¿Does policosanol impairs muscle function of older patients with type II hypercholesterolemia?

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RESUMEN: La enfermedad coronaria (EC) es la principal causa de muerte en individuos de edad media y avanzada. Estudios clínicos han mostrado que la reducción de los niveles de colesterol total (CT) y del transportado por las lipoproteínas de baja densidad (LDL-C) reduce la frecuencia de eventos coronarios, por lo cual las drogas reductoras de colesterol se indican en la prevención de la EC. Las miopatías y la rabdomiolisis son experiencias adversas (EA) asociadas al uso de estas drogas, especialmente al de las estatinas, probablemente debido a la reducción de los niveles de mevalonato inducida por la inhibición de la HMGCoA reductasa que ellas provocan. El riesgo a padecer estas importantes EA se encuentra aumentado en poblaciones vulnerables, tales como la ancianidad. El policosanol es un medicamento purificado de la cera de la caña de azúcar con efectos hipocolesterolemizantes asociados a la inhibición de la biosíntesis de colesterol a través de la regulación de la actividad de la HMGCoA reductasa. El policosanol (5 – 20 mg/d), es efectivo a corto y largo plazo, destacándose su excelente seguridad, ya que hasta el presente no se han demostrado EA asociadas a su uso. Sin embargo, considerando sus efectos sobre la biosíntesis de colesterol, resulta importante establecer si puede inducir EA musculares. Este estudio aleatorizado, a doble ciegas y controlado con placebo se realizó para investigar los efectos a largo plazo del policosanol en pacientes con hipercolesterolemia (HC) Tipo II, enfocando en especial los posibles EA musculares asociados con el tratamiento. Tras 4 semanas de dieta hipolipemiante (período basal), 300 ancianos que cumplieron los criterios de selección fueron distribuidos para recibir, de modo aleatorio y a doble ciegas, policosanol 5 mg o placebo. Las tabletas se ingirieron una vez al día con la cena durante 12 meses. Los exámenes físicos y el control del CT se realizaron cada 6 meses, mientras que los análisis de perfil lipídico completo e indicadores de seguridad se realizaron en condiciones basales y al culminar el tratamiento. Los interrogatorios de EA y la evaluación de la adhesión al tratamiento se realizaron a los 6 y 12 meses de tratamiento. El policosanol (5 mg/d) redujo significativamente ($p < 0.00001$) los niveles de LDL-C (20.5 %), TC (16.8%) y triglicéridos ($p < 0.0001$) (13.2 %), mientras que aumentó ($p < 0.001$) los del colesterol asociado a las lipoproteínas de alta densidad (HDL-C) (9.8 %). La frecuencia de pacientes que alcanzaron reducciones de las LDL-C ≥ 15 % respecto al nivel basal fue mayor ($p < 0.001$) en el grupo policosanol (146/193, 75.6 %) que en el placebo (15/192, 7.8 %) El policosanol resultó seguro, ya que no afectó ningún indicador de seguridad. Los valores finales de presión sistólica y CFK en el grupo policosanol fueron menores ($p < 0.05$) que en el placebo. Durante el estudio no ocurrieron bajas por EA y los reportes de EA fueron similares en ambos grupos. Así, 12 pacientes tratados con policosanol (6.2 %) reportaron 13 EA, mientras que 11 placebo (5.7 %) reportaron 14 EA. Dos pacientes placebo reportaron dolor de los miembros inferiores, mientras ningún paciente del grupo policosanol refirió EA sugerentes de afectación muscular. Se concluye que el policosanol administrado a 5 mg/d durante 12 meses fue efectivo en reducir los niveles de LDL-C, CT y triglicéridos, mientras incrementó los de HDL-C, en ancianos con HC tipo II. El policosanol fue seguro a largo plazo y los resultados no sustentan ni evidencias ni sospechas de daño muscular asociado al tratamiento. Sin embargo, son necesarios posteriores estudios de largo plazo que investiguen los efectos del policosanol sobre indicadores de la función muscular, utilizando algoritmos específicos, para descartar completamente cualquier potencial miotóxico del policosanol.

