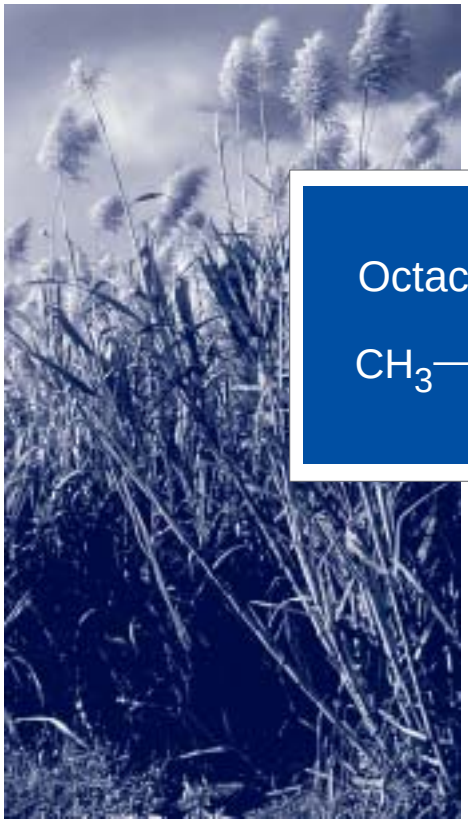

Saccharum offinarum (Sugar Cane) Harold St.John photo

Octacosanol

$CH_3—(CH_2)_{27}—OH$

Policosanol

Introduction

Policosanol, an extract from sugar cane (*Saccharum officinarum* L.), has been heavily researched in Cuba in several human populations for its cholesterol-lowering properties. In addition to improving serum lipids, policosanol reduces LDL oxidation, decreases platelet aggregation, decreases smooth muscle proliferation, and improves symptoms of cardiovascular disease. Side effects are virtually non-existent.

Biochemistry

Cuban-manufactured policosanol is a mixture of alcohols isolated and purified from sugar cane. It consists of 66-percent octacosanol (CH_3-CH_2(26)-CH_2-OH), 12-percent triacontanol, and 7-percent hexacosanol. Other alcohols (15%), namely tetracosanol, heptacosanol, nonacosanol, dotriacontanol, and tetratriacontanol, are minor components.[1]

Mechanisms of Action

Policosanol appears to cause decreased synthesis and increased degradation of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA), the rate-limiting step in cholesterol synthesis.[2,3] This is different than the mechanism of action of statin drugs, which work by competitively inhibiting HMG-CoA. Policosanol has also demonstrated improvement in LDL metabolism by increasing LDL binding, uptake, and degradation in human fibroblasts.[4]

LDL oxidation is thought to be a necessary step in the development of atherosclerosis. Studies on humans and rats show policosanol decreases *in vitro* LDL oxidation using multiple oxidation models.[5,6] Another step in the formation of atherosclerotic plaques is an increase in smooth muscle proliferation. In rabbits, policosanol decreased neointimal formation, indicating decreased smooth muscle cell proliferation.[7] In a comparative study, policosanol demonstrated a greater effect than lovastatin on neointimal formation.[8]

Policosanol decreases platelet aggregation by decreasing the synthesis of platelet-aggregating thromboxane B2 (TXB2), with no effect on prostacyclin (PGI2).[9] Studies demonstrate policosanol reduces platelet aggregation induced by a number of experimental substances,[9-14] with dose-dependent increases from 10-50 mg/day. Policosanol alone at 20 mg/day was more effective than 100 mg aspirin at reducing platelet aggregation induced by ADP, and equally effective when induced by epinephrine and collagen.[13] Despite decreased platelet aggregation, there was no increase in coagulation time when policosanol was taken alone; however, when combined with 100 mg/day aspirin, coagulation time increased.

Clinical Indications

Hypercholesterolemia

The majority of policosanol research is on patients with type II hypercholesterolemia. Fifteen randomized, placebo-controlled, double-blind studies have shown positive results.[15-29] Significant decreases in total cholesterol (TC) (8-23%), LDL (11.3-27.5%), LDL/HDL (15.3-38.3%), and TC/HDL (9.1-30.5%) were observed in all trials. Of the 13 trials measuring HDL, seven showed significant increases and in six HDL was unchanged. Doses ranged from 2-40 mg/day, with decreases in TC, LDL, LDL/HDL, and TC/HDL and increases in HDL being dose-dependent up to 20 mg/day, with no further benefit at 40 mg/day. However, 40 mg/day significantly decreased triglycerides (TG), which was not seen with lower doses.[28]

