 ±11
Body mass index (kg/m^2) ($\bar{X}$ ±SD)	24.2 ±3.20	25.4 ±3.78	NS†	24.8 ±3.53
Sex: Male, n (%)	24 (88.9)	22 (75.9)	NS‡	46 (82.1)
Female, n (%)	3 (11.1)	7 (24.1)	NS‡	10 (17.9)
Duration of the disease (years)	2.3	2.1		2.3
	n (%)	n (%)		n (%)
History of coronary artery disease				
Myocardial infarction	6 (22.2)	8 (27.6)	NS‡	14 (25.0)
Angina	5 (18.5)	5 (17.2)	NS‡	10 (17.9)
Coronary surgery	0 (0.0)	1 (3.4)	NS‡	1 (1.8)
Total	11 (40.7)	14 (48.3)	NS‡	25 (44.6)
Hypercholesterolemia	20 (74.1)	21 (72.4)	NS‡	41 (73.2)
Smoking	20 (74.1)	17 (58.6)	NS‡	37 (66.1)
Hypertension	10 (37.0)	10 (34.5)	NS‡	20 (35.7)
Diabetes	6 (22.2)	5 (17.2)	NS‡	11 (19.6)
Obesity	2 (7.4)	5 (17.2)	NS‡	7 (12.5)
Stroke	2 (7.4)	1 (3.5)	NS‡	3 (5.4)
Concomitant medications*				
Calcium antagonists	10 (37.0)	9 (31.0)	NS‡	19 (33.9)
Nitrovasodilators	4 (14.8)	6 (20.7)	NS‡	10 (17.9)
β-blockers	3 (11.1)	4 (13.8)	NS‡	7 (12.5)
Diuretics	3 (11.1)	2 (6.9)	NS‡	5 (8.9)
Oral hypoglycemic drugs	2 (7.4)	2 (6.9)	NS‡	4 (7.1)
Insulin	3 (11.1)	1 (3.4)	NS‡	4 (7.1)
Digoxine	2 (7.4)	1 (3.4)	NS‡	3 (5.3)
H_2 antagonists	2 (7.4)	0 (0.0)	NS‡	2 (3.6)
Methochlopramide	1 (3.7)	1 (3.4)	NS‡	2 (3.6)
Thyroid hormones	1 (3.7)	1 (3.4)	NS‡	2 (3.6)
Myorelaxants	0 (0.0)	1 (3.4)	NS‡	1 (1.8)

NS†: not significant (Mann Whitney U test). NS‡: not significant (Fisher's exact Test). *The table shows concomitant medications consumed by ≥ 1 patient.

Results

Baseline Characteristics

A total of 62 patients were initially enrolled, 6 of whom were excluded because they did not meet study criteria. The remaining 56 patients were randomly allocated to receive either policosanol or placebo. Of the 56 randomized patients, 40 completed the study (23 policosanol, 17 placebo). The causes of the withdrawals are analyzed in the section on tolerability.

Table I presents a summary of the baseline characteristics of study patients. Both groups were statistically similar at baseline. As expected, the majority of patients were men (82.1%), and the frequency of atherosclerotic risk factors (smoking, hypertension, obesity, diabetes mellitus, hypercholesterolemia) was relatively high.

Efficacy Analysis

Baseline values of claudication distances were also well matched in both groups (Table II). After 6 months on therapy, policosanol, but not placebo, significantly increased ($p < 0.001$) values of ICD and ACD ($p < 0.001$) by 60.1% and 81.0%, respectively, meanwhile in the placebo group these values remained unchanged. Comparisons between groups showed that after therapy values of both variables were significantly greater ($p < 0.01$) in the policosanol than in the placebo group.

These effects did not wear off, but improved after long-term policosanol therapy, so that final values were 333.5 ±28.6 m (ICD) and 648.9 ±54.1 m (ACD); both significantly greater ($p < 0.0001$) than in the placebo group, which reached values of 137.9 ±21.8 m and 237.7 ±28.1 m, respectively.

Table II. Long-term effects of policosanol on claudication distances (m) and the resting ankle/arm pressure index* (mean ±SEM).

