CONCOMITANT USE OF POLICOSANOL AND CARDIAC GLYCOSIDES IN OLDER PATIENTS

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ABSTRACT. Policosanol is a cholesterol-lowering drug with documented efficacy and safety. The potential risk of adverse drug interaction (IDD) with policosanol appears to be low, but some interactions should still be explored. Cardiac glycosides are widely used in geriatric populations to treat congestive heart failure and atrial fibrillation but have a substantial risk of toxicity. As part of a large Prevention Study, we investigated whether concomitant administration of policosanol with cardiac glycosides induces any specific adverse event (AE) or alteration in any safety indicator in older patients. 1 470 elderly patients with high coronary risk were assigned by roasting to a group receiving policosanol 5 mg/d or to another group that would be treated with placebo treatment for three years. For the analysis, the records of all patients and 79 of them who took cardiac glycosides were included. Both groups were well matched at baseline. Effects on serum lipid profile of the policosanol group persisted during the test. At the end of the study, policosanol decreased low-density lipoprotein cholesterol (LDL-C) (33.9 %), total cholesterol (24.1 %), triglycerides (28.7 %) and HDL- C (16.7 %). Twenty-six patients (16 placebos, 10 policosanol, $p < 0.05$) were withdrawn from the study, 12 (9 placebo, 3 policosanol, $p < 0.01$) due to AE. The frequency of severe AE in the treatment with policosanol was lower ($p < 0.05$) than in patients treated with placebo, whereas that of other non-severe AEs was similar in both groups. We conclude that policosanol administered concomitantly with cardiac glycosides to elderly patients was effective and well tolerated, not increasing any AE. These results indicate, that policosanol can be consumed by these cardiac glycosides treated patients without significant risk of IDD.

RESUMEN. El policosanol es un medicamento hipolipemiante con documentada eficacia y seguridad. El riesgo potencial de interacciones medicamentosas adversas con policosanol ha sido bajo, pero aún algunas interacciones necesitan ser exploradas. Los glicósidos cardiacos son indicados en la población geriátrica para el tratamiento de la enfermedad cardíaca congestiva y la fibrilación auricular, pero tienen un riesgo potencial de toxicidad. El objetivo del presente análisis como parte del Estudio de Prevención fue investigar si la administración concomitante de policosanol con glicósidos induce algún evento adverso (EA) específico o altera los indicadores de seguridad en estos pacientes. Fueron aleatorizados 1 470 ancianos con alto riesgo coronario, los cuales recibieron policosanol 5 mg/d o placebo durante tres años. Para el análisis se tomaron los registros de todos los pacientes incluidos y se incluyeron 79 de ellos que tomaban glicósidos cardiacos. Ambos grupos fueron homogéneos al inicio del tratamiento. Los efectos del policosanol se mantuvieron durante todo el tiempo de tratamiento. Al finalizar el estudio, el policosanol redujo el colesterol asociado a lipoproteínas de baja densidad LDL-C (21,7 %), el colesterol total (20,3 %) y los triglicéridos (20,1 %), así como incrementó el colesterol asociado a lipoproteínas de alta densidad HDL-C (8,3 %). De los pacientes que consumían glicósidos, 26 (16 placebo, 10 policosanol, $p < 0.05$) causaron baja del estudio, 12 (9 placebo, 3 policosanol, $p < 0.01$) debido a EA. El policosanol no afectó los indicadores de seguridad en comparación con el placebo. La frecuencia de EA severos (EAS) en el grupo policosanol fue menor ($p < 0.05$) que en grupo placebo, mientras que la frecuencia de otros EA fue similar. Se concluye que el policosanol administrado concomitantemente con glicósidos cardiacos en pacientes ancianos fue efectivo y bien tolerado, no incrementando ningún EA. Estos resultados indican que el policosanol puede ser consumido por estos pacientes tratados con glicósidos sin riesgo relevante de interacción medicamentosa.

