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Research Article

EFFECTS OF POLICOSANOL IN OLDER PATIENTS CONSUMING NITRATES VASODILATORS

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ABSTRACT

Background: Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects. The efficacy and safety of policosanol have been investigated in clinical studies and post-marketing surveillance. Policosanol is very safe and no drug-related adverse events have been demonstrated, even in population subsets with high consumption of concomitant therapy, indicating that the potential risk of drug-drug interaction for policosanol is low. Vasodilators are used in geriatric populations mainly to treat congestive heart failure and acute decompensating of heart failure, although associated to other anti-hypertensive are also used for manage hypertension. Vasodilators, however, have considerable risk of drug-related toxicity, the most frequent symptoms being those derived from excessive vasodilation and hypotension, such as nausea, vomiting, loss of consciousness and reflex tachycardia. Vasodilators show important drug-drug interaction derived from pharmacodynamic interactions with several drugs, those associated to concomitant use of other vasodilators and diuretics being the most relevant. Considering such facts, the interest to study putative drug-drug interaction between policosanol and vasodilators is supported. Objective: To investigate whether policosanol administered to older patients consuming vasodilators induces any specific disturbance on safety indicators and/or increase the frequency or severity of adverse events in such patients. Methods: This report was based in the analysis of the records of all patients (185) taking nitrates vasodilators included in a Prevention Study in the Elderly randomised to policosanol 5 mg/d or placebo for 3 years. Analysis was by Intention-to-treat. Results: Baseline characteristics were well balanced in both groups. After one year on treatment, policosanol lowered significantly low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG), whereas raised high-density lipoprotein-cholesterol (HDL-C). Policosanol effects persisted, even increased, during the 3 years treatment. At the end of the study, policosanol reduced LDL-C (35%), TC (25%), TG (19,3%) and raised HDL-C (16,7%). Of 185 randomised patients taking vasodilators, 44 (23,8 %) withdrew from the trial. The frequency of withdrawals in placebo (31/95; 32,6 %) was greater ($p<0,01$) than in policosanol group (13/90; 14,4 %). Overall, 26/185 (14,1 %) patients discontinued due to some adverse events: 23 placebo (24,2 %) and 3 (3,3 %) policosanol patients ($p<0,01$). Policosanol did not impair safety indicators compared with placebo, but induced additional decreases of systolic pressure compared with placebo, but no individual value or clinical symptom of hypotension was reported. The frequency of policosanol patients experiencing serious adverse events (3/90; 3,3 %) was lower ($p<0,01$) than in respective placebo (23/95; 24,2 %). Likewise, the frequency of policosanol patients who experienced some mild or moderate adverse events during the study (10/90; 11,1 %) was lower ($p<0,05$) than in matched placebo (28/95; 29,5 %). Conclusions: These results indicate that policosanol can be administered to older patients taking vasodilators without risk of relevant adverse drug-drug interaction.

Keywords: policosanol, elderly, cholesterol-lowering, anti-hypertensive, vasodilators, adverse events

INTRODUCTION

Atherosclerotic disease is a major cause of morbidity and mortality in middle-aged and older adults.[1] In particular, coronary heart disease (CHD) is the leading cause of death in adult population worldwide, coronary events being directly related to raised serum levels of low-density lipoprotein cholesterol (LDL-C).[2] End-point clinical trials have convincingly demonstrated the benefits of lowering LDL-C with statins on coronary events.[3-7] Thus, hypercholesterolemia management in adults is a cornerstone of coronary prevention guidelines.[8]

Nevertheless, the treatment of hypercholesterolemia in the elderly was strongly controversial due to elevated LDL-C levels decrease as predictors of relative coronary risk with age.[9] Older individuals are particularly prone to drug-related adverse events (AE), due to they have impaired hepatic and renal drug clearance, electrolyte imbalance, several concomitant diseases and concomitant therapies.[9] In particular, the risk for drug-drug interactions (DDI) in this population is increased respect to younger adults.[8]
Considering that elevated LDL-C values still are strong predictors of absolute coronary risk in the elderly,[9] and the results of strata analysis performed in subgroups of older patients included in end-point studies that demonstrated the benefits of lowering LDL-C in these cases,[3-7] treatment of hypercholesterolemia in the elderly is now recommended.[9]