	Baseline	6 mo	12 mo	18 mo	24 mo
			ICD		
Policosanol	125.9 ±8.7	201.1 ±24.8[②④]	251.0 ±23.8[③⑤]	293.8 ±26.3[③⑥]	333.5 ±28.6[②⑥]
Placebo	122.4 ±10.7	104.1 ±11.3	116.1 ±15.9	132.4 ±18.2	137.9 ±21.8
			ACD		
Policosanol	219.5 ±14.1	380.7 ±50.2[②④]	471.9 ±48.4[③⑤]	545.1 ±56.3[③⑥]	648.9 ±54.1[③⑥]
Placebo	207.7 ±16.4	216.2 ±26.8	219.9 ±31.9	229.7 ±23.8	237.7 ±28.1
			Ankle/arm pressure ratio*		
Policosanol	0.59 ±0.04	0.65 ±0.05	0.69 ±0.06	0.66 ±0.06	0.71 ±0.06[①④]
Placebo	0.61 ±0.04	0.61 ±0.04	0.64 ±0.05	0.64 ±0.06	0.64 ±0.06

ICD: initial claudication distance, ACD: absolute claudication distance. *Measured at rest in the arteries of the worst lower limb. [①]$p < 0.01$; [②]$p < 0.001$; [③]$p < 0.0001$ compared with baseline (Wilcoxon test for paired samples). [④]$p < 0.01$; [⑤]$p < 0.001$; [⑥]$p < 0.0001$ compared with placebo (Mann Whitney U test).

Absolute claudication distance values increased by 140.9% and 249.5% at 12 and 24 months of policosanol treatment; compared with modest increases of 22.7% and 26.9% in the placebo group. These results support differences of more than 100% between drug and placebo. Also, policosanol increased ICD by 111.8% and 187.8% after 12 and 24 months of therapy compared with increases of 12.8% and 24.5% in the placebo group. At study completion, 21 policosanol and 5 placebo patients attained increases in ACD and ICD values > 50% ($p < 0.001$). From 6 months of therapy to study completion, the frequency of patients who reported improvements in lower limb symptoms was greater in the policosanol than in the placebo group (Table III).

At the first interim checkup performed after 6 months of therapy, there was no significant change in either group in the ankle/arm blood pressure ratio. Nevertheless, after long-term therapy, policosanol ($p < 0.01$), but not placebo, significantly increased the ankle/arm pressure index.

Effects on Lipid Profile

Table IV shows the effects of policosanol on lipid profile of claudicant patients with concomitant hypercholesterolemia. After 12 and 24 months on therapy, policosanol significantly ($p < 0.001$) decreased LDL-C (23.5% and 28.0%), total cholesterol (17.8% and 20%), triglycerides (20.4%, $p < 0.01$; 28.7%, $p < 0.001$), compared with baseline, meanwhile significantly increased ($p < 0.01$ and $p < 0.001$) HDL-C values (20.6% and 28.9%).

Tolerability

Safety indicators recorded during the physical examination of the patients, such as body weight, pulse rate, diastolic and systolic blood pressure did not change significantly after policosanol therapy compared with baseline or placebo (data not shown). Of the 56 randomized patients, 16 (12 placebo, 4 policosanol; 28.6%) discontinued the long-term study. Eight patients, all from the placebo group, withdrew from the

Table III. Frequency of patients reporting improvements on lower limb symptoms during the study.

	6 mo n (%)*	12 mo n (%)	18 mo n (%)	24 mo n (%)
		Paresthesia		
Policosanol	17 (63.0)②	20 (74.1)②	19 (70.4)②	21 (77.8)②
Placebo	3 (10.3)	0 (0.0)	2 (6.9)	1 (3.4)
		Coldness		
Policosanol	17 (63.0)①	21 (77.8)②	20 (74.1)②	21 (77.8)②
Placebo	4 (31.0)	1 (3.4)	4 (13.8)	3 (10.3)
		Pain		
Policosanol	19 (70.4)②	18 (66.7)②	20 (74.1)②	21 (77.8)②
Placebo	4 (13.8)	2 (6.9)	5 (17.2)	3 (10.3)

*Referred to randomized patients. ①$p < 0.001$; ②$p < 0.0001$ comparison with placebo (Mann Whitney U test).