INTRODUCTION

Coronary heart disease is a major cause of morbidity and mortality in adults and is directly associated to elevated serum levels of low-density lipoprotein cholesterol (LDL-C).[1-3] End-point clinical trials have proven the benefits of lowering LDL-C with statins on coronary events.[4-8]

Hypercholesterolemia treatment in the elderly was questioned for many years because elevated LDL-C levels decline as predictors of relative coronary risk with age.[9] Older patients frequently have impaired hepatic and renal drug clearance, electrolyte imbalance, several concomitant diseases and consequently, concomitant drugs. Therefore, the frequency of drug-related adverse events (AE) and the drug-drug interactions (DDI) in this population is greater than in the non-elderly.[10]

Nevertheless, since increased LDL-C values still are strong predictors of absolute coronary risk in such population,[9] and analyses of subgroup of older patients included in end-point studies have shown the clinical benefits of lowering LDL-C values in such patients,[4-8] treatment of hypercholesterolemia in the elderly is currently recommended.[11]

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L)* wax[12] with cholesterol-lowering efficacy proven in type II hypercholesterolemia[13-23] and the dyslipidemia due to type 2 diabetes mellitus.[24-26] Policosanol (5-20 mg/d) decreases LDL-C and total cholesterol, whereas raises high-density lipoprotein cholesterol (HDL-C). Effects on triglycerides, however, are modest and not consistent.[12–26] In particular, policosanol is effective, safe and well tolerated in older individuals.

Policosanol, reduces cholesterol levels by inhibiting its biosynthesis between acetate consumption and mevalonate production by suppressing HMG-CoA reductase up-regulation. So that, its inhibitory effects by a depression of *de novo* synthesis of HMG-CoA reductase and/or stimulation of its degradation could be explained.[27-29] Policosanol increases LDL receptor-dependent processing, enhancing the LDL catabolic rate.[30] Policosanol shows also pleiotropic effects, inhibiting platelet aggregation[12,18,31] and LDL lipid peroxidation.[32,33]

Clinical and post marketing surveillance studies have demonstrated that policosanol is safe and well tolerated,[12-26,34-36] even in populations with high consumption of concomitant drugs. Hence, adverse drug-drug interactions with policosanol appear to be not relevant.

DDI commonly comes from pharmacokinetic and/or pharmacodynamic characteristics.[37] Experimental data did not support potential DDI between policosanol and drugs metabolised through the cytochrome P450 hepatic system. Since policosanol orally administered for 21 d did not affect antipyrine or theophylline pharmacokinetics,[38] and administered orally at high doses (250-1 000 mg/kg) during 30 d to rats did not modify the activity of hepatic drug-metabolising enzymes.[39] Since the metabolism of most drugs goes by this system, the risk for DDI based in pharmacokinetic interactions with policosanol is low.

Nevertheless, pharmacodynamic DDI with policosanol cannot be discarded, so that pharmacological DDI of different drugs with policosanol could be possible.

Cardiac glycosides are widely used in geriatric populations to treat congestive heart failure, tachycardia, atrial fibrillation and flutter.[40] They are used for their positive inotropic effects, acting on the myocardium to increase strength and regularity of contractions, and for their ability to alter the conduction through the atrioventricular node, thus helping to restore normal rate and rhythm cardiac. Nevertheless, cardiac glycosides drug have substantial risk of toxicity, ones of the toxicity symptoms include: anorexia, nausea, vomiting, diarrhoea, palpitations, irregular pulse, decreased urine output or excessive urination at night, swelling, decreased consciousness, confusion, breathing difficulty and some visual changes. The most frequent and serious symptoms of digitalis toxicity, however, resemble the clinical condition that they intend to treat: paroxysmal atrial tachycardia with block, premature ventricular contractions, ventricular tachycardia and atrioventricular block.[40-42]

Risks for digitalics toxicity increases with age because of impaired pharmacokinetic properties in older individuals and due to some DDI. Thus, many medications can interact with cardiac glycosides, such as verapamil, amiodarone, quinidine and diuretics. Since many diuretics cause potassium loss and low levels of potassium increases digitalis toxicity, this concomitant therapy needs to be carefully followed.[43]

Considering such background, to investigate DDI between policosanol and cardiac glycosides, especially in the elderly, is rationale. The present analysis was undertaken to determine whether policosanol administered concomitantly with digitalics to older individuals impairs any safety indicator and/or induce some specific AE. We also investigated if cholesterol-lowering efficacy of policosanol in such population is that expected.

