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Concomitant use of policosanol and vitamins in older patients

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Abstract

Introduction: The efficacy and safety of policosanol have been investigated in clinical studies, included elderly patients. 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. The objective of the present analysis we investigated whether concomitant administration of policosanol with vitamins induces some specific adverse event or disturbance on any safety indicator in older patients with hypercholesterolemia.

Methods: We randomised 1470 elderly patients at high coronary risk to policosanol or placebo for 3 years. For this analysis, the records of all patients (150) taking vitamins were included. Analysis was by Intention-to-treat.

Results: Both groups were well matched at baseline. Policosanol significantly reduced low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides and raised high-density lipoprotein cholesterol (HDL-C). Of 150 patients, 27 discontinued the study, 21/67 placebo and 6/83 policosanol patients. Of them, 16 patients (14 placebo, 2 policosanol) discontinued because of some adverse event. No disturbance of any safety indicator was found. The serious vascular adverse event in policosanol patients was lesser than in placebo. The frequency of moderate and mild adverse events in the policosanol group was lower compared with placebo group.

Conclusion: It is concluded that policosanol therapy added to older hypercholesterolemic patients taking vitamins drugs produced relevant benefits on lipid profile and the frequency of serious adverse events respect to placebo, then indicated concomitant with vitamins in elderly, without increase any adverse event.

Keywords: policosanol, vitamins, elderly, hypercholesterolemia, drug interactions

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in middle-aged and elderly patients [1]. The management of the risk factors for atherosclerotic cardiovascular disease, of which elevated LDL-C is one, is called primary prevention, if this process is done in someone who has not previously experienced an atherosclerotic vascular event. The rationale for activities focused on LDL-C reduction is based upon epidemiologic data documenting a continuous, positive, graded relationship between LDL-C concentration and cardiovascular disease events and mortality and evidence that lowering of LDL-C in patients across a broad range of LDL-C levels reduces the risk in patients with and without cardiovascular disease [2, 3].

Patients without known cardiovascular disease are generally at much lower baseline risk of cardiovascular events than patients with known cardiovascular disease. The decision as to whether LDL-C treatment should be recommended depends on a determination of global cardiovascular disease risk, as the potential absolute risk reduction with treatment for hypercholesterolemia will usually be smaller than for patients with established cardiovascular disease [4, 6].

End-point based studies have demonstrated a direct relationship between coronary disease and elevated serum levels of LDL-C and total cholesterol [2], as well as the benefits of lowering LDL-C with statins on clinical end-points [7, 10].

Hypercholesterolemia management in the elderly had been questioned because elevated LDL-C and total cholesterol levels decline with age, as predictors, of the relative coronary risk. However, still it is a strong predictor for absolute coronary risk in the elderly and the evidence obtained from strata analyses of older patients included in statin trials had shown the clinical benefits in this population [11, 13].

Older individual shows impairment of hepatic and renal drug clearance, and commonly consume several concomitant drugs as a consequence of their co-morbid status. Then, the frequency of drug-related adverse events in the elderly is greater than in younger adults [12].

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L)* wax [14] with cholesterol-lowering effects due to the inhibition of cholesterol synthesis by regulating the activity of hydroxymethyl glutaryl Coenzyme (HMG CoA) through the increase of AMP kinase activity [15, 18].

Policosanol also shows important pleiotropic effects that can reinforce its effects on atherosclerosis development, such as inhibition of platelet aggregation [19], and of the susceptibility of LDL to be oxidised [20, 21].

Previous studies conducted in older patients with hypercholesterolemia treated with policosanol showed that policosanol was effective and well tolerated in these patients [22, 30]. Clinical and post-marketing studies have demonstrated that policosanol is safe and well tolerated [31, 33] in populations with high use of concomitant therapy, suggesting that the risk of adverse events coming from drug interactions is low.

Drug interactions come from pharmacokinetic and/or pharmacodynamic link between drug processing and/or drug actions [34, 35]. Nevertheless, pharmacodynamic interactions between policosanol and other drugs cannot be discarded [36, 40].

This background supported to assess the potential interaction between policosanol and vitamins from the analysis of the data of the long-term prevention study with policosanol in the elderly. Then, the present analysis was conducted to determine whether concomitant administration of policosanol with vitamins impairs some safety indicator or increase the report of some adverse events. In addition, we also investigated if cholesterol-lowering efficacy of policosanol was evident and persistent in older patients consuming vitamins.

