Octacosanol in Human Health

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INTRODUCTION

Over the past 10 y, nutritional supplements, or nutraceuticals, have become increasingly popular among the general public. One such supplement, octacosanol, has been the subject of numerous studies.

Octacosanol ($CH_3[CH_2]_{26}CH_2O_{14}$), a high–molecular-weight, primary aliphatic alcohol, is the main component of a natural product wax extracted from plants. This wax commonly exists in fruit, leaves and surface of plants, and whole seeds. Because only very small amounts are ingested in the diet, to gain health benefits octacosanol must be ingested as a supplement. Most studies have used a wheat-germ oil extract, or policosanol, a natural mixture of primary alcohols isolated from sugar cane wax (*Saccharum officinarum* L.), of which octacosanol is the main component.[1,2]

Octacosanol has a number of indications for its use, many of which are currently being researched. In particular, its cholesterol-lowering effects, antiaggregatory properties, cytoprotective use, and ergogenic properties have been widely investigated.

LIPID-LOWERING EFFECT

Much research in recent years has been done on the potential of policosanol in lowering blood cholesterol. Studies have involved a wide range of subjects including experimental animals, healthy volunteers, and elderly patients with hypercholesterolemia.

Cholesterol is an important component in the body as it is a major component of cell membranes, but high levels can cause hypercholesterolemia and eventually atherosclerosis leading to coronary heart disease (CHD). Cholesterol is transported throughout the body and removed from the bloodstream by six main lipoprotein transporters: high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), intermediate-density lipoproteins, very–low-density lipoproteins, chylomicron remnants, and chylomicrons. HDL transports cholesterol from the peripheral tissues to the liver and plays a major role in maintaining cholesterol homeostasis in the body[3]; hence, high levels of HDL are desirable. LDL is the main lipoprotein, which transports cholesterol in the blood plasma and helps incorporate cholesterol into cell membranes. It is also an important precursor for steroid biosynthesis. LDL receptors on cells take up the LDL via a mechanism known as endocytosis for this synthesis. However, there are also cells on the hepatocytes that bind to the LDL and remove LDL from the blood. The more LDL receptors present, the greater the amount of LDL removed, which is desirable. Increased LDL can result in a deficiency in the binding mechanisms, known as type II hypercholesterolemia, and can be genetic or due to a combination of genetics, diet, and lifestyle. Treatment aims to increase HDL and decrease total and LDL cholesterol.[4,5]

Currently in the United Kingdom, two-thirds of the population have a serum cholesterol level above 5.2 mM/L. Also, atherosclerosis and CHD cause one in four deaths in England and Wales.[6]

Researchers have noted that, during motor endurance experiments on mice, octacosanol alters hepatic and serum lipid concentrations.[7] Therefore, they began to study the role of octacosanol as a cholesterol-lowering agent. Policosanol was shown to be a very safe agent in rodents and monkeys, and much early work was carried out in these experimental animals.[8]

In 1995, a report was published outlining a three-part study involving rats fed a high-fat diet and given octacosanol supplements. The aim of the study was to test the effect of octacosanol on lipid metabolism.[1] In the first experiment, four groups of six rats were fed a high-fat or normal fat diet for 20 d; one group on each diet was also given octacosanol supplements. The results showed that supplementation of the high-fat diet with octacosanol led to a significant decrease in the weight of perirenal adipose tissue. Two further experiments examined the effect of octacosanol on the enzymes involved in lipid metabolism and found that the rate-limiting step in the esterification of fatty acid into triacylglycerol was decreased by octacosanol in rats fed a high-fat diet. This indicated that a step in the cholesterol biosynthetic pathway was inhibited by octacosanol, which was dependent on dietary fat content.

In a study published in 1992, healthy volunteers with normal cholesterol levels were given 10 or 20 mg of policosanol or placebo in two divided doses for 4 wk. After this period, subjects taking policosanol had a significant decrease in serum cholesterol levels. The subjects taking the higher dose of policosanol (20 mg) also showed significant decreases in LDL levels and increases in HDL levels. Conversely the placebo showed an increase in serum cholesterol and LDL levels. There was good tolerance in all subjects taking the policosanol.[9] From this study it was concluded that more investigations should be carried out.