PATIENTS AND METHODS

Study Design. The present analysis includes the all patients data consuming cardiac glycosides during three years included Prevention Study of policosanol in the elderly [44]

Patients were enrolled at four Policlinical Centers, "Ramón González Coro"; "Elpidio Berovides," "Educational" and "26 de Julio" from regions names "Marianao, Lisa and Playa" belong from Havana City. All executions were, by medical staff of the Surgical Medical Research Centre controlled. The personnel involved in patient treatment were blinded to treatment allocation. An independent Ethics Committee approved study protocol, the patients being enrolled after provide informed written consent.

Screening initial visits were done in Policlinics, wherein individuals aged between 60 and 80 their risk factors was invited to assess. Enrolled patients (first visit) were instructed to follow as step one cholesterol-lowering diet for five weeks (this period, was called baseline period).

After this baseline period, lipid profile and safety laboratory indicators were assessed and the next week patients attended to second visit. The laboratory values obtained after the baseline period and safety physical indicators determined at second visit 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 three months during the first year (visits third to sixth) and every six months thereafter (visits seventh to tenth).

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 serum levels of total cholesterol ≥ 5.2, LDL-C ≥ 3.4 and triglycerides < 4.52 mmol/L after conclude the baseline period.

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

Withdrawal criteria. Any AE justifying such decision, unwillingness to continue, total cholesterol ≥ 9 mmol/l or major violations of study protocol (including > six weeks without taking the study drugs).

Treatment. Appearance and packaging of study medications was identical, packages being identified by a code number assigned at each Policlinic by progressive inclusion. Treatment was randomised through a random allocation 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 two or four tablets oid if total cholesterol levels were ≥ 7 mmol/L after six or 12 months on therapy.

Compliance assessment. Compliance with study medications was assessed from third to tenth visits 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 AE were performed from third to tenth visits. 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 considered as the primary efficacy variable to assess the cholesterol-lowering efficacy of policosanol in the elderly. Treatment was considered as effective if LDL-C was significantly reduced by ≥ 15 % respect to baseline.[45] Changes on other lipid profile parameters were also analysed.

Safety and tolerability analyses. Patient records were reviewed. Data from all patients taking digitalics 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 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.

AE according to their intensity in mild, moderate and serious were classified. Mild AE not required treatment of the AE and/or withdrawal of study medication, whereas 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.[46] They included all mortality, fatal and non-fatal coronary, cardiovascular, cerebrovascular and vascular SAE. 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.

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 h 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.[47] LDL-C values were calculated using the Friedewald equation.[48]

Laboratory analyses were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Centre. A quality control was performed, so that precision and accuracy versus reference standards were controlled.

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 $\alpha = 0.05$. 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). Most patients were women (64/79, 81 %) and hypertensive (63/79, 79.7 %). The frequency of coronary heart disease and diabetes among study patients was also high (53/79 67.1 % and 27/79, 34.2 %, respectively).

Table 1. Main baseline characteristics of study patients

Characteristics	**Placebo (n = 37)**		**Policosanol (n = 42)**	
Age (years) (X ± SD)	70 ± 5		69 ± 7	
Body mass index (kg/m^2) (X ± SD)	27.8 ± 7.4		26.2 ± 4.4	
	n	%	n	%
Gender: Female	31	83.8	33	78.6
Male	6	16.2	9	21.4
Risk factors				
Arterial hypertension	30	81.1	33	78.6
Smoking	10	27.0	8	19.0
Coronary heart disease*	26	70.3	27	64.3
Diabetes mellitus	13	35.1	14	33.3
Obesity (kg/m^2 > 30)	1	2.7	2	4.8
Cerebrovascular disease**	2	5.4	3	7.1
Consumption of cardiac glycosides				
Digoxin	33	89.2	40	95.2
Digitoxin	4	10.8	2	4.8
Other concomitant medications* **				
Anti-platelets	20	54.0	21	50.0
Diuretics	14	37.8	18	42.9
Vasodilators	13	35.1	17	40.5
Oral hypoglycemic drugs	10	27.0	7	16.7
Calcium antagonists	9	24.3	12	28.6
Anxyolytics	4	10.8	5	11.9
Myorelaxants	5	13.5	4	9.5
β-blockers	5	13.5	3	7.1
Vitamins	5	13.5	3	7.1

n number of patients; X mean, SD standard deviation,
*myocardial infarction, unstable angina, coronary surgery. **stroke, ischemic transient attacks;
***consumed by > 5 study patients. All comparisons were not significant

Most study patients consumed digoxin (73/79, 92.4 %) as cardiac glycoside. The frequency of other concomitant drugs among study patients was high, those more frequently taken being anti-platelets, diuretics, vasodilators and oral hypoglycemic drugs, among others. Both groups were well balanced respect to other concomitant therapies.

