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RESEARCH ARTICLE

Effects of policosanol on older hypercholesterolemic patients consumed calcium channel blockers

Efectos del policosanol en pacientes ancianos hipercolesterolemicos que consumian bloqueadores de canales de calcio

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ABSTRACT

Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects with efficacy, safety and tolerability documented in clinical and post-marketing studies. The objective of this study was investigate whether policosanol modifies the antihypertensive effects of calcium channel blockers and/or if such combination impairs some safety indicator or induces some specific adverse event in older patients. For this report was analysed the records of all patients (313) taking calcium channel blockers included in a Prevention Study in the Elderly in which 1470 older patients at high coronary risk were randomised to policosanol 5 mg/d or placebo for 3 years. Analysis was by Intention-to-treat. Baseline characteristics were well matched in both groups. Cholesterol-lowering efficacy of policosanol was evident and persistent. The policosanol did not affect the safety indicators investigated. The frequency of all serious adverse events in policosanol patients (4/155; 2.6 %) was lower than in respective placebo (24/158; 15.2 %) as well as the frequency of mild or moderate adverse events (36/155; 23.2 %) also was lower than in placebo (52/158; 32.9 %). It is concluded that policosanol was well tolerated, not increasing any adverse events compared with placebo. These results support that policosanol consumption by hypercholesterolemic elderly individuals also taking calcium channel blockers far from reveals any adverse drug-drug interaction, were beneficial for study subjects.

Key words: policosanol; calcium channel blockers; elderly; hypercholesterolemia; adverse events

RESUMEN

El policosanol es un medicamento reductor del colesterol con efectos anti-plaquetarios concomitantes cuya eficacia, seguridad y tolerabilidad se documentan en estudios clínicos y de post-comercialización. El objetivo de este estudio fue investigar si el policosanol modifica los efectos antihipertensivos de los bloqueadores del canal de calcio y/o si dicha combinación daña algún indicador de seguridad o induce algunos eventos adversos específicos en ancianos. Para este estudio se analizaron los registros de todos los pacientes (313) que tomaban bloqueadores de canales de calcio incluidos en un estudio de prevención en ancianos en el que 1470 pacientes con alto riesgo coronario fueron aleatorizados y recibieron policosanol 5 mg/d o placebo durante 3 años. El análisis fue por intención de tratar. Las características basales fueron similares en ambos grupos. La eficacia del policosanol para reducir el colesterol fue evidente y persistente. El policosanol no afectó los indicadores de seguridad investigados. La frecuencia de eventos adversos severos en pacientes tratados con policosanol (4/155; 2,6%) fue menor que en el grupo placebo (24/158; 15,2%), así como la frecuencia de eventos adversos leves o moderados (36/155, 23,2%) también fue menor que en el placebo (52/158; 32,9%). Se concluye que el policosanol fue bien tolerado, sin aumentar

ningún evento adverso en comparación con el placebo. Estos resultados confirman que el consumo de policosanol por ancianos hipercolesterolémicos que también toman bloqueadores de los canales de calcio lejos de revelar cualquier interacción medicamentosa adversa, fue beneficioso para los pacientes del estudio.

Palabras clave: policosanol; bloqueadores de canales de calcio; ancianos; hipercolesterolemia; eventos adversos

INTRODUCTION

Coronary disease is the leading cause of morbidity and mortality in adults (Mozaffarian *et al,* 2016). End-point clinical studies have shown a direct relationship between coronary disease and elevated serum levels of low-density lipoprotein cholesterol (LDL-C) (Aronow and Frishman, 2010), the benefits of lowering LDL-C with statins on clinical end-points being also demonstrated (Cohen *et al,* 2010; Boekholdt *et al*, 2014; Fulcher *et al*, 2015; Jellinger *et al*, 2012; Kastelein *et al*, 2018).

Hypercholesterolemia treatment in the elderly was controversial because raised LDL-C levels fall as predictors of the relative coronary risk with age (Félix *et al*, 2013). In addition, analysis of subgroup of older patients included in statin end-point studies have shown the clinical benefits of lowering LDL-C values in such patients (Cohen *et al,* 2010; Boekholdt *et al*, 2014, Fulcher *et al*, 2015; Jellinger *et al*, 2012; Kastelein *et al*, 2018).

