21 days beginning mean four days post-injury. Significant improvement was achieved in the OKG-treated group, compared with controls, as measured by both biological and clinical end points. Previous studies of OKG-treated burn patients have reported shorter hospitalizations and fewer fatalities.

No conclusions can yet be drawn from scant, preliminary evidence that OKG may exert some positive effects on immunity. And there is no credible research to support claims that OKG can build muscle in healthy individuals or that it can enhance exercise/athletic performance.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

OKG is contraindicated in those with deficiency of ornithine-delta-aminotransferase (OAT). This is a genetic disease resulting in gyrate atrophy of the choroid and retina and progressive blinding chorioretinal degeneration. It is rare.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplemental OKG. OKG supplementation may potentially cause hypoglycemia in starved individuals. Those with eating disorders or those who are on very-low-calorie diets should exercise caution in using OKG.

ADVERSE REACTIONS

None reported for those using supplemental OKG.

DOSAGE AND ADMINISTRATION

There are no typical doses for OKG supplementation. Some athletes use about 2.5 grams before and after exercise, as well as before breakfast and at bedtime.

Doses of 20 to 30 grams daily, given enterally, have been used in burn and trauma patients.

HOW SUPPLIED

Powder — 3.5 mg/teaspoonful

LITERATURE

Czernichow B, Nsi-Emvo E, Galluser M, et al. Enteral supplementation with ornithine alpha ketoglutarate improves the early adaptive response to resection. *Gut.* 1997; 40:67-72.

De Bandt JP, Coudray-Lucas C, Lioret N, et al. A randomized controlled trial of the influence of the mode of enteral ornithine alpha-ketoglutarate administration in burn patients. *J Nutr.* 1998; 128:563-569.

Dumas F, De Bandt JP, Colomb V, et al. Enteral ornithine alpha-ketoglutarate enhances intestinal adaptation to massive resection in rats. *Metabolism.* 1998; 47:1366-1371.

Donati L, Ziegler F, Pongelli G, Signorini MS. Nutritional and clinical efficacy of ornithine alpha-ketoglutarate in severe burn patients. *Clin Nutr.* 1999; 18:307-311.

Duranton B, Schleiffer R, Gosse F, Raul F. Preventive administration of ornithine alpha-ketoglutarate improves intestinal mucosal repair after transient ischemia in rats. *Crit Care Med.* 1998; 26:120-125.

Jeevanandam M, Holaday NJ, Petersen SR. Ornithine-alpha-ketoglutarate(OKG) supplementation is more effective than its component salts in traumatized rats. *J Nutr.* 1996; 126:2141-2150.

Jeevanandam M, Petersen SR. Substrate fuel kinetics in enterally fed trauma patients supplemented with ornithine alpha-ketoglutarate. *Clin Nutr.* 1999; 18; 209-217.

Le Boucher J, Eurengőiol, Farges MC, et al. Modulation of immune response with ornithine A-ketoglutarate in burn injury: an arginine or glutamine dependency? *Nutrition.* 1999; 15; 773-777.

Le Bricon T, Cynober L, Baracos VE. Ornithine alpha-ketoglutarate limits muscle protein breakdown without stimulating tumor growth in rats bearing Yoshida ascites hepatoma. *Metabolism.* 1994; 43; 899-905.

Le Bricon T, Cynober L. Field CJ, Baracos VE. Supplemental nutrition with ornithine alpha-ketoglutarate in rats with cancer-associated cachexia: surgical treatment of the tumor improves efficacy of nutritional support. *Nutr.* J 1995; 125:2999-3010.

Robinson LE, Bussiere FI, Le Boucher J, et al. Amino acid nutrition and immune function in tumour-bearing rats: a comparison of glutamine-, arginine- and ornithine 2-oxoglutarate-supplemented diets. Clin Sci (Colch). 1999; 97:657-669.

Roch-Arveiller M, Fontagne J, Coudray-Lucas C, et al. Ornithine alpha-ketoglutarate counteracts the decrease of liver cytochrome p-450 content in burned rats. *Nutrition.*1999; 15:379-383.

Roch-Arveiller M, Tissat M, Coudray-Lucas C, et al. Immunomodulatory effects of ornithine alpha-ketoglutarate in rats with burn injuries. *Arch Surg.* 1996; 131:718-723.

Varanasi RV, Saltzman JR. Ornithine oxoglutarate therapy improves nutrition status. *Nutr Rev.* 1996; 53:96-97.