ABSTRACT: Coronary heart disease (CHD) is the main cause of mortality in middle-aged and elderly individuals. Clinical studies have shown that lowering total (TC) and low-density lipoprotein-cholesterol (LDL-C) reduces the frequency of coronary events, so that cholesterol-lowering drugs are indicated to prevent CHD. Myopathy and rabdomyolysis are adverse experiences (AE) associated to the use of these drugs, particularly to statins, probably due to the reduction of mevalonate levels induced by the HMGCoA reductase inhibition elicited by them. The risk to these relevant drug-related AE is increased in vulnerable populations, such as in the elderly. Policosanol is a drug purified from sugar cane wax with cholesterol-lowering effects associated to the inhibition of cholesterol biosynthesis through the

regulation of HMGCoA reductase activity. Policosanol (5 – 20 mg/d) is short and long-term effective and its excellent safety is a noticeable advantage of its use, so that no drug-related AE have proven up to date. Nevertheless, taking into account its effects on cholesterol biosynthesis, it is important to discard whether policosanol can induce muscle-related AE. This randomized, double-blinded, placebo-controlled study was conducted to investigate the long-term effects of policosanol on older patients with Type II Hypercholesterolemia (HC), with focus on AE associated to muscle function impairment. After 4 weeks on a baseline cholesterol-lowering diet step, 385 patients were randomized to policosanol (5 mg/d) or placebo. Tablets were taken once a day with the evening meal for 12 months. Physical examination and TC control were done at baseline and every 6 months, while complete laboratory control was performed at baseline and study completion. Drug compliance assessment and AE requests were done after 6 and 12 months on therapy. Policosanol significantly ($p < 0.00001$) lowered LDL-C (20.5 %), TC (16.8 %) and triglycerides ($p < 0.0001$) (13.2 %), whereas increased ($p < 0.00001$) HDL-C (9.8 %). No significant changes on lipid profile variables occurred in placebo. The frequency of patients reaching LDL-C reductions ≥ 15 % vs baseline was greater ($p < 0.001$) in policosanol group (146/193, 75.6 %) than in placebo (15/192, 7.8 %). Policosanol was safe, since the treatment did not impair any safety indicator. Final values of systolic pressure and creatinphosphokinase (CPK) in policosanol were lower ($p < 0.01$) than in placebo group. No withdrawals due to AE occurred during the study. The reports of AE were similar in policosanol and placebo. Thus, 12 policosanol patients (6.2 %) reported a total of 13 AE, whereas 11 placebo (5.7 %) reported 14 AE. Two placebo (1.0 %) reported lower limb pain, while no policosanol patient reported symptoms related with muscle impairment. It is concluded that policosanol at 5 mg/d for 12 months was effective to reduce LDL-C, TC and triglycerides, whereas increased HDL-C on older patients with type II HC. Policosanol was long-term safe and results do not support evidence or suspicion of policosanol-linked muscle damage. Nevertheless, further long-term studies assessing impairment of muscle function indicators through specific algorithms must be conducted to completely discard any myotoxic potential of policosanol.

INTRODUCTION

Atherosclerosis and thrombosis are the basic process involved in coronary (CHD) and cerebro-vascular diseases, which are included among the three major causes of mortality and morbidity of middle aged and elderly population worldwide.[1,2]

Coronary prevention reinforces the control of modifiable risk factors to prevent atherosclerosis and its consequences.[3-5]

Hypercholesterolemia (HC), together hypertension and smoking, represent the major atherosclerotic risk factors,[6–8] being clinically proven that lowering elevated total (TC) and mainly low-density lipoprotein-cholesterol (LDL-C), reduces clinical outcomes in primary and secondary prevention patients.[9–14] Although for many time, HC management in the elderly was controversial,[15] updated guidelines includes this population as a specific taarget.[3, 5]

HC management is focused to reduce LDL-C levels below specific targets and the adherence to a step I cholesterol-lowering represents the first-choice therapy to reach such goal.[3–5] Diet alone, however, often is not enough to reach the targets, mainly in patients at high risk, for whom more restricted goals are established. Then, cholesterol-lowering drugs must be indicated.