The elderly has impaired hepatic and renal drug clearance, several concomitant diseases and consequently, concomitant therapies, so that the frequency of drug-related adverse events and the possibility of occurring drug-drug interactions in this population is increased (Félix *et al*, 2013).

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L.)* wax (Mas, 2000), with cholesterol-lowering effects demonstrated in clinical studies (Benítez *et al*, 1997; Canetti *et al*, 1995; Castaño *et al*, 1995, 1999, 2001, 2002a, 2002b, 2003; Crespo *et al*, 1997; Fernández *et al*, 2001; Mas *et al*, 1999, 2001; Ortensi *et al*, 1997; Torres *et al*, 1995). Policosanol (5-20 mg/d) decreases LDL-C and total cholesterol in a dose-dependent manner, whereas increases high-density lipoprotein cholesterol (HDL-C). The efficacy and tolerability of policosanol in the elderly have been investigated in several clinical trials, being effective, safe and well tolerated in older individuals (Castaño *et al*, 1995, 1999, 2001, 2002a, 2003; Fernández *et al*, 2001; Mas *et al*, 2001; Ortensi *et al*, 1997;).

Policosanol lowers cholesterol by inhibiting cholesterol biosynthesis in a step between acetate consumption and mevalonate production (Menéndez *et al*, 1994, 1997 2001). Policosanol suppresses enzyme up-regulation, suggesting that its inhibitory effects could be explained by a depression of *de novo* synthesis of

hydroxy methyl glutaryl coenzyme A (HMG-CoA) reductase and/or stimulation of its degradation (Menéndez *et al*, 2001). Also, policosanol increases LDL receptor-dependent processing (Menéndez *et al*, 1994), enhancing the LDL catabolic rate (Menéndez *et al*, 1996). Policosanol shows also relevant pleiotropic effects, such as the inhibition of platelet aggregation and the susceptibility of LDL to be oxidised (Arruzazabala *et al*, 1996; Castaño *et al*, 1999; Mas, 2000; Menéndez *et al*, 2000a, 2000b).

Clinical and post-marketing surveillance studies have demonstrated that policosanol is safe and well tolerated, even in populations with high consumption of concomitant drugs, suggesting that adverse drug-drug interactions coming from therapy with policosanol and other drugs appears to be not relevant (Benitez *et al*, 1997; Canetti *et al*, 1995; Castaño *et al*, 1995, 1999, 2001, 2002a, 2002b, 2003; Crespo *et al*, 1997; Fernández *et al*, 1998, 2001; Mas *et al*, 1999a, 1999b, 2001; Ortensi *et al*, 1997; Torres *et al*, 1995).

Relevant drug-drug interactions derive from pharmacokinetic and/or pharmacodynamic characteristics (Palleria *et al*, 2013). Experimental data showed that potential drug-drug interactions between policosanol and drugs metabolised through the cytochrome P450 hepatic system are not expected. Thus, policosanol did not affect antipyrine or theophylline pharmacokinetics (Pérez-Souto *et al*, 1991), and did not modify the activity of hepatic drug-metabolising enzymes (Rodeiro *et al*, 2000). Since the metabolism of most drugs goes by this route, the possibility of drug-drug interactions with policosanol based in pharmacokinetic interactions is relatively low.

Nevertheless, pharmacodynamic drug-drug interactions with policosanol cannot be ruled-out. Clinical studies conducted in patients with both hypercholesterolemia and hypertension had shown that policosanol decreased arterial pressure compared with placebo. Then, the possibility of drug-drug interactions between policosanol and antihypertensive drugs could be possible.

Calcium channels blockers are widely used for hypertension management, which can be divided in two major classes: dihidropyridines, who act predominantly as peripheral vasodilators, and non-dihydropiridines, which slow the heart rate and atrioventricular node conduction. Except nimodipine, all calcium channel blockers are indicated for treat hypertension (Black, 2004; Caballero, 2015; Sica, 2006). These drugs have been used for elderly hypertensive due to they dilate the coronary and peripheral arterial beds, their action do not depend on the renin-angiotensin axis, impaired in the elderly, have negligible adverse metabolic effects, if any, and increase renal blood flow.