Patients and Methods

The present analysis includes the data of all patients consuming vitamins included in the Prevention Study of policosanol in the elderly [41].

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

Study Design. The present analysis was based on data of a prospective, randomized, double-blinded, placebo-controlled study conducted in 1470 older patients treated with placebo or policosanol for 3 years after randomization. In brief, patients were recruited at four Policlinical Centres and followed by medical staff of the Surgical Medical Research Centre.

Initially subjects aged 60 to 80 were invited, through Family Doctors, to assess their risk factors. A total of 1612 patients were recruited after confirming that exclusion criteria were absent (visit 1). Patients were advised to follow a step one cholesterol-lowering diet for 5 weeks, after which lipid profile and safety laboratory indicators were assessed and the next week they attended to visit 2.

Laboratory values obtained at the end of baseline period and safety physical indicators obtained at visit 2 were considered as baseline values for respective parameters. Eligible patients (1470) were randomized, under double-blind conditions, to policosanol 5 mg or placebo tablets. Concomitant medications were recorded. The patients were followed every 3 months during the first year (visits 3 to 6) and at 6 months intervals thereafter (visits 7-10).

Enrollment criteria. Patients of both sexes aged 60 to 80 with documented past history of coronary (myocardial infarction, unstable angina and/or surgery), cerebrovascular disease, hypertension, dyslipidemia, smoking habits or/and diabetes were enrolled in the study. The rationale for the lowest age was to include older individuals with a considerable life expectancy.

Inclusion criteria. Patients were randomized if after the baseline period they showed total cholesterol≥5.2, LDL-C≥3.4 and triglycerides<4.52 mmol/L, if 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 who had experienced unstable angina, myocardial infarction, stroke or any serious adverse events within the 3 months prior to enrollment were also excluded.

Withdrawal criteria. Any serious adverse events or adverse events justifying such decision, unwillingness to follow-up, patients with total cholesterol ≥ 9 mmol/l according to central lab report, major violations of study protocol, including > 6 weeks without taking the study medications.

Treatment. Study medications were identical in appearance. Treatments were administered in identical packages identified by a code number and the number of treatments assigned at each Policlinic by progressive inclusion. Study medications were randomised through a random allocation generated in the Database center, consisting of balanced block of size ten, with a randomization ratio 1:1. Tablets must be taken once a day (oid) with evening meal.

Compliance assessment: Were performed from visits 3 to 10, compliance being assessed by patient questioning and tablet counts and defined as ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Concomitant medications: Consumption of lipid-lowering drugs was forbidden from the time of enrolment to study completion, but no other restriction of concomitant therapy was done. Cases at secondary prevention were encouraged to take aspirin and/or β-blockers.

Assessments: Lipid profile and safety laboratory tests were performed at baseline and after 1, 2 and 3 years of randomization. At each visit dietary reinforcement and physical examination were done.

Effects on lipid profile. Changes on LDL-C were considered as the primary efficacy variable. Treatment was considered as effective if LDL-C was significantly reduced by ≥ 15 %,[42] changes on other lipid profile variables being secondary variables.

Safety and tolerability analyses. Patient records were reviewed and information about concomitant medication collected and analyzed. All patients taking vitamins were included in the analysis. Physical (body weight, pulse rate, blood pressure) and laboratory safety indicators (aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, creatinine) were analyzed. Safety and tolerability analysis included all data on adverse event. Special attention was addressed to explore if policosanol increased the report of any adverse event respect to placebo group.

An adverse event was defined as any new undesirable experience or change in physical or laboratory data or the worsening of any pre-existing condition occurred through the trial, being or not drug-related. Adverse events were classified according to their intensity in mild, moderate and serious. Mild adverse event were those adverse event not requiring treatment or withdrawal of study medication, moderate adverse event required withdrawal of study medication and/or specific treatment of the adverse event.[43]

A serious adverse event was considered any adverse event leading to patient hospitalisation or death, independently of their nature. They included all mortality, as well as fatal and non-fatal coronary, cardiovascular, cerebrovascular and vascular serious adverse event. For the whole study, events were analysed according by time of first event, but for 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 12 hours overnight fasting. Lipid profile and laboratory safety indicators were assessed by enzymatic methods using reagent kits (Roche). Laboratory tests were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Centre. Determinations were done at the

same day of sampling. A quality control was performed, so that within day and between-day variations as well as accuracy vs reference standards were controlled.