Policosanol was effective in three studies on patients with type 2 diabetes mellitus and hypercholesterolemia.[30-32] All three trials used 5 mg twice daily for 12 weeks. Total cholesterol was reduced by 14-29 percent, LDL was reduced by 20-44 percent, LDL/HDL ratio was reduced by 24-52 percent, and HDL was increased by 8-24 percent. No adverse effect on glycemic control was noted in any of the studies. In trials comparing policosanol with lovastatin (20 mg/day), policosanol performed significantly better at raising HDL and lowering the LDL/HDL ratio.[32, 33]

Two studies with a total of 300 patients indicate policosanol is effective in postmenopausal women with hyperlipidemia.[34,35] Both studies started with 5 mg daily, which was later increased (at week 8 in one study[34] and week 12 in the other[33]) to 10 mg daily for a period of eight or 12 more weeks. At the end of the 5-mg portion, TC, LDL, LDL/HDL, and TC/HDL decreased by 13-20 percent, 17-18 percent, 17.0-17.2 percent, and 16.3-16.7 percent, respectively, whereas HDL was unchanged in one trial and increased by 16.5 percent in the other. At the end of the 10-mg/day period policosanol supplementation resulted in decreased TC, LDL, LDL/HDL, and TC/HDL by 17-20 percent, 25-28 percent, 27-30 percent, and 21-27 percent, respectively, and increased HDL 7-29 percent. Significantly more side effects were seen in the placebo group in each trial.

In comparative trials policosanol generated lipid profiles similar to simvastatin,[36,37] pravastatin,[10,38] lovastatin,[32,35,39] probucol,[40] acipimox,[41] and atorvastatin.[42] First, two trials on patients with type II hypercholesterolemia, comparing low dose simvastatin (5 or 10 mg/day) and moderate dose policosanol (5 or 10 mg/day), demonstrated that both substances greatly improved lipid profiles with no significant differences in results or side effects between the groups.[36,37] Second, policosanol (10 mg/day) compared favorably to low-dose pravastatin (10 mg/day) in patients with type II hypercholesterolemia in two studies.[10,38] In one trial, policosanol-treated patients had significantly greater decreases in LDL, LDL/HDL, TC/HDL, and increases in HDL,[38] while in another trial policosanol-treated patients had significantly greater increases in HDL.[10] The pravastatin group had more side effects in both studies. A study comparing policosanol to lovastatin in patients with type 2 diabetes and hypercholesterolemia (type II) found policosanol (10 mg/day) is more effective at lowering LDL/HDL and increasing HDL than 10 mg/day lovastatin, with significantly fewer side effects.[32] In addition, in patients with type II hypercholesterolemia and concomitant coronary risk factors, policosanol (10 mg/day) decreased LDL/HDL and increased HDL more effectively than 20 mg/day lovastatin, with fewer side effects.[39] Policosanol (5 mg twice daily) also compared favorably to probucol (500 mg twice daily) at reducing TC, LDL, and TG in patients with type II hypercholesterolemia.[40] Again, policosanol (10 mg/day) compared favorably to acipimox (750 mg/day), a niacin derivative, in regard to TC, LDL, LDL/HDL, TC/HDL, and HDL, with fewer side effects.[41] Lastly, policosanol was significantly less effective than atorvastatin (Lipitor) in reducing both LDL and TC, although it was similar in reducing both atherogenic ratios and TG. Atorvastatin, however, significantly increased ($p < 0.05$) creatine phosphokinase (CPK) and creatinine, whereas policosanol significantly reduced alanine aminotransferase (AST), glucose ($p < 0.01$), and CPK ($p < 0.05$) levels.[42] These studies suggest a therapeutic benefit to policosanol in type II hypercholesterolemia, while presenting no adverse effects on the liver.

In a trial to determine whether policosanol could safely be used for patients with altered liver function tests, 46 patients with primary hypercholesterolemia and elevated liver enzymes were treated with policosanol (5 or 10 mg/day) or placebo for 12 weeks. Both 5 and 10 mg policosanol significantly lowered lipids and reduced serum levels of ALT, suggesting improvement in liver function.[43]