Nevertheless, concern has been raised that these agents may increase the risk of cardiovascular events, cancer, and suicide, based in result of small studies not

designed as end-point trials (Costanzo *et al*, 2009; Liebson, 2006; Thomopoulos *et al*, 2016; Wen *et al*, 2014). Further prospective and randomised studies compared the effects of calcium channel blockers and other antihypertensive therapies on cardiovascular events in hypertensive patients (Law *et al*, 2009; Shibata *et al*, 2010; Tocci *et al*, 2015). Although such studies failed to demonstrate preventive effects of calcium channel blockers on specified end-points, no concern was evident. Further evidence available from meta-analyses showed, however, that the effects of these agents on cardiovascular events or total mortality were similar to those induced by diuretics or β-blockers (James *et al*, 2014; Mancia *et al*, 2013).

Considering this background, the rationale for investigating the putative drug-drug interactions between policosanol and calcium channel blockers in the elderly is supported. Then, the present analysis performed from the records of older patients consuming these drugs included in a Prevention study of policosanol in the elderly was undertaken to determine whether policosanol affect the antihypertensive efficacy of calcium channel blockers, impairs some safety indicator or increase the report of adverse events. Likewise, we investigated if cholesterol-lowering efficacy of policosanol was maintained in older patients taking calcium channel blockers.

PATIENTS AND METHODS

Ethics considerations: An independent Ethics Committee approved study protocol, the patients being recruited after provide written consent. All study conduction was done underlying that the decision of the patients to start and/or continue in the study was absolutely voluntary and free.

Study Design: This analysis was performed from the records of a prospective, randomized, double-blinded, placebo-controlled study including 1470 older patients receiving placebo or policosanol for 3 years. In brief: patients were enrolled at 4 Policlinical Centers, "Ramón González Coro"; "Elpidio Berovides," "Educational" and "26 de Julio" from Marianao, La Lisa and Playa, being controlled by medical staff of the Surgical Medical Research Center.

The personnel involved in patients follow up were blinded to treatment allocation. A Steering Committee was responsible for the study, a Clinical Coordination Group followed the subjects, an End-point Committee reviewed and categorized endpoint data and a Data Safety Monitoring Committee monitored study conduction.

Screening initial visits were done in Policlinics, wherein individuals aged 60 to 80 were invited, to assess their risk factors, a total of 1612 patients being enrolled (visit 1) and instructed to follow a step one cholesterol-lowering diet for five weeks.

After this baseline period, lipid profile and safety laboratory indicators were assessed and the following week patients attended to visit 2. The laboratory values obtained after the baseline period and safety physical indicators determined at visit 2 were baseline values. Eligible patients (1470) were randomized, under double-blind conditions, to policosanol 5 mg or placebo tablets. Concomitant medications taken by study patients were recorded. The patients were followed at three month intervals during the first year (visits 3 to 6) and every six months thereafter (visits 7-10).

Enrollment criteria: Women and men aged 60 to 80 with documented coronary or cerebrovascular disease, hypertension, dyslipidemia, smoking habits or/and diabetes. The rationale for the lowest cut-off for age was to include older subjects with enough life expectancy.

Inclusion criteria: Patients were randomized if they showed total cholesterol ≥ 5.2, LDL-C ≥ 3.4 and triglycerides < 4.52 mmol/L after conclude the baseline period, whenever exclusion criteria were not present.

Exclusion criteria: Patients were excluded if had active renal or diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg), uncontrolled diabetes or poor cognitive function. Patients with history of unstable angina, myocardial infarction, stroke or any serious adverse event within the three months prior to recruitment were also excluded.

Withdrawal criteria: Any serious adverse events or adverse event justifying such decision, unwillingness to continue, total cholesterol ≥ 9 mmol/L according to the central laboratory, major violations of study protocol, including > 6 weeks without taking the study drugs (policosanol or placebo).

Treatment: Appearance of study medications was identical, being administered in identical packages identified by a code number assigned at each Policlinic by progressive inclusion. Treatment was randomised through a random allocation generated by computer, consisting of balanced block of size ten, with a randomization ratio 1:1. Tablets must be taken once a day (oid) with evening meal. Participants in both groups should be titrated to 2 or 4 tablets oid if total cholesterol levels were ≥ 7 mmol/L after six or twelve months on therapy.

Compliance assessment: Compliance with study medications was assessed from visits 3 to 10 by tablet counts and patient request, including such data in the Case Report Forms.