Policosanol is a mixture of high molecular weight alcohols isolated from sugar cane wax[10] with cholesterol-lowering effects demonstrated in type II hypercholesterolemia[11-21] and the dyslipidemia due to Type 2 diabetes mellitus,[24-26] including older individuals. Policosanol (5-20 mg/d) decreases LDL-C and TC levels, increases high-density lipoprotein cholesterol (HDL-C) and induce modest and not reproducible effects on triglycerides (TG).[10-24]

Policosanol inhibits cholesterol biosynthesis between acetate consumption and mevalonate production[25-27] by suppressing HMG-CoA reductase up-regulation, through a depression of the synthesis of the enzyme and/or stimulation of its degradation.[27] Policosanol increases LDL receptor-dependent processing,[25] enhancing the catabolic rate of such lipoprotein.[26] Policosanol also inhibits platelet aggregation[10,16,28] and LDL lipid peroxidation.[29,30]

Clinical and post-marketing surveillance studies have demonstrated that policosanol is very safe and well tolerated,[10-24,31,32] even in populations with high consumption of concomitant drugs. The frequency of adverse events (AE) in policosanol patients has been similar or even lower than in placebo, no drug-related AE being proven up to date. Hence, adverse drug-drug interactions (DDI) with policosanol appear to be not relevant.

DDI are based in pharmacokinetic and/or pharmacodynamic interactions. Experimental data indicate that DDI between policosanol and drugs metabolised through the cytochrome P450 hepatic system are not expected, and did not modify the activity of hepatic drug-metabolising enzymes.[33] Since most drugs are metabolised by this system, the risk for DDI based in pharmacokinetic interactions with policosanol is low.

Nevertheless, pharmacodynamic DDI with policosanol could be possible. Thus, different clinical studies have shown that policosanol can induce reductions of both systolic and/or diastolic pressure compared with placebo. Thus, potential DDI with drug lowering blood pressure need to be investigated.

Vasodilators are used in geriatric populations mainly to treat congestive heart failure and acute decompensating of heart failure, although associated to other anti-hypertensive are also used for manage arterial hypertension.[34]

Vasodilators, however, have considerable risk of drug-related toxicity, the most frequent symptoms being those derived from excessive vasodilation and hypotension, such as nausea, vomiting, loss of consciousness and reflex tachycardia. Although less frequent, after prolonged use, vasodilators can induce serious toxicity coming from accumulation of thiocyanate, thus resembling cyanide-poisoning symptoms, such as toxic pink mucoses, psychosis and metabolic acidosis. Vasodilators show important DDI derived from pharmacodynamic interactions with several drugs, those associated to concomitant use of other vasodilators and diuretics being the most relevant.[34,35] Then, the rationale for investigating DDI between policosanol and vasodilators, especially in the elderly, is supported. The present analysis was performed to determine whether policosanol administered concomitantly with vasodilators to older patients impairs any safety indicator and/or induce some specific AE. Likewise, we investigated if cholesterol-lowering efficacy of policosanol in these patients is that expected.

PATIENTS AND METHODS

The present analysis includes the data of all patients consuming vasodilators included in the Prevention Study of policosanol in the elderly.[36]

Ethics considerations: An independent Ethics Committee approved study protocol before study starting. All patients were enrolled after providing informed written consent.

Study Design: Patients were enrolled at four Policlinical Centres: "Ramón González Coro"; "Elpidio Berovides," "Educational" and "26 de Julio" from the Havana city zones named Marianao, Lisa and Playa, being followed by medical staff of the Surgical Medical Research Centre. The personnel involved in patient treatment were blinded to treatment allocation.
Enrolled patients (visit 1) were instructed to follow a step one cholesterol-lowering diet for 5 weeks of a diet-only baseline period. After that, 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 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 every 3 months during the first year (visits 3 to 6) and every 6 months thereafter (visits 7-10).