Statistical analysis. Statistical analysis for the whole study was planned in study protocol and amendments. All data were analysed according to Intention to-treat principle, so that analyses were based on data of all randomised patients, as randomised.

ANOVA test was used to compare continuous variables during the study. Comparisons between groups of categorical data were made using the $\chi 2$ 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 of patients taking vitamins were comparable at baseline (Table 1). Most patients were women (80.7 %) and hypertensive (73.6 %) Study patients also showed a high frequency of diabetes (27.3 %) and coronary events (26 %). In turn, the frequency of concomitant medications was also high, the other concomitant medications most consumed being angiotensin converting enzyme inhibitors, β-blockers, anti-platelets, diuretics, calcium antagonists, vasodilators, anxyolytics, oral hypoglycemic drugs and myorelaxants. Concomitant medications consumption was well matched in both groups.

Withdrawal analysis. Table 2 shows withdrawals analysis. The total number of withdrawals in policosanol group was significantly lower ($p<0.05$) than in placebo. Of 150 patients consuming vitamins, 27 (18 %) discontinued the study, 21/67 placebo (31.3 %) and 6/83 policosanol (7.2 %) patients. Of them, 16 patients (14 placebo, 2 policosanol) ($p<0.01$) discontinued prematurely the study because of some adverse events, the frequency of policosanol patients who discontinued the study due to adverse events being also lower than in placebo, a fact consistent with the frequency of serious adverse events in both groups.

Compliance. Compliance with study medications, assessed by tablet count and patient interviews was good as defined by compliance criterion. Compliance was greater in policosanol than in placebo, the main difference being attributable to the withdrawals, since once a patient withdrew from the study, it did not continue on treatment.

Effects in serum lipid profile. Table 3 shows the effects on lipid profile. After one year, policosanol lowered significantly ($p<0.01$ vs placebo) LDL-C, total cholesterol and triglycerides, while raised ($p<0.05$ vs placebo) HDL-C levels. Policosanol effects persisted during the whole study. At study completion, policosanol reduced ($p<0.001$ vs placebo) LDL-C (31.9 %), total cholesterol (21.7 %), triglycerides (21.1 %) and raised ($p<0.001$ vs placebo) HDL-C (18.2 %).

Safety and tolerability. No impairment of safety indicators was observed (Table 4).

Table 5 shows the frequency of adverse events occurred during the study. The serious vascular adverse events in policosanol patients taking vitamins (2/83, 2.4 %) was lesser ($p<0.01$) than in placebo (10/67, 14.9 %). Also, the frequency of moderate and mild adverse events reported in the policosanol group was lower ($p<0.05$) compared with placebo group.

Table 1: Main baseline characteristics of study patients taking vitamins

Characteristics	Placebo (n = 67)		Policosanol (n = 83)	
Age (years) (X ± SD)	67 ± 6		67 ± 6	
Body mass index (kg/m^2) (X ± SD)	25.66 ± 6.25		25.70 ± 3.98	
	n	%	n	%
Gender: Female	52	77.6	69	83.1
Male	15	22.4	14	16.9
Personal history				
Arterial hypertension	40	59.7	44	53.0
Smoking	11	16.4	17	20.5
Coronary disease*	18	26.9	21	25.3
Diabetes mellitus	24	35.8	17	20.5
Obesity (kg/m^2 > 30)	6	9.0	3	3.6
Cerebrovascular disease**	5	7.5	2	2.4
Other concomitant medications (CM)***				
Angiotensin converting enzyme inhibitors	25	37.3	26	31.3
Anti-platelet	27	40.3	20	24.1
Diuretics	12	17.9	13	15.7
Calcium antagonists	11	16.4	14	16.9
Anxyolytics	10	14.9	15	18.1
Vasodilators	13	19.4	11	13.2
Oral hypoglycemic drugs	17	25.4	7	8.43
Myorelaxants	7	10.4	9	10.8
β-blockers	9	13.4	6	7.23

n Number of patients; X mean, SD standard deviation, *myocardial infarction, unstable angina, coronary surgery.