Ideally, high cholesterol should be managed with a low-fat diet; if there is little improvement, a statin is often introduced. Normal levels are those less than 6.5 mM/L, although other risk factors such as smoking, diabetes, family history, and obesity must be taken into account when determining the risk of developing atherosclerosis and, consequently, CHD. There are many statins available including atorvastatin, fluvastatin, pravastatin, and simvastatin. All of these work in the same general way, by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase in the process of cholesterol synthesis.[10]

Statins have many side effects such as myositis and other muscle effects, headache, gastrointestinal effects, rash, angioedema, altered liver function, and hepatitis. These drugs therefore should not be used in patients with renal failure or in people with a high alcohol intake whose liver function may be compromised. Recently, one of the most popularly prescribed statins, cerivastatin, was withdrawn after 31 deaths occurred due to rhabdomyolysis, a severe form of myositis, causing myoglobinuria and acute renal failure.[11]

Policosanol therefore could be a useful alternative to this group of drugs because it

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inhibits the earlier steps of cholesterol biosynthesis. One study[12] investigated the effects of policosanol and pravastatin on lipid profile in older hypercholesterolemic patients. This was a double-blind randomized study involving patients 60 to 80 y, of both sexes, and with a history of hypercholesterolemia (LDL cholesterol levels $\geq$ 3.4, total cholesterol level $\geq$ 5.2, and triacylglycerol level $<$ 4.5). Lipid-lowering medication was discontinued at the recruitment stage, and patients started a 6-wk cholesterol-lowering diet. Policosanol and pravastatin were given at a dose of 10 mg for 8 wk. This study showed that policosanol was more effective than pravastatin in lowering the levels of LDL and the ratios of LDL to HDL and total cholesterol to HDL. In addition, policosanol alone increased HDL, in agreement with previous studies. Moreover, both drugs were considered safe and well tolerated. However, pravastatin induced a moderate, significant rise in serum transaminase, reflecting possible risk of hepatotoxicity, and an increase in serum creatine phosphokinase, reflecting possible risk of myositis.

Overall, the study suggested that policosanol is a more appropriate choice than pravastatin in the treatment of elderly patients with type II hypercholesterolemia and high coronary risk, which predispose the patient to a high risk of atherosclerosis.

Another study compared the effects of policosanol with those of fluvastatin.[13] The study involved an oral dose of 20 mg/d of fluvastatin. Fluvastatin doses can reach 80 mg/d in severe hypercholesterolemia, but this increases the chance of side effects, which are increased in the elderly due to decreased liver function. The oral policosanol dose was 10 mg/d because this dose was shown to be safe, tolerable, and efficacious. Seventy elderly women were involved in the study. Three patients taking fluvastatin, but none taking policosanol, had to withdraw due to side effects of skin rash, gastric pain, blurred vision, and nausea. The study also identified raised levels of transaminase, indicating problems with muscle deterioration and highlighting issues of safety with the statins.

Another comparative study using lovastatin found similar results.[14] In this study patients had non–insulin-dependent diabetes mellitus, where hyperglycemia is a high risk factor for atherosclerosis and heart disease, leading to death.

Many placebo studies have investigated the effects of policosanol on hypercholesterolemia,[15–20] and in all cases the effects seen from policosanol were similar: LDL cholesterol decreased and HDL cholesterol increased slightly.

From these studies octacosanol seems a promising lipid-lowering agent, but larger trials involving more subjects and for longer duration are required. There may be scope for combinations of policosanol and lower doses of statin to lower LDL and triacylglycerols and increase HDL levels. Policosanol produces far fewer side effects than statins, increases HDL cholesterol levels, and has the bonus that it would not be as expensive to treat patients because this is a widely available "natural" product.

Lifestyle changes should be encouraged, or the number of people taking statins for hypercholesterolemia will continue to increase. Octacosanol may have a role as a prophylactic treatment because cholesterol was lowered with octacosanol supplements when studied in healthy volunteers.[21] Octacosanol may be useful in younger people, before atherosclerosis has begun to develop. Although more long-term studies are needed, present research strongly suggests that the benefits of octacosanol compared with statins are much more marked and major side effects of statins do not occur.

ANTIAGGREGATORY PROPERTIES

Ideally, the consistency of the blood should enable smooth flow through the body, avoiding damage to blood vessels and clots. However, when blood platelets aggregate, the blood is converted from this thin consistency to a thicker form or even a solid clot, which may cause deep-vein thrombosis or cerebral ischemia (stroke) and can be life-threatening. Aggregation can occur due to exogenous agents such as arachidonic acid, collagen, and adenosine diphosphate. The aggregating platelets then release thromboxane A_2 (TxA_2), derived from prostaglandin H_2, which induces further platelet aggregation.[22]

Because high cholesterol levels are a major risk for coronary artery disease and platelet function is an important factor in occlusive vascular arterial disease, a drug with cholesterol-lowering and platelet effects is of interest. Inhibition of platelet aggregation should reduce thrombus formation and therefore prevent atherosclerosis development.[23,24] Moreover, patients who are at risk of coronary events have increased platelet aggregation and TxA_2 biosynthesis.[22]