Enrolled criteria: Women and men aged 60-80 with documented CHD, 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 showed serum TC ≥ 5.2, LDL-C ≥ 3.4 and TG < 4.52 mmol/L after the diet-only baseline period.

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 AE (SAE) within the 3 months prior to recruitment were also excluded.

Withdrawal criteria: Any AE justifying such decision, unwillingness to continue, TC ≥ 9 mmol/L or major violations of study protocol (including > 6 weeks without taking the study drugs.

Treatment: Appearance and packages of **s**tudy drugs were identical, packages identified by a code number assigned at each Policlinic by progressive inclusion. Treatment was randomised through a random allocation of balanced block of size ten, with a randomization ratio 1:1. Tablets were taken once a day (oid) with evening meal. Participants in both groups should be titrated to 2 or 4 tablets oid if TC levels were ≥ 7 mmol/L after 6 or 12 months on therapy.

Compliance assessment: Compliance with study medications was assessed from visits 3 to 10 by tablet counts and patient request.

Concomitant medications: Consumption of lipid-lowering drugs was prohibited from the enrolment in the study, but no other restriction for concomitant therapy was done. Cases at secondary prevention were advised to take daily aspirin. Concomitant drugs were controlled through patient questioning, with additional interview to Family Doctors, if necessary.

Assessments: TC was assessed at baseline and every 6 months. Lipid profile and safety laboratory tests were determined at baseline and 1, 2 and 3 years thereafter. Laboratory tests included lipid profile, glucose, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

At each visit physical examination and dietary guiding were done. Compliance assessment and request for AE were performed from visits 3 to 10. Compliance was defined as good if ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Effects on lipid profile: Changes on LDL-C were the primary efficacy variable to assess the cholesterol-lowering efficacy of policosanol, treatment being considered as effective if LDL-C was significantly reduced by ≥ 15 % respect to baseline.[37] Changes on other lipid profile parameters were also analysed.

Safety and tolerability analyses: Patient records were reviewed. Data from all patients taking vasodilators 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 SAE, moderate and mild AE.

An AE was defined as any new undesirable event or change in physical or laboratory data or the worsening of any pre-existing condition happened through the study.

AE were classified according to their intensity in mild, moderate and serious. Mild AE not required the treatment of AE or withdrawal of study drugs, moderate AE required withdrawal of study medication and/or treatment of the AE. A SAE was considered any AE leading to patient hospitalisation or death.

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. In the whole study, 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.

Laboratory analysis: Blood samples were drawn after a 12 hours overnight fasting. Serum TC, LDL-C, HDL-C and TG were determined by enzymatic methods using reagent kits. Laboratory analyses were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Centre. A quality control of the precision and accuracy of the methods was performed.

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

ANOVA test was used to compare continuous variables throughout the study. Comparisons between groups of categorical data were made by Fisher's Exact Probability test. All statistical tests were two-tailed, with significance at α=0,05. Statistical analyses were performed using Statistic 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-balanced respect to main baseline characteristics (Table 1). Most patients were women (155/185; 83,8 %) average age at randomisation being 68 years old. The frequency of study patients with CHD (166/185; 89,7 %) and hypertension (147/185; 79,5 %) was very high, the frequency of diabetes being also relatively high (41/185; 22,2 %).

The vasodilator most consumed by study patients was nitropental, followed by isosorbide nitrate and nitroglycerin. The frequency of other concomitant therapies among study patients was high, those more frequently taken being anti-platelets, calcium antagonists, diuretics, β-blockers, diuretics, oral hypoglycemic drugs and digitalics, among others. Both groups were well-balanced respect to other concomitant drugs too.

Withdrawal analysis: Table 2 shows withdrawals analysis. As observed, the total number of withdrawals was significantly lower in policosanol than in placebo. Of 185 randomised patients taking vasodilators, 44 (23,8 %) withdrew from the trial.

The frequency of withdrawals in placebo (31/95; 32,6 %) was greater ($p < 0,01$) than in policosanol group (13/90; 14,4 %). Overall, 26/185 (14,1 %) patients discontinued due to some AE: 23 placebo (24,2 %) and 3 (3,3 %) policosanol patients ($p < 0,01$).

