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Sugar cane policosanol failed to lower plasma cholesterol in primitive, diet-resistant hypercholesterolaemia: A double blind, controlled study

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Summary Previous clinical studies have shown that oral administration of sugar cane policosanol (SCP) reduces plasma total cholesterol and low-density lipoprotein cholesterol levels. A double blind, randomized, placebo controlled trial was performed in hypercholesterolaemic, diet-resistant patients. Seventy patients meeting the selection criteria were enrolled. Each subject was treated with policosanol 10 mg/d in addition to a dietetic regimen for 8 weeks. At the start and at the end of the study body weight, body mass index (BMI), total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides (TG) plasma levels were measured. Thirty-three subjects in the policosanol and Thirty-one subjects in the control group completed the study. During the study body mass index, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides plasma levels did not change significantly within and between groups. In conclusion, sugar cane policosanol at a dose of 10 mg/d showed no lipid lowering effects in subjects with primitive, diet-resistant hypercholesterolaemia.

Introduction

Policosanol is a mixture of long-chain aliphatic primary alcohols (C24 to C34) originally isolated from sugar cane (*Saccharum officinarum* L.) wax.[1,2] The mixture can also be extracted from a variety of other natural sources such as bee wax, rice bran and wheat germ.[3,4] The major components of the mixture are octacosanol (60—70%, w/w), triacosanol (10—15%, w/w) and hexacosanol (4—10%, w/w). Previous clinical studies have shown that oral administration of sugar cane policosanol (SCP) within a range 5—20 mg/d reduces plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and increases high-density lipoprotein cholesterol (HDL-C) in healthy, hypercholesterolaemic and diabetic patients.[5—8] Reports comparing SCP with statins show the same efficacy in LDL-C lowering, whereas policosanols have a greater efficacy than statins in increasing HDL-C.[9—12] The

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mechanisms by which policosanol improves plasma lipid profile are unclear. It has been suggested that policosanol has an effect on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol synthesis.[13–16] Toxicological studies in animal models have not demonstrated any adverse effects.[17–21]

Most of the published clinical studies on SCP have been conducted only by one research group and have not been confirmed by other laboratories in different populations. Despite this, policosanol is successful in world-wide markets and is sold as a lipid-lowering supplement in more than 40 countries.[22]

The objective of this study was to investigate the effects of SCP on the serum lipid profile in adults with primitive, diet-resistant hypercholesterolaemia.

Materials and methods

Subjects and study design

This study was conducted in the Clinical Nutrition Unit, Azienda Ospedaliera of Padua, Italy. We screened all patients consecutively admitted to the Clinical Nutrition Unit from March 2005 to March 2006 for primitive hypercholesterolaemia who obtained an LDL-C reduction lower than 0.3 mmol/L after normocaloric diet treatment, according to the *National Cholesterol Education Program Adult Treatment Panel III*.[23]

Inclusion criteria were the following: age between 20 and 60 years, body mass index (BMI) between 18 and 27 kg/m^2, LDL-C serum levels between 4.0 and 5.2 mmol/L. Exclusion criteria included history of cardiovascular disease, more than two cardiovascular risk factors, triglycerides (TG) serum levels above 2.5 mmol/L, pregnancy, lactation and the use of lipid-lowering drugs or estroprogestinic preparations in the last 6 months.

This study was a double blind, randomized, placebo controlled trial (Fig. 1). Seventy patients meeting the selection criteria were randomized. A computer-derived random allocation sequence, without blocking or stratification, performed the randomization. Thirty-five patients were allocated in each group. BMI, age and sex distribution did not differ significantly between two groups at the start of the study.

The trial lasted 8 weeks. Each subject received 56 tablets in a vial labeled with the blinded code. The patients were instructed to assume one tablet after dinner. They were asked to continue their usual lifestyle and normocaloric diet regimen for 8 weeks. At the start and at the end of the study, body weight, TC, HDL-C, LDL-C and TG plasma level were measured and an interview was performed in order to check the adherence to the dietetic protocol.

Calculation of the sample size was performed by a power analysis based on an expected reduction in serum LDL-cholesterol levels of 20%, as observed in a previous study.[24] To achieve 80% power of detecting such a difference (at a two-sided significance level of 5%) 30 subjects were needed to be randomly assigned into the study.