**stroke, ischemic transient attacks; ***CM consumed by > 6 % of study patients. All comparisons were not significant

Table 2: Withdrawal analysis of study

Withdrawals due to AE	Placebo (n=67)	Policosanol (n=83)	p value*	Total

Withdrawals due to vascular SAE	10	2	p<0.01	12
Withdrawals due to SAE from other causes	3	0		3
Subtotal due to SAE	13	2	p<0.01	15
Withdrawals due to mild and moderate AE	1	0		1
Subtotal due to all AE	14 (19.4)	2 (4.6)	p<0.01	16
Withdrawals due to other reasons				
Unsatisfactory efficacy	4	0	p<0.05	4
Travels abroad + changes to other towns	2	0		2
Unwillingness to follow-up	0	2		2
Protocol violations	1	2		3
Subtotal due to other reasons	7 (10.4)	4 (4.8)	ns	1 (7.3)
Total of withdrawals	21 (29.3)	6 (7.2)	p<0.05	2 (18.0)

*Comparison with placebo ($\chi 2$ test)

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

Treatment	Baseline	1 year	2 years	3 years
Total cholesterol (mmol/L)				
Policosanol	6.81 ± 0.85	5.39 ± 0.66^{++}	5.27 ± 0.66^{+++}	5.33 ± 0.74^{+++}
Placebo	6.56 ± 0.79	6.56 ± 0.80	6.53 ± 0.75	6.48 ± 0.75
LDL-C (mmol/L)				
Policosanol	4.73 ± 0.91	3.59 ± 0.67^{++}	3.31 ± 0.60^{+++}	3.22 ± 0.70^{+++}
Placebo	4.54 ± 0.89	4.51 ± 0.95	4.61 ± 0.80	4.63 ± 0.77
HDL-C (mmol/L)				
Policosanol	1.21 ± 0.32	1.28 ± 0.24^{+}	1.36 ± 0.29^{++}	1.43 ± 0.28^{+++}
Placebo	1.18 ± 0.29	1.16 ± 0.30	1.17 ± 0.18	1.16 ± 0.17
Triglycerides (mmol/L)				
Policosanol	2.28 ± 0.79	1.79 ± 0.49^{++}	1.80 ± 0.34^{++}	1.80 ± 0.24^{+++}
Placebo	2.31 ± 1.13	2.25 ± 0.77	2.24 ± 0.54	2.26 ± 0.68

X mean, SD standard deviation, $^{+}p < 0.05$; $^{++}p < 0.01$; $^{+++}p < 0.001$, ANOVA test

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

Treatment	Baseline	1 year	2 years	3 years
Weight (kg)				
Policosanol	65.43 ± 10.83	65.79 ± 10.80	65.73 ± 10.97	65.58 ± 10.89
Placebo	65.04 ± 13.36	66.06 ± 12.14	66.30 ± 11.99	65.71 ± 12.11
Pulse (beats/min)				
Policosanol	72.32 ± 6.32	72.05 ± 5.99	72.80 ± 5.06	72.47 ± 4.06
Placebo	71.37 ± 5.70	72.04 ± 6.96	71.37 ± 4.34	71.63 ± 5.86
Diastolic pressure (mm Hg)				
Policosanol	79.88 ± 9.03	79.87 ± 5.33	78.53 ± 6.08	79.80 ± 6.78
Placebo	80.45 ± 8.60	81.12 ± 6.56	80.53 ± 6.10	80.75 ± 5.72
Systolic pressure (mm Hg)				
Policosanol	131.8 ± 16.32	127.4 ± 11.04	127.7 ± 11.6	127.6 ± 13.35
Placebo	131.6 ± 15.55	133.4 ± 12.92	130.3 ± 9.81	130.0 ± 11.98
ALT (U/L)				
Policosanol	19.66 ± 9.25	18.70 ± 8.70	18.90 ± 7.32	19.28 ± 8.84
Placebo	21.82 ± 9.64	22.30 ± 8.25	21.96 ± 6.49	23.14 ± 4.44
AST (U/L)				
Policosanol	22.10 ± 8.25	20.88 ± 6.46	20.73 ± 7.45	20.68 ± 7.25
Placebo	24.36 ± 7.91	22.78 ± 8.54	23.02 ± 6.24	21.20 ± 4.56
Creatinine (μmol/L)				
Policosanol	88.43 ± 20.02	88.82 ± 12.48	88.03 ± 11.77	88.78 ± 10.60
Placebo	90.22 ± 17.23	90.82 ± 16.72	90.19 ± 12.38	89.83 ± 13.40
Glucose (mmol/L)				
Policosanol	5.49 ± 0.93	5.40 ± 1.46	5.37 ± 1.274	5.29 ± 0.76
Placebo	5.72 ± 1.56	5.64 ± 1.44	5.63 ± 1.52	5.56 ± 0.85