Compliance: Compliance with study medications was good according to compliance criterion.

Effects in serum lipid profile: Table 3 shows the effects on lipid profile. Both groups were well matched regarding all lipid profile variables at randomisation.

After one year on treatment, policosanol lowered significantly ($p<0,0001$ *vs* placebo) LDL-C (20,9 %), TC (15,9 %) and TG (19,3 %), whereas raised HDL-C (8,3 %).

Policosanol effects persisted, even increased, during the 3 years treatment. At the end of the study, policosanol reduced ($p<0,0001$ *vs* baseline and placebo) LDL-C (35,0 %), TC (25,0 %), TG (19,3 %) and raised ($p<0,0001$ *vs* placebo) HDL-C (16,7 %).

Safety and tolerability: Policosanol did not impair safety indicators compared with placebo (Table 4), but after one year on therapy induced additional decreases of systolic pressure compared with placebo, that were maintained up to study completion. A mild, but significant reduction of systolic pressure was also observed at the end of the study compared with placebo. Nevertheless, no individual value or clinical symptom of hypotension was reported. Values of both serum transaminases (ALAT and ASAT) were also lower in policosanol than in placebo group from one year after treatment up to the final check-up.

Twenty-six (26) (14,1 %) withdrawals were due to some AE: 23 in placebo (24,2 %) and 3 (3,3 %) in policosanol group ($p<0,01$). Table 5 summarizes the frequency of SAE occurred during the study. The frequency of policosanol patients experiencing SAE (3/90; 3,3 %) was significantly lower ($p<0,01$) than in respective placebo (22/95; 23,2 **%**). Seven patients (6 placebo, 1 policosanol) died during the study. All placebo died due to vascular events, while the policosanol patient died due to adenocarcinoma de colon.

Table 6 summarizes all moderate and mild AE reported during the study. As can be observed, no AE was particularly increased in policosanol group respect to placebo. Overall, the frequency of policosanol patients who experienced some mild or moderate AE during the study (10/90; 11,1 %) was lower ($p<0,05$) than in matched placebo (28/95; 29,5 %).

DISCUSSION

The present report demonstrates that in older hypercholesterolemic patients receiving vasodilators, policosanol induced persistent reductions of LDL-C and TC, while increased HDL-C, without impairing any safety indicator or increasing the frequency of AE. By the contrary, the frequency of SAE and all AE was lower in policosanol than in placebo.

Table 1: Main baseline characteristics of study patients

Characteristics	Placebo (n = 95)		Policosanol (n = 90)	
Age (years) (X±SD)	68 ± 6		68 ± 6	
Body mass index (kg/m²) (X±SD)	28,17 ± 4,97		27,14 ± 5,25	
Diastolic blood pressure (mm Hg) (X±SD)	83,01 ± 11,64		79,89 ± 9,89	
	n	**%**	**n**	**%**
Gender: Female	81	85,3	74	82,2
Male	14	14,7	16	17,8
Risk factors:				
Coronary heart disease*	86	90,5	80	88,9
Hypertension	76	80,0	71	78,9
Diabetes mellitus	25	26,3	16	17,8
Smoking	18	18,9	11	12,2
Obesity (kg/m² > 30)	6	6,3	8	8,9
Cerebrovascular disease**	8	8,4	5	5,6
Consumption of vasodilators				
Nitropental	58	61,1	54	60,0
Isosorbide mononitrate	20	21,1	27	30,0
Nitroglycerin	15	15,8	5	5,6
Other concomitant medications (CM)* **				
Antiplatelets	40	42,1	40	44,4
Calcium antagonists	30	31,6	26	28,9
Diuretics	28	29,5	24	26,7
β-blockers	24	25,3	26	28,9
Oral hypoglycemic drugs	16	16,8	6	6,7
Digitalics	13	13,7	17	18,9
Vitamins	16	16,8	11	12,2
Anxyolytics	11	11,6	12	13,3

n number of patients; X mean, SD standard deviation, *myocardial infarction, unstable angina, coronary surgery, **stroke, ischemic transient attacks; ***CM consumed by >10 study patients,
All comparisons were not significant