Table IV. Effects of policosanol on lipid profile ($\bar{X} \pm SD$) of claudicant patients with concomitant hypercholesterolemia (n = 41).

	Baseline	12 mo	Δ%	24 mo	Δ%
			Total cholesterol		
Policosanol	6.16 ±0.40	5.05 ±0.36[②⑤]	-17.8[⑥]	4.91 ±0.38[②⑥]	-20.0[⑥]
Placebo	6.15 ±0.41	6.17 ±0.68	**-1.0**	6.28 ±0.75	2.1
			LDL-C		
Policosanol	4.53 ±0.33	3.37 ±0.54[②④]	-23.5[④]	3.24 ±0.38[②⑥]	-28.0[⑥]
Placebo	4.55 ±0.42	4.90 ±0.30	**0.2**	4.56 ±0.67	1.1
			HDL-C		
Policosanol	0.92 ±0.08	1.12 ±0.19[①③]	**20.6**[④]	1.18 ±0.16[②⑤]	28.9[⑥]
Placebo	0.95 ±0.07	0.91 ±0.15	**-5.2**	0.90 ±0.12	-3.9
			Triglycerides		
Policosanol	1.96 ±0.60	1.67 ±0.65[①]	-20.4[③]	1.31 ±0.44[②④]	-28.7[⑤]
Placebo	1.75 ±0.53	1.95 ±0.83	**6.2**	2.23 ±0.77	20.2

[①] $p < 0.01$; [②] $p < 0.001$ compared with baseline (Wilcoxon test for paired samples). [③] $p < 0.05$; [④] $p < 0.01$; [⑤] $p < 0.001$; [⑥] $p < 0.0001$ compared with placebo (Mann Whitney U test).

study because of AE (27.6% of the placebo randomized patients and 47.1% of the overall withdrawals); meanwhile, other patients discontinued the study because of lack of improvement (1 placebo); 2 major protocol violations (bad compliance; 1 placebo and 1 policosanol); changes in address to other towns (1 placebo and 1 policosanol); and unwillingness to follow up (1 placebo and 2 policosanol).

Eight placebo, but not policosanol patients, experienced a total of 10 serious AE during the study. Thus, 2 placebo patients died because of hemorrhagic stroke and respiratory arrest, respectively; meanwhile, 8 other serious AE occurred in the placebo group: 2 nonfatal myocardial infarction, 1 unstable angina, 1 nonfatal stroke, 2 ischemic transient attacks, 1 hypertensive status, and 1 surgical intervention. Eight serious AE (fatal + nonfatal) were of vascular etiology.

In addition, 3 policosanol and 3 placebo patients reported mild AE during the study. Overall, 11/29 (37.9%) patients in the placebo group and 3/27 (11.1%) in the policosanol group complained of at least one AE after randomization, showing a significant difference between both groups for the frequency of patients who experienced AE ($p < 0.05$) (Table V).

Discussion

Atherosclerosis is the primary cause of PAD, but since it is a generalized disease, patients with

Table V. Adverse events during the study.