Inhibitors of HMGCoA reductase (statins or HMGRI) have been positioned as the dominant drug class for HC treatment, since convincing proofs that they prevent coronary and cerebrovascular events in secondary and primary prevention patients are available.[8–13] Statins induce their cholesterol-lowering effects through the competitive inhibition of the pacemaker enzyme of cholesterol biosynthesis, namely HMGCoA reductase. Also, statins shows several vascular pleiotropic effects that contribute, beyond its lipid-lowering properties, to prevent clinical outcomes.[16-17]

Statins are generally well tolerated, so that most of their drug-related adverse experiences (AE) are mild and transient. Gastrointestinal symptoms are the most frequent AE induced by statins, but the most serious arise from liver and skeletal muscle impairment.[18–21] Disturbances on liver function indicators, such as increases on serum transaminases, occur in approximately 1 % of the patients. Nevertheless, although less common, myotoxicity is the most serious AE related with statin treatment because it accounts for serious AE such as myopathy and specifically, rhabdomyolysis leading to myoglobinuria, acute renal failure and death.[18–25]

Myopathy has been defined as any abnormal condition of the muscle tissues, commonly involving skeletal muscle Drug-induced myopathy is frequent and usually develops insidiously, so that early clinical symptoms can occurs after days to months of exposure to the treatment. Patients commonly present progressive and generalized muscle weakness, proximal muscle weakness of the arms and the legs being the main symptom. Also, muscle pain (myalgia), cramps and fatigue are frequently present.[26, 27]

In suspected cases of drug-induced myopathy, serum levels of damaged muscle indicators can be measured, such as creatinphosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, myoglobin, potassium and phosphorum. Up to date, CPK is considered as the most sensitive laboratory indicator of muscle function, but it has a low specificity that limits its use in the diagnosis of drug-induced myopathy. Thus, in these cases CPK may be normal to seriously elevated.

In addition, although drug-induced myopathy can increase CPK levels, other causes can induce similar effects.[26-29]

Other definition of myopathy widely used for practical objectives defines such condition as the presence of ≥ two clinical symptoms with CPK levels increased > 10 fold. In turn, myalgia is referred to a combination of muscle pain, weakness or tenderness in a proximal or regional pattern with a frequent cramping feeling of the muscle, wherein CPK levels can be normal or justly mildly raised.[30]

The withdrawal of cerivastatin from the US market on 2001 by decision of its manufacturer (Bayer), in agreement with the Food and Drug Administration,[31] has focused the interest on the essential features of myopathy induced by lipid-lowering drugs. Cerivastatin was withdrawn because the reports of fatal and nonfatal rhabdomyolisis occurred in cerivastatin users were more frequent than in other statin treated patients. Nevertheless, an analysis of 385 reports of this condition among patients consuming other statins supported the petition of Public Citizen to FDA to issue strong warnings about the myotoxic potential of statins.[32]

The onset of myopathies induced by lipid-lowering drugs generally occurs after 2 to 3 months of starting treatment, their duration range from days to years and recovery from days to months after stopping drug.[25-29] Among statin-treated patients myopathy is less frequent (< 0.5 %) than myalgia (1 %-7 %) or CPK increases (1 %) alone. Thus, this last symptom has been considered as an early alert sign of a future appearance of myopathy in those patients reporting such effect. Some risk factors are associated to statin-induced myopathy, such as hepatic failure, renal insufficiency, metabolic enzyme inhibition, aging, and concomitant use of other myotoxic agents.

Although the exact mechanism of statin-induced myopathy has not been fully demonstrated, it may involve the mevalonate dependent reduction of cholesterol precursors. Thus, specific depletion of ubiquinone (CoQ 10) levels as a consequence of affected mevalonate synthesis leads to disturbances in cell energy production. Also, altered excitation-contraction coupling, decreased membrane fluidity, sarcolemma ionic flux and impaired Ca^{+2} modulation can also play a role in this drug-induce myopathy.[24]

Policosanol is a mixture of higher aliphatic primary alcohols purified from sugar cane (*Saccharum officinarum, L.*) wax[33,34] with cholesterol-lowering efficacy proven in type II HC[35-46] and in the dyslipidemia due to Type 2 diabetes.[47-49] Policosanol inhibits cholesterol biosynthesis,[50-52] through a an indirect regulation of HMG CoA reductase activity instead of a competitive inhibition. Clinical studies[35-49] and post-marketing surveillance[53, 54] have demonstrated that policosanol is safe and well tolerated. Thus, no policosanol-related AE has been proven up to date.