The protocol was in accordance with the Helsinki Declaration of 1975 as revised in 1983. Each subject provided written informed consent before protocol-specific procedures were performed.

Test and placebo tablets

The Polico 10 test tablets containing 10 mg of aliphatic primary alcohol mixture from Cuban sugar cane wax (Dalmer Laboratories S.p.A., Havana; Cuba) were supplied by BF Pharma S.p.A. (Fossano, Italy). The placebo tablets were similar in appearance to the supplement but contained only calcium phosphate, calcium carbonate and magnesium stearate.

Laboratory analysis

Blood samples for biochemical assays were collected between 08.00 and 10.00 a.m. from the antecubital vein after a 12 h overnight fast. Plasma, separated immediately by centrifugation for 10 min at 3000 rpm, was divided into aliquots and stored at −20 °C. Serum TC and TG level were measured using CHOD-PAP kits and GPO-PAP kits, respectively (Roche Diagnostics, Mannheim, Germany). HDL-C was measured after precipitation of low-density lipoproteins and very-low-density lipoproteins with phosphotungstate and magnesium. Plasma LDL-C was calculated using the Friedewald equation.[24]

Statistical analysis

The differences of means within groups and between groups were determined with the *t*-test for dependent and independent variables. A *P* value less than 0.05 was considered

Figure 1 Flow participants through the trial.

Table 1 Clinical characteristics of subjects who concluded the study

	Policosanol group (mean ± S.D.)	Control group (mean ± S.D.)
Males	11	14
Females	22	17
Age (years)	48 ± 5	53 ± 6
BMI	23.9 ± 1.1	23.7 ± 1.2

statistically significant. The computer software STATISTICA (StatSoft®), Version 7, was used for analysis.

Results and discussion

Thirty-three subjects in the policosanol and 31 subjects in the control group completed the study. One subject in policosanol group and one in the placebo group were excluded because they had discontinued the diet treatment and had gained more than 3 kg by the end of the study. One patient in the policosanol group and three patients in the placebo group dropped out of the study for personal reasons.

The clinical characteristics of the patients who concluded the study are shown in Table 1. Over the 8 weeks, neither the supplementation with policosanol nor the placebo significantly changed BMI, TC, LDL-C, HDL-C or TG when compared to baseline values and when compared between groups (Table 2). Compliance with the treatment was very good in both groups and no participant dropped out for adverse effects. Headache was reported in two cases in the policosanol group and in one case in the placebo group, nevertheless the subjects continued the study.

In this double blind, randomized, placebo controlled study the supplementation with 10 mg/d SCP for 8 weeks did not show any effect on plasma lipid levels in adults with primitive, diet-resistant hypercholesterolaemia. We excluded diet-confounding effects. BMI did not change within groups and all subjects followed the same nutritional regimen. Our results are in contrast to previous studies that have demonstrated the efficacy of SCP as a cholesterol-lowering agent most of which have been conducted by the same cardiovascular center with populations from Cuba and Central or South America.[25] The dose of policosanol employed in human studies has ranged between 2 and 40 mg/d.[26] Some authors have shown a significant reduction of plasma cholesterol at doses of 5 and 10 mg for 5 weeks (6) and 8 weeks (5), respectively. It has been reported that sugar cane policosanol in humans lowers plasma cholesterol to the same extent that statins do.[9,12,16] Dalmer Laboratories, a Cuban commercial enterprise which markets policosanol, funded almost all of these studies. Unlike statins, which inhibit the rate-controlling enzyme in cholesterol biosynthesis, the 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase, the mechanism of the putative effect of SPC is still unclear. It has been suggested that policosanol does not effect HMG-CoA reductase activity but that it might down-regulate its cellular expression.[27] In a recent study, Singh et al. observed that policosanol in cultured rat hepatoma cells increased AMP-kinase phosphorilation, decreasing HMG-CoA reductase activity.[28]