One placebo-controlled study using rats found that 5 to 20 mg/kg of policosanol causes an antiaggregatory effect. The mechanism was due to the inhibition of arachidonic acid metabolism, at the stage where TxA_2 is formed.[25]

Another study[22] found that when a daily dose of policosanol (25 mg/kg) was administered, there was little effect on platelet aggregation in the rat blood plasma. However, when a higher dose (50 to 200 mg/kg) was administered, there was significant inhibition of platelet aggregation. The aggregation occurred in two stages, the first due to exogenous adenosine diphosphate and the second when proaggregatory products were released. This second stage was blocked by aspirin, which is a cyclo-oxygenase inhibitor showing anti-ischemic effects by inhibiting TxA_2 biosynthesis. This study highlights the need for policosanol to be at a sufficient dose to cause antiaggregation.

A randomized, double-blind, placebo-controlled study using healthy volunteers investigated the effects of policosanol and aspirin on platelet aggregation.[21] Policosanol (20 mg) administered daily showed a significant reduction in platelet aggregation induced by adenosine diphosphate, epinephrine, and collagen, respectively. Aspirin (100 mg/d), however, showed significant decreases in collagen and epinephrine-induced platelet aggregation. Currently, aspirin is widely used to prevent thrombosis and cerebral ischemia, but it causes side effects such as gastric irritation. Because policosanol directly inhibits TxA_2 synthesis, prostaglandin synthesis is unaffected, and there are fewer side effects. During the trial, several volunteers taking aspirin suffered from headache, epigastralgia, and nose bleeding. One volunteer experienced gum bleeding while taking the combination therapy. The results indicated that 20 mg/d of policosanol daily is as effective as 100 mg/d of aspirin, but no side effects were noted.

A similar animal study involving policosanol and aspirin found that non-effective doses of each afforded protection when taken in combination. This significant level of protection suggested that the drugs act synergistically, even though they have different mechanisms.[22]

Because policosanol seems to be an efficient inhibitor of platelet aggregation, overdose could cause problems associated with hemorrhage. An overdose could cause the blood to become too thin, and this can occur even when patients are unaware of the injury such as in gastric ulcers or bleeding in the brain. Therefore, policosanol should not be taken with other anticoagulation therapy, such as warfarin.

ATHLETIC PERFORMANCE

Many supplements are taken as *ergogenic aids*, a term used for substances that enhance athletic performance and increase stamina and capability to exercise. Ergogenic aids are believed "to increase performance either by renewing or increasing energy stores in the body, facilitating the biochemical reactions contributing to fatigue, or maintaining optimal body weight."[26] Athletes take nutritional supplements as an alternative to anabolic steroids, which can cause a variety of complications in the body, in addition to being illegal. Many "supplements" claim to have ergogenic properties, such as carnitine, growth hormone releasers, octacosanol, and ginseng.[26] However, because nutritional supplements are not covered by the UK Medicines Act, there are no regulations for manufacture, quality, or usage, making them subject to abuse. The US Food and Drug Ad-

ministration also does not require that they be proved safe or effective because they are not classed as drugs.[27] Often people do not realize their full potential because "natural" substances are thought to be safe and contraindications and overdose are not considered.

Early octacosanol studies on human subjects investigated effects for grip, chest strength, stamina, cardiovascular function, and reaction time.[2] In one study, octacosanol was identified as an "active energy releasing factor" compared with placebo and improved performance.[2] The study showed that 1000 μg of octacosanol significantly improved grip strength and reaction time in response to a visual stimulus. This suggested that octacosanol also exhibits properties affecting the nervous system because reaction time would change according to nerve impulses throughout the body. Another study showed that octacosanol causes a statistically significant decrease in body fat.[27] However, because the study was not "blind," there could have been a placebo effect. Further, diet was not controlled, and the control and placebo groups participated in different sports, both of which could have affected the results. Therefore, more rigorous trials should be done to research into this aspect more accurately and try to identify an appropriate reason for the result.

A study was published in 1998,[2] involving 45 patients with CHD and myocardial ischemia, monitored exercise tolerance while running on a treadmill with electrocardiography. Fifteen patients took 5 mg policosanol twice daily, another 15 took 5 mg of policosanol and 125 mg of aspirin, and the remainder took placebo and 125 mg of aspirin (as a safety precaution). The results showed that the groups taking policosanol had a significant decrease in cardiac events after 20 mo. These effects were linked to a decrease in cholesterol, which leads to a lower risk of developing atherosclerosis, and hence ischemic disease or CHD, and antiaggregatory effects, which lead to a decreased risk of clots forming and lowers the risk of stroke and deep-vein thrombosis. There also was an improved response to exercise angina and an increase in maximum oxygen uptake.