Nevertheless, since policosanol inhibited cholesterol synthesis in a step located between acetate consumption and mevalonate production, myotoxic effects dependent from the reduction of cholesterol precursors and particularly, from ubiquinone depletion, cannot be completely excluded.

Considering this background, the present study was undertaken to investigate whether policosanol long-term administered induces AE related with muscle function impairment different from placebo. In addition, long-term efficacy of policosanol was also assessed.

PATIENTS AND METHODS

Study design.

The present study was a randomized, double-blinded, parallel-group, placebo-controlled, long-term study conducted in older patients with type II HC.

At enrollment (visit 1) patients entered in a 4 week run-in period, during which they discontinued all lipid-lowering therapy and were instructed to follow a step I cholesterol-lowering diet.[4,6] After this diet-only period study, two consecutive lipid profile determinations were done within 15 days. In the occasion that samples for the second determination were taken, aliquots for safety laboratory tests were done. Three hundred (300) eligible older hypercholesterolemic patients received policosanol 5 mg or placebo tablets. Study medications were taken once a day with the evening meal for 12 months.

Study patients.

Older patients, aged 65 to 80 years old, from both sexes and documented HC were recruited in the study: All patients provided written informed consent before enrolling the trials. Patients met inclusion criteria if their LDL-C and TC values after baseline period were ≥ 3.4 mmol/L and 5.2 mmol/l, respectively. Triglycerides should be < 4.52 mmol/L to can apply Friedewald Equation for LDL-C calculation.[55]

Patients with active renal or hepatic diseases, diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg) and uncontrolled diabetes (glucose > 7.5 mmol/L) were excluded from the study. In addition, those who had had unstable angina, myocardial infarction, stroke, transient ischemic attacks or coronary surgery within the 3 months previous to the study were also excluded.

Assessments

At recruitment (visit 1), a complete medical history including physical examination was performed. Physical examination and control of TC were done at baseline (visit 2) and every 6 months (visits 3 and 4), while complete laboratory control was performed at visits 2 and 4. AE requests and drug compliance, assessed by tablet count and patient's interview, were done at visits 3 and 4.

Laboratory analysis

Blood samples were drawn from 8:00 to 8:30 a.m. after an evening fasting of 12 hours and aliquots were obtained for laboratory analysis. TC and triglycerides were determined by colorimetric enzymatic methods using reagent kits from Roche (Switzerland). Levels of HDL-C were determined according to the cholesterol content present in the supernatant obtained

after β-lipoproteins precipitation.[56] LDL-C values were calculated using the Friedewald equation.[55]

Laboratory safety tests included determinations of glucose, creatinine, AST, ALT and CPK, which were performed by enzymatic methods using reagent kits from Roche (Switzerland). Laboratory tests were performed in the Hitachi 712 autoanalyzer (Tokyo, Japan) located at the laboratory of the Center for Surgical and Medical Research (Havana, City, Cuba).

A quality control was per-formed throughout the study, so that the precision and accuracy of the methods were controlled. Precision was assessed according to repeatability (r) (within-day va-riations) and reproducibility (R) (between-day variations); mean-while accuracy was evaluated against standard re-ferences. Taking into account that the main efficacy variable (LDL-C) was cal-culated by Friedewald equation, the quality of the determination of the lipid parameters included in such Equation was the target of quality control. The coefficient of variations were TC: r = 2.7; R=3.1; Triglycerides r = 3.7, R = 4.0; HDL-C r = 3.0; R = 3.5. The differences against the standard reference were < 4% for TC and < 5% for triglycerides.

Efficacy variables

Changes on LDL-C levels were established as primary efficacy variable. The treatments were considered as effective only if LDL-C levels were reduced by ≥ 15 % compared with baseline.[57] Another lipid profile variables were considered as secondary efficacy variables.

