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Rice Policosanol Does Not Have Any Effects on Blood Coagulation Factors in Hypercholesterolemic Patients

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A B S T R A C T

Policosanol is an agent that includes mixtures of aliphatic primary alcohols extracted primarily from sugercane wax. Policosanol has been shown to lower total and LDL cholesterol in animal models, healthy volunteers and hypercholesterolemic patients. However, these findings have been challanged recently. Up to now, there has been no study investigating the effects of policosanol on blood coagulation factors.This study investigated the effects of rice policosanol (Oryza sp.) 10 mg/day on blood coagulation factors in 66 hypercholesterolemic patients of both sexes aged 20 to 78 years in a single center, randomized, double-blind, placebo-controlled, crossover trial. After an 8-week run-in period in which patients were placed on therapeutic lifestyle changes, in particular a cholesterol-lowering diet, they were randomly assigned to receive rice policosanol 10 mg tablets or placebo tablets once daily with the evening meal for 8 weeks. During next 8 weeks those receiving policosanol during the first 8 weeks, received placebo and those taking placebo during the first 8 weeks, received policosanol. Plasma fibrinogen, factors VII,VIII, XII and XIII were measured before and after the treatment. Rice policosanol treatment did not change significantly neither fibrinogen nor factors VII,VIII, XII and XIII.

***Key words**: policosanol, hypercholesterolemia, fibrinogen, factor VII, factor VIII, factor XII, factor XIII*

Introduction

Policosanol is a natural mixture of long-chain primary aliphatic alcohols extracted primarily from sugarcane (Saccharum officinarum L) wax. Its main components are octacosanol (62.9%), triacontanol (12.6%) and hexacosanol (6.2%).[1] Sugarcane policosanol has been reported to lower total and LDL-cholesterol in healthy volunteers[2] and in patients with hypercholesterolemia of all ages[3–8] as well as to increase slightly HDL-cholesterol[3,5,10]. The results of several trials with sugar cane policosanol even suggested similar efficacy with established lipid-lowering drugs, such as statins.[7,11–13] Other effects attributed to policosanol are antithrombotic and antioxidant actions.

We have recently shown that rice policosanol has much fewer effect on total cholesterol and no significant effect on LDL-cholesterol, HDL-cholesterol, triglycerides, Ox-LDL, HDL2-cholesterol, HDL3-cholesterol, apoprotein B, lipoprotein (a), homocysteine and C-reactive protein.[14]

Since so far there were no trials investigating the effects of policosanol from any origin on blood coagulation factors, the aim of this study was to investigate the effects of rice policosanol on plasma fibrinogen, and blood coagulation factors VII, VIII, XII and XIII.

Patients and Methods

Patients and study design

66 patients of both sexes (23 males and 43 females) age range 20 to 78 years (median age 53 years) with a documented type II a or II b hypercholesterolemia who were not taking any antiplatelet or anticoagulation drug therapy participated in the study. A randomized, double-blind, placebo-controlled, crossover study design in two phases was used at intervals of 8 weeks. A complete medical history was taken and a physical examination

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was performed prior to the study in all patients. The eligibility characteristics of patients were assessed during an 8 week dietary (American Heart Association/National Cholesterol Education Program step 1 diet) baseline period prior to randomization, while the participants were off all lipid-lowering medications. The same diet was maintained throughout the treatment period. For patients who were not treatment-naive, a 8-week wash-out period for all classes of lipid-lowering treatment was mandatory prior to start of the dietary run-in.

All participants provided written informed consent, and the study was approved by the Ethics committee of the University Hospital Center Zagreb, Croatia.

The lipid entry criteria were: total cholesterol of ≥ 5 mmol/L (190 mg/dL) to 10 mmol/L (390 mg/dL) and/or LDL-cholesterol of ≥ 3 mmol/L (110 mg/dL) to 8 mmol/L (310 mg/dL). Triglyceride concentration had to be ≥2 mmol/L (180 mg/dL) to 10 mmol/L (890 mg/dL). All but two subjects were nonsmokers.

The exclusion criteria were: increased alcohol consumption (>21 units per week), unregulated diabetes, obesity (body mass index >30), pregnant or lactating women, clinical hypo- or hyperthyroidism, clinical liver or renal disease, chronic or acute pancreatitis, former or present malignant disease, autoimmune diseases, history of myocardial infarction, angioplasty or other major surgery within 6 months prior to entry, antiplatelet or anticoagulation drug therapy.