Concomitant medications: Consumption of lipid-lowering drugs was prohibited from the recruitment in the trial no other restriction for concomitant therapy being done. Cases at secondary prevention were advised to take daily aspirin.

Concomitant drugs were controlled through patient questioning, with additional requesting to Family Doctors, if necessary.

Assessments: Total cholesterol was assessed at baseline and every six months, while lipid profile and safety laboratory tests were performed at randomisation and one, two and three years thereafter. Laboratory tests included lipid profile, glucose, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

At each visit physical examination and dietary counselling were done. Compliance assessment and request for adverse event were performed from visits 3 to 10, compliance being assessed by tablet counts and patient interview. Compliance was defined as good if ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Effects on lipid profile: For this analysis, changes on LDL-C were considered as the primary efficacy variable to assess whether calcium channel blockers impaired the cholesterol-lowering efficacy of policosanol in older patients. Treatment was considered as effective if LDL-C was significantly reduced by ≥ 15 % respect to baseline (Schectman and Hiatt, 1996). Changes on other lipid profile parameters were also analysed.

Safety and tolerability analyses: Patient records were reviewed and information on concomitant medication recorded and analyzed. All patients taking calcium channel blockers were included in the analysis. Physical indicators (body weight, pulse rate, blood pressure) and laboratory values (glucose, creatinine, AST, ALT) were analysed. Safety and tolerability analysis included data on serious, moderate and mild adverse events.

An adverse event was defined as any new undesirable event or change in physical or laboratory data or the worsening of any pre-existing condition occurred through the study, independently if was drug-related. The adverse events were classified according to their intensity in mild, moderate and serious. Mild adverse event not required treatment or withdrawal of study medication, whereas moderate adverse event required withdrawal of study medication and/or treatment of the adverse event.

A serious adverse event was considered any adverse event leading to patient hospitalisation or death. They included all mortality, fatal and non-fatal coronary, cardiovascular, cerebrovascular and vascular serious adverse events. In the whole study, all events were analysed according by time of first event. In the present analysis, the sample size and event number was too small for survival and hazard ratio analyses, the groups being compared by relative proportions.

To conduct the study in conditions similar to Cuban clinical practice, end-points were evaluated through the official records of hospitals, Death Registry and Family Doctors. At each visit, the occurrence of any event was documented from patients' recall, and further verified with hospitals and Family Doctors.

The End-point Committee of the whole study blindly reviewed and categorized endpoint data, the events being diagnosed and classified by personnel blinded to treatment allocation and not involved in the trial. For each category, events with definite + suspect causes were included.

Laboratory analysis: Blood samples were drawn after a 12 hours overnight fasting. Serum total cholesterol and triglycerides were determined by enzymatic methods using reagent kits. HDL-C levels were determined according to the cholesterol content present in the supernatant obtained after β-lipoproteins precipitation (Seigler and Wu, 1981). LDL-C values were calculated using the Friedewald equation (Friedewald *et al*, 1972). Laboratory analyses were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Center.

Lab determinations were done at the same day of sampling. A quality control was performed, so that precision and accuracy versus reference standards were controlled. The assay bias of such parameters was constant throughout the study.

Statistical analysis: Statistical analysis followed a plan specified in study protocol or in amendments. All data were analyzed according to Intention to-treat principle.

Baseline statistics was reported as mean ± standard deviation for continuous variables and as number and % for categorical variables. ANOVA was used to compare continuous variables throughout the study. Comparisons between groups of categorical data were made by Fisher's Exact Probability test and corroborated by chi square test. All statistical tests were two-tailed, with significance at $\alpha = 0.05$. Statistical analyses were performed using Statistica for Windows (Release 4.2; Copyright StatSoft, Inc. US) and SAS/STAT (Stat Soft, Version 8, US).

RESULTS

Baseline patient characteristics: Both groups were well matched at randomization (Table 1). Practically all patients were hypertensive (311/313, 99.4 %), most women (252/313, 80.5 %). In addition, study patients showed a high frequency (> 30 %) of coronary disease.

Table 1. Main baseline characteristics of study patients.