Safety and tolerability

Data from physical examination, laboratory tests and interview for AE were included for the analysis of drug safety and tolerability. AE predefined as "serious" were fatal or disabling events, leading to or prolonging hospitalization. Moderate AE were those requiring therapy

Table 1. Baseline characteristics of study patients: Long-term study

Characteristics	Policosanol (n = 193)		Placebo (n = 192)	
Age (years) (X ± SD)	66 ± 6		66 ± 6	
Body mass index (kg/m^2) (X ± SD)				
Sex: Female n (%)	160	82,9	148	77,1
Male n (%)	33	17,1	44	22,9
Subtype of Type II HC n (%)				
II a or isolated HC	108	56,0	112	58,3
II b or combined HC	85	44,0	80	41,7
Personal risk factors: n (%)				
Hypertension	118	61,1	112	58,3
Secondary prevention	44	22,8	47	24,5
Smoking	37	19,2	38	19,8
Diabetes mellitus	26	13,5	26	13,5
Concomitant medications* (CM) n (%)				
Diuretics	50	25,9	48	25,0
β-blockers	30	15,5	38	19,8
Calcium antagonists	37	19,2	34	17,7
Acetyl Salycilic Acid (ASA)	26	13,5	30	15,6
Anxyolitics	25	13,0	31	16,2
Vasodilators	20	10,4	16	8,3
Myorelaxants	16	8,3	13	6,8
Oral hypoglycemic drugs	15	7,8	15	7,8
Angiotensin Converting Enzyme inhibitors	12	6,2	11	5,7

n Number of patients; (X ± SD) (mean ± standard deviation)

*The table 1 A includes only those CM consumed by ≥ 2 % of study patients, while Table 1 B includes those consumed by ≥ 6 % of study patients

Table 2. Long-term effects of policosanol (5 mg/d) and placebo on lipid profile (X ± SD) of patients with type II HC

Treatment	Baseline	12 months	% changes
LDL-C (mmol/L)			
Policosanol	4,83 ± 0,84	3,78 ± 0,48***+++++	**- 20,5+++++**
Placebo	4,77 ± 0,87	4,76 ± 0,73	**+ 1,2**
TC (mmol/L)			
Policosanol	6,78 ± 0,71	5,61 ± 0,51***+++++	**16,8+++++**
Placebo	6,74 ± 0,84	6,65 ± 0,73	**- 0,9**
HDL-C (mmol/L)			
Policosanol	1,06 ± 0,11	1,16 ± 0,14*****++++	**+ 9,8+++++**
Placebo	1,06 ± 0,08	1,07 ± 0,12	**+ 1,4**
Triglycerides (mmol/L)			
Policosanol	2,35 ± 0,92	1,82 ± 0,37***++	**- 13,2**+++
Placebo	2,36 ± 0,90	2,13 ± 0,50 *	**- 2,6**

X mean, SD standard deviation; % Percent changes
*p < 0.05; **p < 0.01, ***p < 0.001 ****p < 0.0001, *****p < 0.00001 Comparison with baseline
++p < 0.01; +++p < 0.001, ++++p < 0.0001; +++++p < 0.00001 Comparison with placebo

discontinuation according to the physician and/or specific treatment of the AE, while those AE not requiring discontinuation of study drugs and/or specific treatment were classified as "mild".

The AE were also classified as unlikely, doubtfully, possibly or probably drug related according to their probable relationship with study drugs. Since the classification of an AE as definitively drug-related requires the challenge of the study drug and the suspension of treatment was predefined as a cause of withdrawal, this concept was not applied to the AE occurred during the study.

Statistical analysis

All data were analyzed according to the Intention-to-Treat approach**,** it means that available data of withdrawals were included in all analysis. Within group comparisons of continuous variables were performed using the Wilcoxon test for paired samples; meanwhile between group comparisons were done using the Mann Whitney U Test. Comparison of categorical variables were done using the Fisher's Exact Test. All tests were two tailed. A value of $\alpha = 0.05$ was assumed for statistical significance. Statistical analyses were performed using the Statistica for Windows package program.

RESULTS

Baseline characteristics

Table 1 lists the baseline characteristics of study patients. Both groups were comparable regarding to all baseline characteristics. The frequency of arterial hypertension among study patients was high (> 50 %), being also relatively frequent the cases at secondary prevention and smokers (> 15 %). These conditions were well matched in both groups too.