After randomization the subjects were instructed to take identical 10 mg placebo capsule or 10 mg rice policosanol (Oryza sp.) wax capsule once daily with their evening meal for 8 weeks. During next 8 weeks those receiving policosanol during the first 8 weeks, received placebo and those taking placebo during the first 8 weeks, received policosanol. Drug compliance was assessed by tablet count and interviews with the patients.

Laboratory analysis

Laboratory tests were performed at the beginning of the study, after the diet period, i.e. before taking the capsules, after the first 8 weeks of treatment and after the second 8 weeks of treatment. The following parameters were measured: total cholesterol, LDL cholesterol, HDL cholesterol, triglycericerides, fibrinogen, blood coagulation factors. All blood samples were drawn between 8:00 AM and 9:00 AM after an overnight fast of 12 hours, and aliquots were obtained for laboratory determinations.

Serum concentrations of cholesterol and triglycerides were measured by standard enzymatic methods using commercial kits from Boehringer Mannheim Diagnostica. Serum concentration of HDL cholesterol was measured after precipitation with phosphotungstic acid and magnesium chloride.[15] Fibrinogen was measured by coagulometry[16], factors VII, VIII and XII by coagulometry using Innovin and Actin FS[17], and factor XIII by photometry using a chromogenic substrate – Berichrom Heparin, Dade Behring.[18]

Statistical analysis

The validity of crossover design was checked on HDL cholesterol. The results showed acceptable validity of crossover design (period effect: t=0.30; df=65; p=0.768 and treatment-period interaction: t=1.36; df=65; p= 0.178).

All data were analyzed according to the intent-to-treat principle; thus, available data from patients who withdrew from the study were included in all analyses.

Results

After the 8-week diet-only period 70 of 78 patients initially recruited were included in the study; of these 66 completed the study. The reasons for withdrawals were unwillingness to follow up during the placebo period and change of residence during the treatment period. Compliance as assessed by capsules count and patient interviews was >95%.

Rice policosanol 10 mg /day did not significantly reduce plasma neither fibrinogen, nor coagulation factors VII, VIII, XII and XIII (Table 1).

TABLE 1
EFFECT OF RICE POLICOSANOL ON SOME BLOOD COAGULATION FACTORS

Parameter	N	Baseline	After treatment	p – Value
Fibrinogen	66	3.89±0.78	3.90±0.96	0.356
Factor VII	65	1.14±0.27	1.16±0.33	0.653
Factor VIII	65	1.85±0.67	1.86±0.56	0.769
Factor XII	64	1.09±0.30	1.07±0.31	0.455
Factor XIII	66	1.23±0.23	1.27±0.23	0.188

Data are given as mean±SD

With regards to the effects of policosanol treatment on safety parameters, no significant differences from baseline values were observed for systolic or diastolic blood pressure, glucose, creatinin, bilirubin, serum aminotransferases or CK.

Discussion

This study demonstrates that rice policosanol administered at the dose of 10 mg daily does not have any significant effect on fibrinogen or blood coagulation factors. Rice policosanol treatment did not result in any adverse effects as indicated by reports of the patients, physical examinations and plasma activities of glucose, creatinin, bilirubin, AST, ALT,GGT and CK.

Despite very optimistic results of about 30 trials published virtually all by a single research group from Cuba, showing significant lipid lowering effects of sugercane policosanol, four recent studies have challanged these findings.[19–22] In a randomised, double-blind, placebo-con-

trolled study we have also recently shown that rice policosanol (Oryza sp.) has much fewer effect on total cholesterol than claimed by the Cuban authors for sugercane policosanol, and no significant effect on LDL-cholesterol, HDL-cholesterol and triglycerides as well as no effect on Ox-LDL, HDL2 cholesterol, HDL3 cholesterol, apoprotein B, lipoprotein (a), homocysteine and C-reactive protein.[14] A clinical trial performed with wheat germ-derived policosanol could also not find any significant effects on total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides.[23]

Up to now, there has been no study demonstrating significant efficacy of policosanol from any origin on clinical cardiovascular disease (CVD) endpoints. Only two Cuban studies with sugarcane policosanol demonstrated an improvement of initial and absolute claudication distance.[24,25]

It is well known that conventional risk factors such as hypercholesterolemia do not fully account for the occurrence of atherothrombotic vascular disease. Haemostatic factors associated with biological systems regulating platelets, coagulation and fibrinolysis seem to be closely associated with the development of coronary heart disease (CHD) and cardiovascular events such as myocardial infarction (MI) and stroke. For example increased fibrinogen seems to be associated not only with CHD[26–31] but also with peripheral vascular disease[32] and stroke.[33] The association of coagulation factors and cardiovascular diseases remains incompletely understood.