Withdrawal analysis. The total number of withdrawals was significantly lower in policosanol than in placebo (Table 2). Of 79 included patients consuming digitalics, 26 (32.9 %) withdrew from the study. The frequency of withdrawals in placebo (16/37 43.2 %) was greater ($p < 0.05$) than in policosanol group (10/42, 23.8 %). Overall, 12/79 15.2 %) patients discontinued due to some AE, 9 from placebo (24.3 %) and 3 (7.1 %) ($p < 0.01$) from policosanol group. Compliance with study medications was good according to compliance criterion.

Table 2. Withdrawal analysis in patients taking digitalics

	Placebo (n = 37)	Policosanol (n = 42)	P value[+]
Withdrawals due to AE			
Withdrawals due to SAE	9	2	$p < 0.05$
Withdrawals due to mild and moderate AE	0	1	ns
Subtotal due to all AE (n %)	**9 (24.3)**	**3 (7.1)**	$p < 0.05$
Withdrawals due to other reasons			
Unsatisfactory efficacy	4	0	$p < 0.05$
Travels abroad+changes to other places	1	1	ns
Unwillingness to follow-up	2	5	ns
Protocol violations	0	1	ns
Subtotal due to other reasons	**7**	**7**	ns
Total of withdrawals (n %)	**16 (43.2)**	**10 (23.8)**	ns

[+]Comparison with placebo (Fisher's Exact probability test)

Effects in serum lipid profile. Both groups were similar regarding all lipid profile variables at baseline (Table 3). After one year, policosanol lowered significantly ($p < 0.000\ 1$ *vs* placebo) LDL-C (21.7 %), total cholesterol (20.3 %) and triglycerides (20.1 %), whereas raised ($p < 0.05$ *vs* placebo) high-density lipoprotein-cholesterol (HDL-C) (8.3 %). Policosanol effects persisted, even increased, during the three years treatment. At study completion, policosanol lowered ($p < 0.000\ 1$ *vs* placebo) LDL-C (33.9 %), total cholesterol (24.1 %), triglycerides ($p < 0.05$) (28.7 %) and increased ($p < 0.001$ *vs* baseline and placebo) HDL-C (16.7 %).

Table 3. Long-term effects of policosanol on study patients taking digitalics (x ± SD)

Study groups	Baseline	1 year	2 years	3 years
		Total cholesterol (mmol/L)		
Policosanol	6.76 ± 1.08	5.39 ± 0.65^{+++}	5.24 ± 0.52^{+++}	5.13 ± 0.45^{+++}
Placebo	6.52 ± 0.88	6.54 ± 1.07	6.35 ± 0.66	6.38 ± 0.71
		LDL-C (mmol/L)		
Policosanol	4.60 ± 1.05	3.60 ± 0.67^{+++}	3.35 ± 0.73^{+++}	3.04 ± 0.41^{+++}
Placebo	4.31 ± 0.85	4.46 ± 0.94	4.60 ± 0.89	4.51 ± 0.70
		HDL-C (mmol/L)		
Policosanol	1.20 ± 0.39	1.30 ± 0.26^{+}	1.30 ± 0.34^{++}	1.40 ± 0.29^{++}
Placebo	1.23 ± 0.33	1.14 ± 0.33	1.06 ± 0.18	1.06 ± 0.08
		Triglycerides (mmol/L)		
Policosanol	2.54 ± 1.02	2.03 ± 0.78	1.92 ± 0.38^{+}	1.81 ± 0.36^{+}
Placebo	2.75 ± 1.29	2.39 ± 0.96	2.22 ± 0.58	2.29 ± 0.88

$^{+}p < 0.05$; $^{++}p < 0.001$; $^{+++}p < 0.0001$ Comparison with placebo (ANOVA test)

Safety and tolerability. No policosanol-related impairment of safety indicators was observed (data not shown for simplicity). Study patients did not experience symptoms of digitalis toxicity.