Effects on lipid profile

Table 2 shows the effects on lipid profile. Both groups showed similar values of lipid profile variables at baseline (end of the diet-only period). After 12 months on therapy, policosanol at 5 mg/d significantly ($p < 0.00001$) lowered LDL-C, the main efficacy variable (20.5 %), TC (16.8 %) and triglycerides ($p < 0.0001$) (13.2 %). In addition, policosanol significantly increased ($p < 0.001$) HDL-C (9.8 %). No significant changes on lipid profile were observed in placebo group and all changes occurred in policosanol groups were significantly different from placebo.

The frequency of randomized patients reaching LDL-C reductions ≥ 15 % respect to baseline was greater ($p < 0.0001$) (146/193, 75.6 %) in policosanol than in placebo group (15/192, 7.8 %).

Safety and tolerability

Policosanol significantly decreased systolic blood pressure compared with baseline ($p < 0.01$) and placebo ($p < 0.01$), whereas all others safety indicators determined throughout the physical examination remained unchanged (Table 3). Regarding to blood biochemistry indicators, policosanol significantly lowered ($p < 0.05$) AST values compared with baseline, but it did not change any other safety indicator. Unfortunately, CPK values were not determined at baseline, so that it was not possible to compare whether the treatment changed these values respect to baseline conditions. Nevertheless, comparison with placebo showed that final values of CPK were significantly lower in policosanol ($p < 0.01$) than in placebo group, which indicates that the treatment did not increased such values differently from placebo.

DISCUSSION

The present study demonstrates that policosanol long-term administered at 5 mg/d lowered LDL-C, TC

Table 3. Long-term effects of policosanol on safety indicators (X ± SD) on patients with type II HC

Treatment	Safety indicators	
	Body weight (kg)	
Policosanol	66,96 ± 12,80	67,59 ± 12,03
Placebo	66,93 ± 12,59	67,42 ± 12,53
	SBP (mm Hg)	
Policosanol	133,39 ± 15,61	129,95 ± 9,44**++
Placebo	131,98 ± 15,66	133,17 ± 13,59
	DBP (mm Hg)	
Policosanol	80,00 ± 8,49	80,78 ± 4,78
Placebo	79,14 ± 8,40	80,58 ± 5,91**
	ALT (U/L)	
Policosanol	18,81 ± 8,56	20,55± 6,80*
Placebo	19,46 ± 8,37	22,15 ± 6,32*****
	AST (U/L)	
Policosanol	23,24 ± 6,63	18,63 ± 4,79*****+++
Placebo	24,12 ± 6,70	21,86 ± 6,17*****
	CPK (UI/L)	
Policosanol	nt	96,26 ± 32,16++
Placebo	nt	107,18 ± 36,99
	Glucose (mmol/L)	
Policosanol	5,33 ± 0,88	5,26 ± 0,65
Placebo	5,38 ± 0,89	5,33 ± 0,92
	Creatinine (μmol/L)	
Policosanol	94,17 ± 15,59	89,00 ± 9,87+
Placebo	95,65 ± 14,19	92,64 ± 13,90

HC hypercholesterolemia, X mean, SD standard deviation; nt not tested
*p < 0.05; **p < 0.01; ***p < 0.001, ****p < 0.0001, ***p < 0.00001 Comparison with baseline
+p < 0.05 ++p < 0.01, +++p < 0.001 Comparison with placebo

and triglycerides, whereas increased HDL-C levels on patients with type II HC. The changes achieved are consistent with all previous data on long-term policosanol efficacy.

Thus, the averaged decrease of LDL-C (20.5 %), the main efficacy variable, was grossly similar to that reported in previous long-term studies using a similar dose of policosanol and the same was true for the changes on TC, triglycerides and HDL-C.[36,43,46] The frequency of randomized patients reaching LDL-C reductions ≥ 15 % was 75-6 % at study completion.