Intermittent Claudication

Two studies demonstrated positive results using policosanol for patients with intermittent claudication. In 62 patients treated with 10 mg policosanol twice daily for six months, the distance individuals could walk on a treadmill before noticing claudication symptoms increased 63.1 percent, and absolute distance to being unable to walk any further increased 65.1 percent, while placebo had no effect on walking distances. Policosanol also improved lower extremity symptoms of coldness and pain compared to placebo.[44] In a two-year follow-up study with 56 patients, improvements were progressive throughout the study, with the distance walked before initial claudication symptoms improving 60.1 percent after six months and 187.8 percent after 24 months. Absolute walking distance increased 81 percent after six months and 249 percent after 24 months. Policosanol also significantly decreased symptoms of claudication and increased the ankle/arm pressure ratio at 12 and 24 months. Even more impressive, significantly more patients in the placebo group experienced serious vascular events (8 patients with 10 total serious adverse events), while none were experienced in the policosanol group.[45]

Recently, intermittent claudication was investigated in comparative double-blind studies with lovastatin or ticlopidine.[33,46] Policosanol significantly increased the initial and absolute claudication distances in both studies, surpassing ticlopidine (a platelet-aggregation inhibitor) in one study, while significantly out-competing lovastatin (which had minimal effect) in the other study.

Ischemic Heart Disease

Forty-five patients with documented ischemic heart disease were placed on 5 mg policosanol twice daily, 5 mg policosanol twice daily plus 125 mg aspirin (ASA), or 125 mg ASA for 20 months.[47] The policosanol groups showed an insignificantly lower percentage of patients with functional progression of ischemia and a significantly greater partial regression of ischemia. Furthermore, exercise capacity and left ventricular function improved significantly in the policosanol groups compared to the ASA-only group. Both policosanol groups were more effective than ASA alone, but policosanol plus aspirin therapy was more effective than policosanol alone. There were four vascular events in ASA alone (1 fatal myocardial infarction, 2 unstable angina, 1 cardiac failure), one in the group taking policosanol alone (non-fatal myocardial infarction), and none in the combined group. A follow-up study on the same patients examined treadmill exercise ECG-testing performance.[48] Those taking policosanol demonstrated decreases in cardiovascular functional class, rest- and exercise-induced angina, cardiac events, and ischemic ST-segment response. These benefits were greatest in the policosanol plus aspirin group. In addition, policosanol showed an increase in maximum oxygen uptake, a decline in double product (peak heart rate times peak systolic blood pressure), and an increase in aerobic functional capacity compared to placebo.

Atherosclerotic lesions resulting in carotid-vertebral atherosclerosis improved in a study of 22 patients given 10 mg/day policosanol for one year.[49] Carotid-vertebral atherosclerosis assessed using Doppler-ultrasound showed progression of disease in three of 11 patients on placebo and no patients on policosanol. Disease regression occurred in six of 11 patients on policosanol and one on placebo. Neither of these values reached statistical significance; however, when a progression/regression ratio was calculated it did reach statistical significance for improvement with policosanol.

Policosanol (2 mg/day) improved abnormal rest and stress ECG patterns, and decreased symptoms of angina in a single-blind, 14-month, placebo-controlled trial in 23 middle-aged patients with primary or marginal hypercholesterolemia. No patient had a new coronary event, but significantly more patients (5/12) in the policosanol group with stable angina or silent ischemia had improved coronary symptoms and/or rest and stress ECG patterns, compared to placebo (0/11). Policosanol-treated patients also had no deterioration in symptoms or ECG patterns, while three of 11 placebo-treated patients deteriorated.[25]

Drug-Nutrient Interactions

Policosanol inhibits platelet aggregation, and may enhance the effect of other anticoagulant medications. When combined with aspirin, policosanol increased coagulation time in humans.[13]

Side Effects and Toxicity

In post-marketing studies looking at 27,879 patients, the most significant adverse effects were weight loss (0.07%), polyuria (0.07%), insomnia (0.05%), or polyphagia (0.05%).[50] Only 22 patients had to discontinue treatment because of side effects. In clinical trials there were either no significant differences in adverse events or significantly more adverse events in placebo groups compared to policosanol.

Toxicity studies in rats, dogs, mice, and monkeys have shown policosanol to be non-toxic and not carcinogenic at doses 1,500-times the normal human dosage.[51-55] Reproductive studies on rats and mice show policosanol at 1,500-times the normal human dose has no adverse effect on fertility, reproduction, teratogenesis, or development.[56-58]

Dosage

Significant reduction in cholesterol levels can be achieved with doses as low as 2 mg/day; however, maximum reductions should be seen at 5-20 mg/day. Greater than 20 mg/day seems to offer no further benefit; however, higher doses (40 mg/day) may be indicated for lowering triglycerides. A prudent recommendation would be to start with 5 mg daily and increase to 10 mg twice daily or more if needed.

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