Table 2: Withdrawal analysis of study patients taking vasodilators

	Placebo (n = 95)		Policosanol (n = 90)		Total (n= 185)	
Withdrawals due to adverse events (AE)	**n**	**%**	**n**	**%**	**n**	**%**
Withdrawals due to vascular serious AE	15	15,8	3	3,3	18	$9,7^{++}$
Withdrawals due to non-vascular serious AE	7	7,4	0	0,0	7	$3,8^{++}$
Subtotal due to serious AE	**22**	**23,2**	**3**	**3,3**	**25**	**$13,5^{+++}$**
Withdrawals due to mild and moderate AE	1	1,1	0	0,0	1	0,5
Subtotal due to AE	**23**	**24,2**	**3**	**3,3**	**26**	**$14,1^{+++}$**
Withdrawals due to other reasons						
Unsatisfactory efficacy	4	4,2	1	1,1	5	2,7
Travels abroad + address changes	1	1,1	2	2,2	3	1,6
Unwillingness to follow-up	1	1,1	5	5,5	6	3,2
Protocol violations	2	2,1	2	2,2	4	2,2
Subtotal due to other reasons	**8**	**8,4**	**10**	**11,1**	**18**	**9,7**
Total of withdrawals	**31**	**32,6**	**13**	**14,4**	**44**	**$23,8^{++}$**

$^{++}p < 0,01$; $^{+++}p < 0,001$ Comparison with placebo ($\chi 2$ test)

Table 3: Long-term effects of policosanol on lipid profile (X±SD) of study patients

Treatment	Baseline	1 year	2 years	3 years
TC (mmol/L)				
Policosanol	6,80 ± 0,96	$5,72 \pm 0,77^{++++}$	$5,38 \pm 0,57^{++++}$	$5,10 \pm 0,27^{++++}$
Placebo	6,69 ± 0,80	6,58 ± 0,79	6,72 ± 0,85	6,52 ± 0,85
LDL-C (mmol/L)				
Policosanol	4,83 ± 0,86	$3,82 \pm 0,68^{++++}$	$3,42 \pm 0,61^{++++}$	$3,01 \pm 0,31^{++++}$
Placebo	4,59 ± 0,84	4,61 ± 0,85	4,81 ± 0,81	4,61 ± 0,84
HDL-C (mmol/L)				
Policosanol	$1,16 \pm 0,32^{+}$	1,20 ± 0,17	$1,31 \pm 0,23^{++}$	$1,42 \pm 0,21^{+++}$
Placebo	1,26 ± 0,32	1,16 ± 0,24	1,15 ± 0,28	1,13 ± 0,20
Triglycerides (mmol/L)				
Policosanol	2,18 ± 0,79	$1,76 \pm 0,50^{++++}$	$1,79 \pm 0,30^{++++}$	$1,72 \pm 0,19^{++++}$
Placebo	2,36 ± 1,08	2,21 ± 0,75	2,11 ± 0,59	2,11 ± 0,52

X mean, SD standard deviation, $^{+}p < 0,05$; $^{++}p < 0,01$; $^{+++}p < 0,0001$; $^{++++}p < 0,00001$ ANOVA

Table 4: Long-term effects of policosanol on safety indicators (X±SD) on study patients