Adverse events	Policosanol (n = 27) n (%)	Placebo (n = 29) n (%)	Total (n = 56) n (%)
Serious adverse events			
Fatal			
Respiratory failure	0 (0.0)	1 (3.4)	1 (1.8)
Hemorrhagic stroke	0 (0.0)	1 (3.4)	1 (1.8)
Total	0 (0.0)	2 (6.9)	2 (3.6)
Nonfatal adverse events			
Ischemic transient attacks	0 (0.0)	2 (6.9)	2 (3.6)
Myocardial infarction	0 (0.0)	2 (6.9)	2 (3.6)
Unstable angina	0 (0.0)	1 (3.4)	1 (1.8)
Uncontrolled hypertension	0 (0.0)	1 (3.4)	1 (1.8)
Nonfatal stroke	0 (0.0)	1 (3.4)	1 (1.8)
Surgical intervention	0 (0.0)	1 (3.4)	1 (1.8)
Total	0 (0.0)	8 (27.6)②	8 (14.3)
Total of serious adverse events	0 (0.0)	10 (34.5)③	10 (17.9)
Mild adverse events			
Loss of memory	0 (0.0)	2 (6.9)	2 (3.6)
Acidity	2 (7.4)	0 (0.0)	2 (3.6)
Insomnia	1 (3.7)	0 (0.0)	1 (1.8)
Nervousness	1 (3.7)	0 (0.0)	1 (1.8)
Dizziness	0 (0.0)	1 (3.4)	1 (1.8)
Weight loss	0 (0.0)	1 (3.4)	1 (1.8)
Total of mild adverse events	4 (14.8)	4 (13.8)	8 (14.3)
Total of patient reported mild adverse events	3 (11.1)	3 (10.3)	6 (10.7)
Overall frequency of adverse events	4 (14.8)②	14 (48.3)	18 (32.1)
Total of patients who reported adverse events	3 (11.1)①	11 (37.9)	14 (25.0)

①$p < 0.05$; ②$p < 0.01$; ③$p < 0.001$ compared with placebo (Fisher's exact test).

PAD commonly present other arterial disorders so that the general prognosis for them is negative. Thus, there is a high prevalence of CHD and cerebrovascular disease in such patients. This information, together with the disability induced by the intermittent claudication itself justify the importance of adequate long-term management of this disease.

To our knowledge, this is the first randomized, double-blind study in which the long-term effects of policosanol, a cholesterol-lowering drug with concomitant antiplatelet effects, are compared with those of placebo in patients with moderately severe intermittent claudication. The study population showed similar characteristics to those reported by other authors, including a majority of male patients and a high frequency of risk factors.

This study demonstrates that policosanol significantly increased both ICD and ACD and improves the ischemic symptoms of intermittent claudication. In addition, efficacy was not only sustained, but improved, after long-term therapy. The improvement in ICD and ACD derived from policosanol therapy is supported not only by the significant differences of posttherapy values compared with baseline and placebo, but also in terms of the respective percent changes. Although in the placebo group a mild upward drift of both walking distances was observed, this effect was not significant, which reinforces the clinical relevance of the increases obtained in the treated group.

The difference between both groups was already present after 6 months on therapy but more pronounced 6 months onward as reflected not only in final values of both ACD and ICD but also by the frequency of responders defined according to increases in ICD and ACD $>50\%$ compared with baseline.

In addition, the frequency of increases in ACD and ICD $>50\%$ was also significantly larger in the policosanol than in the placebo group. Smoking and walking daily habits did not change significantly throughout the study in either group, which reinforces the fact that the improvement noted in the treated group was actually drug-related.

As reported in the previous study,[31] the ankle/arm pressure index at rest was unaffected after 6 months on policosanol therapy. Nevertheless, from 12 months to study completion, policosanol moderately, but significantly, increased the values of the ankle/arm pressure index of the worst limb. Perhaps the longer duration of the treatment administered in this study could contribute to a better impact of policosanol on the atherosclerosis disease underlying the PAD condition, since the ankle/arm pressure index has been considered as an established indicator of atherosclerotic disease.[38]

Taking into account that policosanol shows cholesterol-lowering and antiplatelet effects at the same therapeutic dosage (5–20 mg/d), it is not surprising that long-term administration can improve the ankle/arm pressure index. In addition, policosanol also inhibits LDL susceptibility to lipid peroxidation in experimental models and such pleiotropic effect also can contribute to a better antiatherosclerotic effect able to counteract the endothelial dysfunction associated with the atherosclerotic disease underlying the PAD.