Twelve withdrawals (nine placebo and three policosanol) ($p < 0.05$) were due to some AE. The frequency of policosanol patients experiencing serious AE (2/42, 4.8 %) was lower ($p < 0.05$) than in respective placebo (9/37, 24.3 %) and the frequency of mild or moderate AE in policosanol group (8/42, 19 %) was similar than in placebo (10/37, 27 %) (Table 4).

Table 4. Adverse events in older patients taking digitalics

Adverse events	Placebo (n = 37)		Policosanol (n = 42)	
	n	%	n	%
Serious adverse events (SAE)				
All cardiovascular SAE	3	8.1	0	0.0
All cerebrovascular SAE	1	2.7	2	4.8
All vascular SAE	**5**	**13.5**	**2**	**4.8**
Non-vascular SAE	**4**	**10.8**	**0**	**0.0**
All SAE (fatal + non fatal)	**9**	**24.3**	**2**	**4.8**$^{+}$
Fatal SAE (Deaths)				
Cerebrovascular	1	2.7	0	0.0
Cardiovascular	1	2.7	0	0.0
Deaths due to vascular SAE	**2**	**5.4**	**0**	**0.0**
Non-vascular deaths	**0**	**0.0**	**1**	**2.4**
All deaths	**2**	**5.4**	**1**	**2.4**
Moderate and mild AE				
Muscle-skeletal system disorders	2	5.4	2	4.8
Cardiovascular disorders	3	8.1	1	2.4
Respiratory system disorders	2	5.4	1	2.4
White cell and RES disorders	1	2.7	0	0.0
Skin and appendages disorders	3	8.1	0	0
Nervous system disorders	1	2.7	1	2.4
Gastrointestinal system disorders	0	0.0	1	2.4
Body as a whole disorders	0	0.0	4	9.5
Patients with moderate or mild AE	**10**	**27.0**	**8**	**19.0**

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.
$^{+}p < 0.05$ Comparison with placebo (Fisher's Exact Probability test)

DISCUSSION

The present analysis demonstrates that in older patients receiving cardiac glycosides, policosanol sustainedly lowered LDL-C and total cholesterol, while increased HDL-C, without impair any safety indicator or increase the frequency of AE. By the contrary, the frequency of SAE was lower in policosanol than in respective placebo patients.

The baseline characteristics were similar in both groups, which indicate that randomisation was adequate and groups were homogeneous. The larger proportion of women respect to men is characteristic of the patients attending to the Policlinics of this Havana City area,[49] also reflecting the high motivation of such women to participate and adhere to study protocol.

The frequency of concomitant drugs was high, as expected in the elderly. Thus, the present analysis is not performed in a population only treated with cardiac glycosides and placebo or policosanol, but to patients receiving other concomitant therapies, as commonly occurs in clinical practice. Most patients consumed digoxin, the most toxic of common cardiac glycosides.[40] The other concomitant drugs consumed by study patients were consistent with their risk condition.

The present results support that policosanol was as effective as expected,[12-26] 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 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 those due to AE, since the frequency of withdrawals due to SAE was greater in placebo than in policosanol group, while the withdrawals due to other reasons were similar. Thus, the frequency of all SAE was lower in policosanol than in placebo, consistently with LDL-C lowering and other pleiotropic effects of policosanol.

Policosanol was safe and well tolerated. No drug-related impairment of safety indicators was observed. Moderate and mild AE reports did not show increase resulting from concomitant use of policosanol and cardiac glycosides. In addition, the frequency SAE was lower in policosanol than in placebo. This result, together with withdrawal analysis, discards any potential risk due to policosanol administered with digitalics, particularly considering that most study patients received digoxin, the most toxic of both cardiac glycosides (digoxin and digitoxin).[40,50]

CONCLUSIONS

Policosanol was well tolerated in older individuals consuming cardiac glycosides, not affecting any safety indicator or increasing any AE compared with placebo. Also, the frequency of SAE, was lower in policosanol than in placebo. Cholesterol-lowering efficacy of policosanol was persistent, as expected. These results indicate that policosanol consumed by hypercholesterolemic older patients also digitalics did not induce any adverse DDI.

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