Overall, many studies have assessed the use of octacosanol in athletes, but all seem to be non-specific. Trials and studies need to be done in which participants take part in similar sports regimens and have the same diet, and the trial should be randomized and double blind. This eliminates the chance of the placebo effect occurring.

CYTOPROTECTIVE MECHANISMS

The gastric side effects of aspirin can be a major problem especially for patients with gastric irritation or ulcers who would benefit from the antiaggregatory and cardiac advantages of daily aspirin. Aspirin causes these gastric effects by blocking the protective effects of prostaglandins, which act in the stomach to protect the gastric mucosa and so prevent ulceration and irritation from occurring. If, as suggested, aspirin is equivalent to policosanol in the protection against ischemic and thrombolytic events, perhaps policosanol would be a favorable alternative because it has an action that does not interfere with prostaglandin production of this kind.

Studies involving octacosanol have investigated whether it has any antiulcer activity. One study[28] used a mixture of higher primary alcohols of wax, called D-002, containing triacontanol, octacosanol, dotriacontanol, hexacosanol, and tetracosanol as major components. Octacosanol was in a concentration of 17.49%. When administered orally to rats, it induced a mild anti-inflammatory effect. The effect of D-002 was monitored on indomethacin-induced and ethanol-induced gastric ulcers. Ulcers induced by indomethacin were significantly inhibited when D-002 was administered orally. Doses of 25 and 50 mg/kg proved to be the most effective. At these doses the inhibitory effect of 50% is similar to the efficacy of cimetidine. In the case of the ethanol-induced ulcer, maximal inhibition of 66.9% occurred at a dose of 50 mg/kg.

One factor causing ulceration is gastric acid. However, in a further experiment, D-002 was shown to be independent of gastric acid[29]; therefore, its mode of action is different from that of cimetidine, which is an H_2 antagonist and acts by blocking H_2 receptors in the stomach that produce acid. It was suggested that the cytoprotective role of D-002 was related to its prostaglandin effects rather than to its inhibition of gastric acid.

Therefore, as opposed to aspirin, which causes gastric irritation, policosanol offers cytoprotection, which makes it a favorable option in patients in whom aspirin is contraindicated.

CONCLUSIONS

In summary, octacosanol has many uses for treating various conditions. The most widely studied of these are its cholesterol-lowering properties, and many studies have shown that octacosanol is very effective in lowering LDL and increasing HDL. In addition, it has been shown that policosanol is as effective as aspirin in terms of its antiaggregatory effects. Perhaps octacosanol could be given as a single supplement to patients with high LDL cholesterol and perhaps hypertension or high risk of clot formation.

Octacosanol (policosanol) also offers cytoprotective effects. This affords an opportunity for octacosanol to be taken as an alternative to aspirin in patients who have a history of or suffer from gastric irritation.

Thus, octacosanol could be an ideal alternative in three types of conditions, which commonly occur simultaneously. High LDL cholsterol in relation to hypertension, where an antiaggregatory agent is required but the patient suffers gastric irritation. Because only one type of medication is needed, patients would have a high degree of compliance. More studies should investigated whether there are any long-term problems with octacosanol.

With regard to the use of octacosanol as a nutritional supplement by athletes, this could be advantageous because some studies have suggested that octacosanol can improve stamina and exercise capability. However, many claims for improving athletic performance have yet to be proven.

Few studies have investigated combinations of octacosanol with other treatments. There may be problems or benefits in taking medication that has the same indication. If, for example, a statin were taken with octacosanol, the combined effects might be extremely beneficial because LDL cholesterol levels almost definitely would be lowered. However, problems would arise if octacosanol were to be taken with anticoagulation therapy, such as warfarin or aspirin, because octacosanol may act synergistically and an overdose could have drastic consequences. Because there are no defined limits of octacosanol dosing, patients may be inclined to take more tablets and this could result in a risk of hemorrhage. There also may be contraindications with other therapy, so patients on multiple therapy should take octacosanol with caution.

Octacosanol has the potential to treat numerous conditions without major side effects and thus would be beneficial to many patients. Also, there are opportunities for octacosanol to be taken as a dual-action treatment for hypertension and high cholesterol, with no gastric irritation or muscle problems. This could be an important drug for the future, with the ever-increasing problem of obesity and increased risk of atherosclerosis and CHD throughout the world.

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