Many products are available today as ''policosanol'', extracted by sources other than sugar cane. Their composition in long-chain aliphatic primary alcohols, which differs little among the different sources,[29] may affect their efficacy in improving the lipid plasma profile. Octacosanol is the main aliphatic primary alcohol in the policosanol mixture and it is thought to be the most active component. Some studies, performed by researchers other than those of the Cuban center, using mixtures containing an amount of octacosanol similar to that in sugar wax policosanol, failed to demonstrate any improvement of the lipid profile. Rice and sugar wax policosanol did not show

Table 2 Plasma lipids and BMI in policosanol ($n = 33$) and control ($n = 31$) groups

	Policosanol group (means ± S.D.)	*P* value (within group)	Placebo group (means ± S.D.)	*P* value (within group)	*P* value (between groups)
Total cholesterol (mmol/L)					
Baseline	6.64 ± 0.73	0.93	6.68 ± 0.66	0.62	0.69
8 weeks	6.63 ± 0.71		6.63 ± 0.68		
LDL-C (mmol/L)					
Baseline	4.53 ± 0.66	0.86	4.46 ± 0.61	0.93	0.94
8 weeks	4.52 ± 0.69		4.57 ± 0.72		
HDL-C (mmol/L)					
Baseline	1.50 ± 0.32	0.15	1.50 ± 0.28	0.32	0.66
8 weeks	1.57 ± 0.34		1.53 ± 0.29		
Triacylglycerol (mmol/L)					
Baseline	1.40 ± 0.52	0.68	1.40 ± 0.55	0.82	0.69
8 weeks	1.41 ± 0.55		1.38 ± 0.55		
BMI					
Baseline	24.03 ± 1.10	0.07	23.88 ± 1.2	0.09	0.66
8 weeks	23.98 ± 1.03		23.84 ± 1.2		

LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol.

significant effects on lipid profile in hamster[4]; sunflower and sugar cane policosanol demonstrated a lack of effect on plasma cholesterol in rabbits.[30] In humans, Lin et al. demonstrated that wheat germ policosanol at 20 mg/d, administered in the form of chocolate pellets, had no beneficial effects on blood lipid profiles, although chemical analysis found a similar composition in the long-chain aliphatic alcohols of cane sugar and those in wheat germ policosanol (octacosanol 67%, triacosanol 12% and hexacosanol 8%, w/w).[31] Minor components in the mixture of aliphatic primary alcohols might be effective in cholesterol lowering but this is very unlikely. Moreover, policosanols are not well absorbed in the intestine of the terrestrial organisms[22] and if the minor components are really effective, they would need to have a portentous lipid lowering effect.

In this study we employed a product marketed by an Italian company and supplied by Dalmer Laboratories, the originally patented Cuban manufacturer. Recently two European studies investigating the Cuban SCP effects on lipid profile have been published. Greyling et al. found no significant effect using 20 mg/d sugar cane policosanol for 12 weeks in heterozygous familiar hypercholesterolaemic subjects.[29] In other hypercholesterolaemic subjects they showed a small reduction of TC (6%) and LDL-C (9%) from baseline levels, but these changes did not differ significantly from placebo. Berthold et al. published the results of a multicenter trial conducted in Germany from 2000 to 2001 on patients with hypercholesterolaemia and combined hyperlipidemia. In this study Cuban SCP at doses of 10, 20, 40 and 80 mg/d for 12 weeks did not demonstrate a reduction in lipid levels beyond placebo.[22] Policosanol enriched margarin at dose of 10 mg of SCP/d did not show beneficial effects on lipid profile in hypecholesterolemic Canadian subjects.[32] In a controlled, double blind study 20 mg/d of SCP for 8 weeks did not alter the serum lipid profile in North American adults with mild hypercholesterolaemia.[33] Ethnic and environmental factors are unlikely to explain the differences among Cuban and other studies. Diet and other lipid lowering agents, such as statins and ezetimibe, have been shown to have similar effects in different populations.[34–36]

In conclusion, SPC at a dose of 10 mg/d for 8 weeks showed no lipid lowering effects in subjects with primitive, diet-resistant hypercholesterolaemia. Although many authors have supported the policosanol lipid-lowering activity, our data confirm recent animal and clinical studies, which showed the lack of efficacy of SCP in improving lipid profiles. Therefore, we believe that policosanol supplementation is useless for people with hypercholesterolaemia.

Conflicts of interest

Authors do not have any conflict of interest.

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