X mean, SD standard deviation ALT alanin amino transferase, AST aspartate amino transferase.
All comparisons were not significant

Table 5: Adverse events in study patients

	Placebo (n = 67)		**Policosanol (n = 83)**	
Serious adverse events (SAE)	N	%	n	%
All cardiovascular SAE	7	9.0	1	1.5^{+}
All cerebrovascular SAE	3	4.5	1	1.5

All vascular SAE	10	13.4	2	2.4^{++}
All SAE (fatal + non-fatal)	13	17.9	2	2.4^{++}
Fatal SAE (Deaths)				
Deaths to vascular causes	3	4.5	0	0.0
Deaths to non-vascular causes	1	1.5	0	0.0
All deaths	4	6.0	0	0.0^{+}
Patients with moderate and mild AE	20	29.9	8	9.6^{+}

$^{+}p < 0.05$, $^{++}p < 0.01$ Comparison with placebo ($\chi 2$ test)

Discussion

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

The present analysis demonstrates that policosanol administered to elderly patients taking vitamins no affecting any safety indicator or increasing the report of adverse events. In addition, the efficacy of policosanol was consistent with that expected.

Both groups were comparable at baseline, which supports their homogeneity. The mean age of study patients was around 67 years at baseline, being still young for preventive measures and related effects on life quality and expectancy. The larger proportion of women is a characteristic of the patients attending to the Policlinics [44] who are also more motivated to participate in clinical studies than men.

The frequency of concomitant medications was high, which is characteristic in the elderly. Taking into account this fact the analyses here reported are not related with a population only treated with vitamins and placebo or vitamins and policosanol, but receiving other therapies. The other concomitant drugs consumed by patients were well matched in both groups and those most frequent were consistent with the risk condition of study patients.

The present results support that policosanol efficacy is evident also in older patients taking vitamins and are consistent with previous report of the concomitant use of policosanol and others drugs [36, 40].

Thus, policosanol lowered LDL-C, the primary efficacy variable, total cholesterol and triglycerides, while raised HDL-C levels. The responses were maintained, or even enhanced, throughout the study. The changes here reported for LDL-C; total cholesterol and HDL-C are consistent with the expected response to policosanol long-term therapy, but reductions on triglycerides, however, were superior that those reported in previous studies, a finding without any conclusive explanation. No significant change of any lipid profile variable occurred in placebo group.

The different withdrawal rate in both groups was a consequence of the discontinuations due to serious adverse events and those due to unsatisfactory efficacy for achieving levels over those considered as upper cut-off for premature discontinuations. Thus, the frequency of all vascular serious adverse events, cardiovascular, cerebrovascular, all deaths to vascular causes and all deaths was lower ($p<0.05$) than in placebo, consistently with LDL-C lowering and pleiotropic effects of policosanol, all beneficial for vascular function, thus preventing the occurrence of vascular events.

Policosanol was very well tolerated in elderly hypercholesterolemic patients consuming vitamins, similar to other studies in the elderly [22, 30], and to studies of concomitant use of policosanol and others drugs [36, 40].

The frequency of serious adverse events was lower in policosanol than in placebo, suggesting that policosanol can contribute to reduce the risk of older patients consuming vitamins. Policosanol did not increase the frequency of adverse events compared with placebo, thus minimizing any potential risk derived from the concomitant use of policosanol and vitamins, even in older patients at high coronary risk, highly medicated with concomitant therapy and sensitive to drug-related adverse events and drug/drug interactions.

Conclusions

It is concluded that policosanol therapy added to older hypercholesterolemic patients taking vitamins produced relevant benefits on lipid profile and the frequency of serious adverse events respect to placebo, then indicated concomitant with vitamins in elderly, without increase any adverse event.

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