The effects of policosanol on lipid profile of hypercholesterolemic patients agree with those expected.[14-25] Nevertheless, although significant and marked changes in total cholesterol, LDL-C, and HDL-C were obtained in this study, the mean changes were less pronounced than those obtained with a similar daily dose (20 mg/d) administered for 1 year to hypercholesterolemic patients at high coronary risk.[38] This difference could be related to the difference in baseline characteristics of both study populations, since in that study most of the cases (88.2%) showed severe and moderate hypercholesterolemia and a high frequency of cases with low HDL-C (44.1%), meanwhile in this study, only 73.2% of the patients had hypercholesterolemia, mainly showing mild and moderate hypercholesterolemia. The previous study was conducted with an open design,[39] but this study was a randomized, double-blind trial, which represents a better design to evaluate the effects of any drug dosage. In conclusion, further studies performed with this dosage in patients with type II hypercholesterolemia and a broad range of cholesterol levels are needed to corroborate the long-term cholesterol-lowering response related to such dosage, which was not the main goal of this study.

Policosanol, more than placebo, improved lower limb symptoms associated with exercise, which also reveal the efficacy of the treatment according to patient's subjective perception. Finally, the very good tolerability of policosanol agrees with that expected from previous data.[14-25] The 8 serious AE occurred during the study were in 8 placebo patients, not in the policosanol group.

Conclusions

These results indicate that policosanol (20 mg/d) administered for 2 years shows a sustained efficacy to increase markedly walking distances, improve ischemic symptoms, and moderately increase the ankle/arm pressure index in patients with intermittent claudication.

This study also shows a lesser extent of AE in the policosanol than in the placebo group. Since most of the serious AE were vascular, a beneficial effect of policosanol on peripheral vascular function could be involved. Further comparative studies of policosanol vs different antiplatelet drugs are needed to conclude the benefit-to-risk ratio of policosanol therapy in the treatment of patients with intermittent claudication.

REFERENCES

1. Verhaeghe R: Epidemiologic et pronostic de l'arteriopathic obliterante des membres inferieurs. Drug 56(suppl 3):1-10, 1998.
2. Marquis P: Evaluation de l'impact de l'arteriopathic obliterante des membres inferieuos sur la quarte de vie. Drugs 56(suppl 3):25-35, 1998.
3. Criqui M, Langer RD, Fronek A: A mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 326:381-386, 1992.
4. Bowlin SJ, Medalie JH, Flocke SA, et al: Epidemiology of intermittent claudication in middle-aged men. Am J Epidemiol 140:418-430, 1994.
5. Fowkes FGR, Housley E, Riemersma RA, et al: Smoking, lipids, glucose intolerance and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol 135:331-340, 1992.
6. Lowe GDO, Fowkes FGR, Dawes J, et al: Blood viscosity, fibrinogen and activation of coagulation and leucocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. Circulation 87:1915-1920, 1993.
7. European Working Group on Critical Leg Ischemia: Second European consensus document on chronic critical leg ischemia. Circulation 84(suppl IV):1-26, 1991.
8. Gardner AW, Poehlman ET: Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 274:975-980, 1995.
9. Lindagarde F, Bjorkman H, Adielsson G, et al (for the Scandinavian Study Group): Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. Circulation 80:1549-1556, 1989.
10. Reich T, Cutler BS, Lee BY, et al: Pentoxifylline in the treatment of intermittent claudication of the lower limb. Angiology, 35:389-393, 1984.
11. Tonnesen KH, Albuerque P, Baitsch G, et al: Double-blind, controlled multicenter study of indubofen versus placebo in patients with intermittent claudication. Intern Angiol 12:371-377, 1993.
12. Verhaeghe R: Platelets in peripheral arterial disease. Crit Ischaemia 4:21-25, 1994.
13. Gresele P, Catalano M, Giammaresi C, et al: Platelet activation markers in patients with peripheral arterial disease. A prospective comparison of different platelet function tests. Thromb Haemost 78:1434-1437, 1997.
14. 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 XIV:27-33, 1994.
15. Aneiros E, Más R, Calderón B, et al: Effect of policosanol in lowering-cholesterol levels in patients with type II hypercholesterolemia. Curr Ther Res 56:176-182, 1995.
16. Castaño G, Más R, Nodarse M, et al: One-year study of the efficacy and safety of policosanol (5 mg twice daily) in the treatment of type II hypercholesterolemia. Curr Ther Res 56:296-304, 1995.
17. Castaño G, Canetti M, Morera M, et al: Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: A 12 months study. Curr Ther Res 56:819-828, 1995.
18. Canetti M, Morera M, Illnait J, et al: A 2-year study on the efficacy and tolerability of policosanol in patients with type II hypercholesterolemia. Int J Clin Pharmacol Res XV:159-165, 1995.
19. 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 57:568-577, 1996.
20. Ortensi G, Gladstein H, Valli H, et al: A comparative study of policosanol versus simvastatin in elderly patients with hypercholesterolemia. Curr Ther Res 58:390-401, 1997.
21. Benítez M, Romero C, Más R, et al: A comparative study of policosanol versus pravastatin in patients with type II hypercholesterolemia. Curr Ther Res 58:859-867, 1997.
22. Canetti M, Morera MS, Más R, et al: Effects of policosanol on primary hypercholesterolemia: A 3-year open follow-up. Curr Ther Res 58:868-875, 1997.
23. Más R, Castaño G, Illnait J, et al: Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. Clin Pharmacol Thera 65:439-447, 1999.
24. Torres O, Agramonte AJ, Illnait J, et al: Treatment of hypercholesterolemia in NIDDM with policosanol. Diabetes Care 18:393-397, 1995.
25. Crespo N, Alvarez R, Más R, et al: Effect of policosanol on patients with non-insulin-dependent dia-