Treatment	Baseline	1 year	2 years	3 years
Weight (kg)				
Policosanol	64,45 ± 11,78	64,77 ± 10,72	64,17- ± 10,25	65,16 ± 10,60
Placebo	66,28 ± 12,95	64,84 ± 12,24	65,93 ± 12,08	66,32 ± 11,15
Pulse (beats/min)				
Policosanol	72,68 ± 7,32	72,70 ± 5,95	71,12 ± 5,26	71,82 ± 3,13
Placebo	72,33 ± 7,15	72,00 ± 5,90	72,28 ± 5,10^{+}	72,39 ± 5,24
Diastolic pressure (mm Hg)				
Policosanol	79,89 ± 9,89	81,46 ± 5,73	79,49 ± 5,79	80,22 ± 3,98
Placebo	83,01 ± 11,64	81,60 ± 7,05	81,59 ± 7,20	81,91 ± 6,47
Systolic pressure (mm Hg)				
Policosanol	133,8 ± 15,03	132,7 ± 13,84	29,4 ± 15,06^{+}	127,1 ± 10,14^{++}
Placebo	137,2 ± 18,14	136,2 ± 15,12	134,9 ± 12,90	134,0 ± 12,80
Alanin amino transferease (U/L)				
Policosanol	18,67 ± 10,10	17,77 ± 5,82^{++}	18,22 ± 5,53^{++}	18,44 ± 4,15^{+}
Placebo	20,16 ± 10,62	21,65 ± 8,18	21,69 ± 8,29	20,90 ± 4,97
Aspartate amino transferase (U/L)				
Policosanol	21,87 ± 6,78	17,69 ± 4,95^{++}	18,71 ± 5,46^{++}	17,37 ± 4,16^{++}
Placebo	21,74 ± 9,15	20,75 ± 7,19	22,24 ± 6,74	20,49 ± 5,05
Creatinine (µmol/L)				
Policosanol	91,57 ± 19,41	88,78 ± 11,99	90,72 ± 10,76	91,37 ± 10,71
Placebo	90,82 ± 17,73	90,15 ± 17,67	90,35 ± 8,87	91,27 ± 9,03
Glucose (mmol/L)				
Policosanol	5,29 ± 0,92	5,36 ± 0,78	5,20 ± 0,60	5,41 ± 0,68
Placebo	5,50 ± 1,17	5,54 ± 1,04	5,30 ± 0,63	5,29 ± 0,60

X mean, SD standard deviation, $^{+}p < 0,05$; $^{++}p < 0,01$ ANOVA

Table 5: Serious adverse events (SAE) in study patients taking vasodilators

	Placebo (n= 95)		**Policosanol (n = 90)**	
Endpoints	**n**	**%**	**n**	**%**
All cardiovascular SAE	13	13,7	2	2,2^{++}
All cerebrovascular SAE	2	2,1	1	1,1
All vascular SAE	**15**	**15,8**	**3**	**3,3^{++}**
Non-vascular SAE	**7**	**7,4**	**0**	**0,0^{++}**
All SAE (fatal + non fatal)	**22**	**23,2**	**3**	**3,3^{+++}**
Fatal SAE (Deaths)				
Cardiovascular	5	5,3	0	0,0^{+}
Cerebrovascular	1	1,1	0	0,0
Deaths due to vascular SAE	**6**	**6,3**	**0**	**0,0^{+}**
Non-vascular deaths	**0**	**0,0**	**1**	**1,1**
All mortality	**6**	**6,3**	**1**	**1,1**

Study subjects are counted only once with a specific endpoint; However, they may be listed more than once because of experiencing an event included in more than one endpoint analysis, $^{+}p < 0,05$; $^{++}p < 0,01$; $^{+++}p < 0,001$ Comparison with placebo ($\chi 2$ test)