Characteristics	Placebo (n = 158)		Policosanol (n = 155)	
Age (years) (X ± SD)	66 ± 5		66 ± 5	
Body mass index (kg/m^2) (X ± SD)	27.8 ± 5.5		28.4 ± 5.0	
	n	**%**	**n**	**%**
Gender: Female	130	82.3	122	78.7
Male	28	17.7	33	21.3
Isolated hypercholesterolemia	66	41.8	73	47.1
Combined hypercholesterolemia	92	58.2	82	52.9
Risk factors:				
Arterial hypertension	157	99.4	154	99.3
Smoking	29	18.3	23	14.8
Coronary disease	54	34.2	60	38.7
Diabetes mellitus	40	25.3	29	18.7
Obesity (kg/m^2 > 30)	12	7.6	14	9.0
Cerebrovascular disease	12	7.6	7	4.5
Consumption of calcium channel blockers				
Nifedipine	152	96.2	149	96.1
Verapamil	2	1.3	3	1.9
Diltiazem	4	2.5	3	1.9
Other concomitant medications				
Diuretics	48	30.4	55	35.5
β-blockers	26	16.5	28	18.1
Antiplatelet	30	19.0	47	30.3
Diuretics	48	30.4	55	35.5
Vasodilators	30	19.0	26	16.8
Anxyolytics	24	15.2	31	20.0
Vitamins	11	7.0	15	9.7
Oral hypoglycemic drugs	24	15.2	14	9.0
Digitalics	9	5.7	12	7.7
Myorelaxants	23	14.6	18	11.6

Note: n: number of patients; X: mean; SD: standard deviation; Coronary disease (myocardial infarction, unstable angina, coronary surgery); Cerebrovascular disease (stroke, ischemic transient attacks); Concomitant medications consumed by > 6 % of study patients. All comparisons were not significant.

Most study patients (301/313, 96.2 %) consumed nifedipine as calcium antagonist therapy, a condition similar in both groups too. The frequency of other concomitant drugs among study patients was high, those more frequently taken being diuretics, anti-platelets, diuretics, β-blockers, vasodilators, anxyolytics and oral hypoglycemic drugs. Concomitant medications consumption was balanced in the two study groups.

Withdrawal analysis: Table 2 shows the premature withdrawals from the study. As observed, the total number of withdrawals was significantly lower in policosanol than in placebo. Sixty-nine of 313 patients (22.0 %) consuming calcium channel blockers discontinued prematurely the study, 55/158 (34.8 %) were from placebo and 14/155 (9.0 %) from policosanol group. Of them, 35 patients (29 placebo, 6 policosanol) withdrew from the study due to some adverse event.

Table 2. Withdrawal analysis of study patients taking calcium channel blockers.

Withdrawal reasons	Placebo (n = 158)		Policosanol (n = 155)		Total (n= 313)	
	n	%	n	%	n	%
Withdrawals due to adverse events (AE)						
Withdrawals due to vascular serious AE	16	10.1	3	1.9^{++}	19	6.1
Withdrawals due to non-vascular serious AE	8	5.1	1	0.6^{+}	9	2.9
Subtotal due to serious AE	**24**	**15.2**	**4**	**2.6^{+++}**	**28**	**8.9**
Withdrawals due to mild and moderate AE	5	3.2	2	1.3	7	2.2
Subtotal due to all AE	**29**	**18.4**	**6**	**3.9^{+++}**	**35**	**11.2**
Withdrawals due to other reasons						
Unsatisfactory efficacy	14	8.9	0	0.0^{+++}	14	4.5
Travels abroad + address changes	2	1.3	2	1.3	4	1.3
Unwillingness to follow-up	6	3.8	6	3.9	12	3.8
Protocol violations	4	2.5	0	0.0^{+}	4	1.3
Subtotal due to other reasons	**26**	**16.5**	**8**	**5.2^{++}**	**34**	**10.9**
Total of withdrawals	**55**	**34.8**	**14**	**9.0^{+++}**	**69**	**22.0**

Note: $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$ Comparison with placebo ($\chi 2$ test).

Compliance: Compliance with study medications was good according to compliance criterion. Compliance was greater in policosanol than in placebo, the main difference being related with the withdrawals, since once a patient discontinued the study did not continue on treatment.

Effects in serum lipid profile: Table 3 shows the effects on lipid profile. As observed, both groups were similar regarding all lipid profile variables at randomisation.

Table 3. Long-term effects of policosanol on lipid profile (X ± SD) of study patients taking calcium channel blockers.