betes mellitus (NIDDM) and hypercholesterolemia. Curr Ther Res 58:44-51, 1997.

26. Arruzazabala ML, Carbajal D, Más R, et al: Effects of policosanol on platelet aggregation in rats. Thromb Res 69:321-327, 1992.
27. Arruzazabala ML, Valdés S, Más R, et al: Effect of policosanol successive dose increases on platelet aggregation in healthy volunteers. Pharmacol Res 34:181-185, 1996.
28. Scazziota A, Pons S, Altman R: Efecto del policosanol sobre la función de las plaquetas en voluntarios sanos. Rev Iberoamer Tromb Hemost 9:58-62, 1996.
29. Carbajal D, Arruzazabala ML, Valdés S, et al: Effect of policosanol on platelet aggregation and serum levels of arachidonic acid metabolites in healthy volunteers. Prostaglandins Leukocytes Essential Fatty Acids 58:61-64, 1998.
30. Arruzazabala M de L, Valdés S, Más R, et al: Comparative study of policosanol, aspirin and the combination of policosanol-aspirin on platelet aggregation in healthy volunteers. Pharmacol Res 36:293-297, 1997.
31. Castaño G, Más R, Fernandez L, et al: A double-blind placebo-controlled study of the effects of policosanol in patients with intermittent claudication. Angiology 50:123-130, 1998.
32. Iatt WR, Nawaz D, Regensterner JG, et al: The evaluation of exercise performance in patients with peripheral vascular disease. J Cardiopulm Rehabil 12:525-532, 1998.
33. Heidrich H, Allenberg J, Cachovan M, et al: Guidelines for therapeutic studies on peripheral arterial occlusive disease in Fontaine stages II–IV. Vasa 21:339-343, 1992.
34. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. National Cholesterol Education Program (NCEP). Second report of the Expert Panel on Detection. Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). III Drug treatment. Circulation 89:1405-1419; 1432-1445, 1994.
35. Seigler L, Wu T: Separation of serum high-density lipoprotein for cholesterol determination: Ultracentrifugation vs precipitation with sodium phosphotungstate and magnesium chloride. Clin Chem 27:838-841, 1981.
36. Friedewald WT, Levy RI, Friederickson SD: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972.
37. O'Brien PC, Shampo MC: Statistical considerations for performing multiple test in as single-experiment 5. Comparing 2 therapies with respect to several endpoints. Mayo Clin Proc 63:1140-1143, 1988.
38. Fowkes FGR, Leng GC, Lee AJ, et al: The ankle arm index as a predictors of cardiovascular events and death in the general populations. Abstracts from the 4th International Conference in Preventive Cardiology 267B, 1997. Can J Cardiol 13(suppl 13).
39. Castaño G, Fernandez JC, Más R, et al: A long-term open study on the efficacy and tolerability of policosanol in patients with high global coronary risk. Curr Ther Res 60:379-391, 1998.