F VII is an initiator of extrinsic blood coagulation. F VII clotting activity, despite initial observations that it might be a risk factor for CHD, especially in the presence of other risk factors[34], at least seems not to be a factor independent of other risk factors. [28,29] However, several authors have not proved any significant changes of F VII in patients with CHD[31] or any relationship between F VIIc levels and severity of atheroma.[35]

F VIII seems to be associated with CHD and mortality in men, as well as with stroke and transitory ischaemic attacks (TIA) in women.[36–38] An association of F VIII antigen but not F VIII coagulation activity with MI has been also noticed.[39]

F XII is an initiator of intrinsic blood coagulation. It is activated in contact with various biologic surfaces, including subendothelial tissues and lipoprotein particles which suggests its possible role in atherothrombosis. It has been shown that activated F XII (F XIIa) is involved in vascular injury and repair, participating in inflammation, thrombosis and fibrinolysis. Although it is under strong genetic control it reflects plasma triglycerides and endothelial activation/dysfunction. Some authors have found that F XII could predict recurrent coronary events after MI[40] and that plasma F XIIa, which is an initial product of contact activation, is increased in men at high risk of CHD.[41] Others claim that F XII is not a predictor of coronary events and has no relationship with CHD whatsoever.[42,43] Anyhow, F XIIa appears unlikely to be directly atherogenic. However, TT genotype of F XII 46C> T polymorphism, which determines FXII levels, seems to be associated with a high CHD risk in subjects with hypercholesterolemia.[44]

There are few studies indicating that higher F XIII levels might be associated with increased risk of MI.[45,46] On the other hand, it has been observed that F XIII Val 34 Leu polymorphism is associated with a significant protective effect against the occurrence of MI.[47]

There are no data in the literature on possible effects of policosanol on blood coagulation factors. Only two studies performed with sugarcane policosanol indicated that this substance might induce modest reduction of fibrinogen.[13,25] We could not confirm such an effect with rice policosanol neither could we prove any effect of rice policosanol on the investigated coagulation factors.

Conclusion

We can conclude that rice policosanol 10 mg/day does not have any significant effect on plasma fibrinogen, coagulation factors VII,VIII, XII and XIII.

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POLIKOZANOL IZ RIŽE NEMA NIKAKVIH UČINAKA NA ČIMBENIKE ZGRUŠAVANJA KRVI U BOLESNIKA S HIPERKOLESTEROLEMIJOM

S A Ž E T A K

Polikozanol je mješavina alifatskih primarnih alkohola koja se poglavito ekstrahira iz šećerne trske. Pokazano je da polikozanol smanjuje ukupni i LDL kolesterol u pokusnih životinja, zdravih dragovoljaca i bolesnika s hiperkolesterolemijom. Međutim, nedavno je to dovedeno pod znak sumnje. Do danas još nije načinjeno istraživanje u kojem bi se ispitali učinci polikozanola na čimbenike zgrušavanja. U ovom su istraživanju ispitani učinci polikozanola iz riže (Oryza sp.) u dozi od 10 mg/dan na čimbenike zgrušavanja u 66 bolesnika oba spola s hiperkolesterolemijom starih između 20 i 78 godina. To je randomizirano, dvostruko slijepo, placebom kontrolirano, križno ispitivanje provedeno u jednom centru. Nakon razdoblja od 8 tjedana tijekom kojih su se bolesnici pridržavali promijenjenog načina života, poglavito dijete za snižavanje kolesterola u krvi, randomizirani su da uzimaju kapsule sa 10 mg polikozanola ili placeba jednom dnevno uz večernji obrok tijekom 8 tjedana. Tijekom slijedećih 8 tjedana oni koji su prvih 8 tjedana uzimali polikozanol, uzimali su placebo i obratno, oni koji su prvih 8 tjedana dobivali placebo, uzimali su polikozanol. Prije i nakon liječenja određivani su im fibrinogen, te čimbenici zgrušavanja VII,VIII, XII i XIII u plazmi. Uzmanje polikozanola iz riže nije uzrokovalo nikakve značajnije promjene ni fibrinogena ni čimbenika VII,VIII, XII i XIII.