Table 6: Moderate and mild adverse events (AE) reported by patients

Moderate AE				
Body System/AE	**Placebo (n = 95)**		**Policosanol (n=90)**	
Muscle-skeletal system disorders				
Bursitis	0	0,0	1	1,1
Fractures	1	1,0	0	0,0
Cardiovascular disorders				
Dyspnea at effort	1	1,0	0	0,0
Moderately uncontrolled hypertension	0	0,0	1	1,1
Respiratory system disorders				
Asthma	2	2,1	0	0,0
Pneumonia	2	2,1	1	1,1
Reproductive disorders				
Breast dysplasia	0	0,0	1	1,1
White cell and RES disorders				
Lymphangitis	1	1,0	0	0,0
Urinary system disorders				
Renal sepsis	3	3,2	0	0,0
Mild AE				
Skin and appendages disorders				
Mouth dryness	2	2,1	0	0,0
Muscle-skeletal system disorders				
Arthralgia	3	3,2	2	2,2
Legs pain	2	2,1	0	0,0
Muscle cramps	4	4,2	0	$0,0^{+}$
Central and peripheral nervous system disorders				
Dizziness	1	1,0	1	1,1
Headache	1	1,0	0	0,0
Gastrointestinal system disorders				
Diarrhoea	4	4,2	0	$0,0^{+}$
Vomiting	1	1,0	0	0,0
Endocrine disorders				
Hypoglycemia	0	0,0	1	1,1
Cardiovascular disorders				
Chest pain	9	9,5	1	$1,1^{+}$
Mildly uncontrolled hypertension	0	0,0	1	1,1
Heart rate and rhythm disorders				
Tachycardia	0	0,0	1	1,1
Respiratory system disorders				
Pneumonia	1	1,0	0	0,0
Urinary system disorders				
Renal colic	0	0,0	1	1,1
Renal sepsis	1	1,0	0	0,0
Body as a whole				
Anorexia	1	1,0	0	0,0
Asthenia	0	0,0	2	2,2
Fever	1	1,0	0	0,0
Loss on weight	1	1,0	1	1,1
Patients with moderate or mild AE	**28**	**29,5**	**10**	**$11,1^{++}$**

$^{+}p < 0,05$; $^{++}p < 0,01$ Comparison with placebo ($\chi 2$ test)

At randomisation both groups were similar. Hence, random allocation to treatment was adequate and groups were homogeneous. The large proportion of women is characteristic of the patients attending to the Policlinics of this area,[38] and also reflects the high motivation of such women to participate and adhere to study protocol.

The preponderance of the use of nitropental as compared with other vasodilators was consistent with the situation present in Cuban routine clinical practice in the time of the trial. Consumption of other concomitant drugs was high, a common finding in the elderly. Thus, the present report is not conducted in an ideal population only consuming vasodilators and placebo or policosanol, but also receiving other concomitant therapies, as occurs with real patients in clinical practice. The other concomitant drugs consumed by study patients were consistent with their risk condition.

As expected, policosanol showed persistent efficacy for lowering LDL-C, the primary efficacy variable, CT, whereas increased HDL-C.[10-23] Reductions on TG were greater than in previous studies, a finding without conclusive explanation.

The frequency of withdrawals in placebo was greater than in policosanol group, a finding related with discontinuations due to AE, since the frequency of withdrawals due AE, mostly SAE, was greater in placebo than in policosanol group, while the frequency of other withdrawals was similar.

The lesser extent of SAE in policosanol respect to placebo is consistent with drug effects, since most SAE were of vascular nature and policosanol lowers LDL-C and also inhibit platelet aggregation and LDL oxidation, all consistent with vascular protection.

Policosanol was safe and well tolerated. No policosanol-related impairment of safety indicators was observed. Thus, the additional reduction of systolic pressure (and in lesser extent of diastolic pressure) induced by policosanol was not considered as a drug-related AE, since individual values remained within normal range and hypotension was not referred as AE. By the

contrary, in a population with a high frequency of CHD and hypertension, like the study population, such effect could be beneficial to reduce the global atherosclerotic risk of the patients, mainly because a decrease on systolic pressure has been associated to a reduction of coronary events in the elderly.[39]

On the other hand, the reduction of serum transaminases here reported agrees with previous results, underlying that policosanol does not affect liver function. Although the conclusive explanation of the policosanol-induced reduction of transaminase values is not available, recent experiences suggest that policosanol can exert some protective effects on liver cells.[40]

AE reports did not show increases resulting from concomitant use of policosanol and vasodilators. Conversely, the frequency of both SAE and other AE (mild + moderate) was lower in policosanol than in placebo. This result, together with withdrawal analysis, indicates that concomitant administration of policosanol and vasodilators is well tolerated and potential risk due to adverse DDI is low.

CONCLUSION

Policosanol was well tolerated in older patients taking vasodilators, not affecting safety indicators or increasing AE compared with placebo. Other benefits were observed in policosanol group, such as the additional reduction of systolic pressure and a lesser extent of SAE, in addition to the expected cholesterol-lowering efficacy of policosanol These results show that policosanol long-term consumed by older individuals taking vasodilators did not induce adverse DDI.

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