Treatment	Baseline	1 year	2 years	3 years
		Total cholesterol (mmol/L)		
Policosanol	6.82 ± 0.86	$5.74 \pm 0.69^{++++}$	$5.40 \pm 0.62^{++++}$	$5.36 \pm 0.62^{++++}$
Placebo	6.85 ± 0.96	6.73 ± 0.99	6.71 ± 0.95	6.50 ± 0.93
		LDL-C (mmol/L)		
Policosanol	4.80 ± 0.90	$3.76 \pm 0.63^{++++}$	$3.39 \pm 0.60^{++++}$	$3.28 \pm 0.63^{++++}$
Placebo	4.74 ± 0.93	4.74 ± 0.90	4.70 ± 0.93	4.64 ± 0.98
		HDL-C (mmol/L)		
Policosanol	1.16 ± 0.31	1.27 ± 0.26	$1.31 \pm 0.26^{++++}$	$1.36 \pm 0.24^{++++}$
Placebo	1.19 ± 0.35	1.20 ± 0.32	1.15 ± 0.27	1.15 ± 0.21
		Triglycerides (mmol/L)		
Policosanol	2.35 ± 0.95	$1.84 \pm 0.64^{++}$	$1.84 \pm 0.46^{+++}$	$1.85 \pm 0.57^{+}$
Placebo	2.32 ± 1.12	2.12 ± 0.90	2.12 ± 0.67	2.16 ± 0.45

Note: X mean, SD standard deviation, LDL-C low-density lipoprotein-cholesterol, HDL-C high-density lipoprotein-cholesterol; $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$; $^{++++}p < 0.00001$ ANOVA Test.

After one year, policosanol lowered significantly ($p < 0.0001$ *vs* placebo) low-density lipoprotein-cholesterol (LDL-C) (21.7%), total cholesterol (15.8%) and triglycerides ($p<0.01$) (21.7%), whereas raised high-density lipoprotein-cholesterol (HDL-C) (9.5%). Policosanol effects persisted, even enhanced, during the 3-year follow-up.

At study completion, policosanol lowered ($p < 0.0001$ *vs* placebo) LDL-C (31.7 %), total cholesterol (21.4%), triglycerides ($p<0.05$) (21.3 %) and increased ($p < 0.0001$ *vs* placebo) HDL-C (17.2 %).

Safety and tolerability: No policosanol-related impairment of safety indicators was observed (Table 4). Policosanol, it is modestly, but significantly lowered transaminases (ALAT, ASAT) values.

Table 4. Long-term effects of policosanol on safety indicators (X ± SD) of study patients taking calcium channel blockers.

Treatment	Baseline	1 year	2 years	3 years
		Weight (kg)		
Policosanol	69.49 ± 12.15	69.03 ± 11.22	68.30 ± 11.22	68.78 ± 11.12
Placebo	67.68 ± 12.84	67.45 ± 12.58	68.48 ± 12.52	69.82 ± 12.07
		Pulse (beats/min)		
Policosanol	72.29 ± 7.43	72.95 ± 8.14	72.51 ± 7.03	71.29 ± 6.49
Placebo	74.42 ± 8.29	72.26 ± 7.35	72.98 ± 8.72	72.69 ± 6.44
		Diastolic pressure (mm Hg)		
Policosanol	86.71 ± 11.17	82.93 ± 9.25	82.13 ± 7.40	82.00 ± 7.38
Placebo	85.61 ± 10.57	82.81 ± 7.97	83.51 ± 7.13	83.70 ± 8.12
		Systolic pressure (mm Hg)		
Policosanol	145.0 ± 21.29	136.7 ± 18.36	135.2 ± 17.86	133.3 ± 17.47
Placebo	144.4 ± 18.71	139.7 ± 19.88	137.9 ± 17.14	138.1 ± 15.46
		ALT (U/L)		
Policosanol	20.10 ± 9.26	19.30 ± 6.77^{+}	19.66 ± 6.26^{+}	19.81 ± 5.30^{+}
Placebo	19.65 ± 9.36	21.80 ± 8.25	21.95 ± 8.50	22.12 ± 6.49
		AST (U/L)		
Policosanol	21.02 ± 7.73	20.12 ± 8.61	19.89 ± 6.70^{++}	18.18 ± 5.54^{++}
Placebo	22.32 ± 8.62	20.64 ± 6.58	23.07 ± 7.70	21.92 ± 8.10
		Creatinine (μmol/L)		
Policosanol	92.36 ± 18.64	87.68 ± 15.30	90.67 ± 11.89	91.35 ± 11.53
Placebo	91.50 ± 16.47	91.21 ± 17.36	93.67 ± 17.50	92.67 ± 10.19
		Glucose (mmol/L)		
Policosanol	5.51 ± 1.23	5.55 ± 1.65	5.39 ± 1.19	5.35 ± 1.36
Placebo	5.53 ± 1.25	5.65 ± 1.75	5.77 ± 2.27	5.47 ± 1.13