On the other hand, policosanol administered at 5 mg/d did not induce any drug-related disturbance. The only change significant versus baseline and placebo was a decrease on systolic pressure, which is consistent with previous results obtained in populations with a high percent of hypertensive subjects.[46] This reduction on arterial pressure induced by policosanol, however, is not considered as a drug-related AE, since no hypotension values or related-clinical symptoms were reported. By the contrary, it could represent a relative advantage to reduce the global coronary risk in such population. Policosanol modestly, but significantly reduced AST, a result consistent with previous data, but without conclusive explanation up to date. Anyway, this result justly confirms the lack of hepatoxicity induced by policosanol, a characteristic different from other lipid-lowering drugs.

In addition, since ALT and AST have been also considered as relative indicators of muscle function, the fact that policosanol did not increase these enzymes also evidences that it did not impair muscle function indicators. Likewise, creatinine levels, a renal function indicator frequently increased in rhabdomyolysis, were unchanged by policosanol.

Unfortunately, study protocol did not establish performance of CPK determination at baseline, so that this determination was added to the original protocol, which based the evaluation on subjective AE analysis. The lack of baseline values limits the affirmation that policosanol long-term administered to hypercholesterolemic patients does not change these values. Nevertheless, since the study was double-blinded and placebo-controlled, the fact that final values were lower in policosanol than in placebo group discards any tendency of the treatment to increase such values. In addition, since all individual values

Table 4 Adverse experiences (AE) reported during the study

AE	Intensity	Policosanol (n = 193)		Placebo (n = 192)	
		n	%	n	%
Nervous system					
Headache	**M**	0	0,0	3	1,6
Dizziness	**M**	1	0,5	1	0,5
Insomnia	**M**	1	0,5	1	0,5
Facial paralysis	**Mod**	**0**	**0,0**	1	0,5
Subtotal		**2**	**1,0**	**6**	**3,1**
Gastrointestinal					
Diarrhea	**M**	**3**	**1,5**	**1**	**0,.5**
Bone and muscle					
Lower limb pain	**M**	0	0,0	2	1,0
Arthralgia	**M**	1	0,5	1	0,5
Subtotal		**1**	**0,5**	**3**	**1,6**
Respiratory					
Asthma	**Mod**	**1**	**0,5**	**0**	**0,0**
Skin and appendages					
Mouth dryness	**M**	1	0,5	2	1,0
Pruritus	**M**	0	0,0	1	0,5
Psoriasis	**M**	1	0,5	0	0,0
Subtotal		**2**	**1,0**	**3**	**1,6**
Renal					
Renal sepsis	**M**	**1**	**0,5**	**1**	**0,5**
Endocrine					
Hypothyroidism	**Mod**	**1**	**0,5**	**0**	**0,0**
Body as a whole					
Asthenia	**M**	1	0,5	0	0,0
Polyphagia	**M**	1	0,5	0	0,0
Subtotal		**2**	**1,0**	**0**	**0,0**
Total of AE reported	**13 (6,7)**		**14 (7,3)**		**ns**
Total of patients reporting AE	**12 (6,2)**		**11 (5,7)**		**ns**

Mod moderate, M mild, ns no significant (Fisher's Exact Probability test)

remained within the normal limits, this concept is reinforced.

Policosanol was very well tolerated. No AE that can be considered or confused with any manifestation of myophaties was reported. This fact, together with the absence of increases on creatinine, AST and ALT levels and the decrease of CPK values compared with placebo supports that no impairment of muscle function indicators was induced by policosanol treatment, even after long-term treatment.

CONCLUSIONS

Policosanol administered at 5 mg/d for 12 months was effective to reduce LDL-C, TC and triglycerides, whereas increased HDL-C on older patients with type II HC. Policosanol was long-term safe and no drug-related AE were found. In particular, policosanol did not induce any symptom of impairment of muscle function such as muscular, weakness, myalgia or muscle cramps, nor increased serum creatinine, AST, ALT or CPK levels. Taking into account that these results were obtained after 12 months of policosanol therapy in older individuals, who are particularly sensitive to myotoxic effects of lipid-lowering drugs, they indicate that policosanol is devoid of such action. Nevertheless, further long-term studies assessing specific algorithm to discard disturbances on muscle function must be conducted to reach wider conclusions to discard any myotoxic potential of policosanol.

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