Note: X mean, SD standard deviation, ALT alanine aminotransferase, AST aspartate aminotransferase; +p < 0.05; ++p < 0.01 ANOVA Test.

Thirty-five (35) withdrawals (29 placebo, 6 policosanol) were due to some adverse event. Table 5 summarizes the frequency of adverse event occurred during the study. The frequency of all serious adverse events in policosanol patients (4/155; 2.6 %) was lower ($p < 0.01$) than in respective placebo (24/158; 15.2 %). Policosanol did not increase the frequency of mild or moderate adverse event

respect to placebo, but surprisingly, such frequency (36/155; 23.2 %) was lower ($p < 0.01$) than in placebo (52/158; 32.9 %).

Table 5. Adverse events in older patients taking calcium channel blockers.

Adverse Events (AE)	Placebo (n= 158)		Policosanol (n = 155)	
	n	%	n	%
Serious AE				
All cardiovascular serious AE	12	7.6	1	0.6^{++}
All coronary serious AE	11	6.7	1	0.6^{++}
All cerebrovascular serious AE	4	2.5	2	1.3
All vascular serious AE	16	10.1	3	1.9^{++}
All deaths	7	4.4	0	0.0^{++}
Serious AE (fatal + non-fatal)	**24**	**15.2**	**4**	$\mathbf{2.6^{+++}}$
Moderate and mild AE				
Skin and appendages disorders	8	5.1	2	1.3
Muscle-skeletal system disorders	20	12.7	19	12.3
Nervous system	20	12.7	9	5.8^{+}
Gastrointestinal system disorders	5	3.2	5	3.2
Endocrine system	1	0.6	0	0.0
Cardiovascular	10	6.3	12	7.7
Heart rate and rhythm	1	0.6	3	1.9
Respiratory system	5	3.2	6	3.9
Red blood cell	1	0.6	0	0.0
White cell and RES	1	0.6	1	0.6
Urinary system	5	3.2	3	1.9
Body as a whole	7	4.4	12	7.7
Patients with moderate or mild AE	**52**	**32.9**	**36**	**23.2**

Note: For serious AE, subjects are counted only once with a specific endpoint. However, they may be listed more than once because of experiencing an event include in more than one endpoint analysis. $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$ Comparison with placebo ($\chi 2$ test).

DISCUSSION

The prevention study demonstrated that lowering LDL-C with policosanol in older hypercholesterolemic patients lowered the risk of all serious adverse events, primary endpoint, all mortality, and vascular, cardiovascular and coronary serious adverse events respect to placebo, defined as secondary endpoints. The study also demonstrated that policosanol did not increase the frequency of non-vascular serious adverse events.

The present analysis demonstrates that in older patients receiving calcium channel blockers, policosanol sustainedly lowered LDL-C and total cholesterol, while induced additional reduction of systolic pressure, without impair any safety indicator or increase the frequency of adverse events.

The baseline characteristics were similar in both groups, which indicate that randomisation was well performed and groups were homogeneous. The mean age of study patients (around 66 years at baseline) show that they were still young for preventive measures aimed to improve their life quality and expectancy. The larger proportion of women respect to men is characteristic of the patients

attending to the Policlinics of this Havana City area (Cuban National Statistics Bureau of the Ministry of Public Health, 2015), and also reflects the high motivation of such women to participate and adhere to study protocol respect to men.

It must be underlines that most study patients taken short acting nifedipine as antihypertensive therapy (3 tablets/day). This finding is not related with any characteristic of study protocol, but reflects a common fact of hypertension management in Cuban clinical practice. Since the main concern about calcium channel blockers is precisely related with this type of calcium antagonists, then the negative results about adverse drug-drug interactions between policosanol and calcium channel antagonists here presented are remarkable.

The frequency of other concomitant drugs was high, a distinctive characteristic of older patients. Taking into account this fact, the present analysis is not performed from a population only treated with calcium channel blockers and placebo or policosanol, but to patients receiving other concomitant drugs, as commonly occurs in clinical practice. The other concomitant drugs consumed by study patients were consistent with the risk condition of study population. Consumption of anxyolytics, mostly benzodiazepines, was also high since they are frequently prescribed in Cuba as adjuvant of hypertension management and for the management of anxiety and sleep disorders common in older patients. The consumption of inhibitors of angiotensin converting enzyme was absent, which agrees with the limited introduction of such drugs in Cuban market, the physicians being more prone to prescribe other antihypertensive drugs.

The present results support that policosanol was as effective as expected (Benitez *et al*, 1997; Canetti *et al*, 1995; Castaño *et al*, 1995, 1999, 2001, 2002a, 2002b, 2003; Crespo *et al*, 1997; Fernández *et al*, 1998, 2001; Mas *et al*, 1999a, 1999b, 2001; Ortensi *et al*, 1997; Torres *et al*, 1995), lowering LDL-C, the primary efficacy variable, total cholesterol and triglycerides, whereas increased HDL-C. The responses were persistent throughout the study, the changes of LDL-C and HDL-C being not only maintained, but even enhanced.

Reductions on triglycerides, however, were superior that in previous studies, a finding without any conclusive explanation.

The different withdrawal rate in both groups was related with the discontinuations due to adverse event, since the frequency of withdrawals due to serious adverse events and all adverse events was greater in placebo than in policosanol group, while the withdrawals due to other reasons was similar.

Thus, the frequency of all vascular, cardiovascular and coronary serious adverse events was lower in policosanol than in placebos, consistently with LDL-C

lowering and other pleiotropic effects of policosanol, all beneficial to vascular function, thus preventing the occurrence of clinical events.

The frequency of serious adverse events here reported is relatively low compared with other studies (Boekholdt *et al*, 2014, Fulcher *et al*, 2015; Kastelein *et al*, 2018), which could be explained by study characteristics, such as women outnumbered men, the high frequency of individuals at primary prevention and the average age of study patients. Some procedures routinely applied in Cuban clinical practice for people ≥ 60 years old also contribute to a low event rate, since they are commonly included in "Grandparent Circles" organized by health areas, with regular practice of physical exercise. As a result of all preventive measures, deaths due to coronary disease have lowered in Cuba in the last years (Cuban National Statistics Bureau of the Ministry of Public Health, 2015).

Policosanol was safe and well tolerated. No drug-related impairment of safety indicators was observed. Policosanol significantly reduced systolic pressure compared with placebo, an effect that could contribute to the lesser frequency of vascular serious adverse events in policosanol group, since lowering systolic pressure significantly reduces coronary events and total mortality in the elderly (Cuban National Statistics Bureau of the Ministry of Public Health, 2015). It is important to note that no hypotension was reported in policosanol group, which limits the extent of a potential risk resulting from the interaction between policosanol and calcium channel blockers. The reasons supporting such additive effect on arterial pressure must be related with pleiotropic effects of policosanol, mainly those supporting beneficial effects on endothelial function.

Adverse events reports did not show increase of adverse events resulting from concomitant use of policosanol and calcium channel blockers. Paradoxically, the frequency of mild and moderate adverse events was lower in policosanol than in placebo. This result, together with serious adverse events and withdrawal analysis, discards any increase in particular adverse events due to policosanol administered with calcium channel blockers.

CONCLUSIONS

Policosanol was very well tolerated in older patients at high coronary risk consuming calcium channel blockers. Cholesterol-lowering efficacy of policosanol was evident and persistent throughout the study. An additional reduction of systolic pressure was observed in policosanol patient respect to placebo. The frequency of serious adverse events was lower in policosanol than in placebo, indicating that adding policosanol to patients treated with calcium channel blockers is beneficial to risk reduction. Safety analyses did not show increase in adverse events resulting from concomitant consumption of policosanol and calcium channel blockers. These results support that policosanol is effective for

lowering LDL-C and total cholesterol in patients taking calcium channel blockers, providing benefits in lowering systolic pressure and the frequency of serious adverse events respect to placebo, in a population like the elderly, highly medicated and sensitive to drug-related adverse events and drug-drug interactions.

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