Pantethine

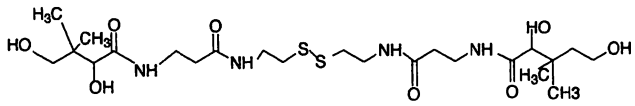
TRADE NAMES

Pantethine 500 (Westlake Laboratories)

DESCRIPTION

Pantethine is the disulfide dimer of pantetheine, the 4'-phosphate derivative of which is an intermediate in the conversion of the B vitamin pantothenic acid to coenzyme A (see Pantothenic Acid). Pantethine is found naturally in small quantities in most forms of life, and therefore, in food sources. Very large doses of pantethine have been found to have lipid-lowering effects, and pantethine is used in Europe and Japan as a lipid-lowering agent. Pantethine is marketed in the United States as a nutritional supplement.

Pantethine is also known as D-bis(N-pantothenyl-beta-aminoethyl)disulfide and (R)-N,N'-[dithiobis(ethyleneiminocarbonylethylene]bis(2,4-dihydroxy-3,3-dimethylbutyramide). Its molecular formula is $C_{22}H_{42}N_4O_8S_2$ and its molecular weight is 554.73 daltons. Pantetine is represented by the following chemical structure:



Pantethine

ACTIONS AND PHARMACOLOGY

ACTIONS

Pantethine may have lipid-modulating activity. It has putative antiatherogenic, ophthalmoprotective and detoxification activities.

MECHANISM OF ACTION

Pantethine has been found to decrease serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B and triglycerides. It has also been found to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 levels. The mechanism of the possible lipid-modulating activity of pantethine is not understood. In isolated hepatocytes, pantethine has been shown to inhibit both cholesterol and fatty acid synthesis. It is speculated that pantethine, by acting as a precursor of coenzyme A, may enhance the beta-oxidation of fatty acids. However, this has not been confirmed. Another hypothesis is that the lipid-modulating effect of pantethine may be mediated via its metabolite cysteamine. It is argued that there is little pantethine found in the serum following its ingestion and that most of a dose is metabolized to pantothenic acid and cysteamine. Since pantothenic acid does not possess lipid-modulatory activity, cysteamine might. This lipid-modulatory activity could occur via the inhibition of acetyl coenzyme A carboxylase activity and the stimulation of hepatic fatty acid oxidation, resulting in lowered triglyceride levels, and via the inhibition of HMG-CoA reductase activity, resulting in lowered cholesterol levels. Again, this has not been confirmed. Further, cysteamine, a treatment for cystinosis, has not been found to have lipid-lowering activity in those with this rare genetic disorder. Nor, does pantethine appear to be efficacious in the treatment of cystinosis.

The putative antiatherogenic activity may be accounted for, in large part, by pantethine's possible lipid-modulatory activity. In addition, pantethine may have antioxidant activity and also may decrease platelet aggregability. A few studies suggest that pantethine may have antioxidant activity. One *in vitro* study found inhibition of peroxidation of LDL, but only under certain concentrations.

The mechanism of pantethine's possible antioxidant activity is unclear. Other studies have reported that pantethine may decrease platelet aggregability. Possible mechanisms, include decreased thromboxane production and modulation of platelet membrane fluidity. Treatment with pantethine has been found to decrease the cholesterol content of platelet membranes. This could result in increased platelet membrane fluidity and decreased platelet aggregability.

Parenterally administered pantethine has been demonstrated to inhibit lens opacification, in some animal studies. The mechanism of this possible ophthalmoprotective effect is not understood. One possibility is that pantethine may inhibit the formation of protein aggregates in the lens of the eye by forming mixed disulfides with cysteine residues of certain lens proteins. There is no evidence that orally administered pantethine has any activity in inhibiting lens opacification.

Other animal experiments have demonstrated that pantethine protects the liver against certain hepatotoxins, such as carbon tetrachloride. Again, pantethine was administered parenterally in these studies. This hepatoprotective activity may be accounted for, in part, by the possible antioxidant activity of pantethine.

Pantethine has been shown to lower serum acetaldehyde in a small human study, following ethanol ingestion. Acetaldehyde is thought to mediate some of the hepatotoxic effects of ethanol. It is speculated that pantethine-induced lowering of blood acetaldehyde levels following alcohol ingestion is due, in part, to accelerated acetaldehyde oxidation by an interaction between hepatic aldehyde dehydrogenase and pantethine-related intermediates formed in the liver.

PHARMACOKINETICS

The pharmacokinetics of pantethine in humans are incomplete. Following ingestion, pantethine is absorbed from the small intestine into the enterocytes where some is reduced, via glutathione reductase, to pantetheine. Some pantetheine is metabolized in the enterocytes to coenzyme A and the rest, along with pantethine, is released by the enterocytes into the portal circulation. It appears that pantethine undergoes significant metabolism in the blood to pantothenic acid and cysteamine. These metabolites, along with pantethine and pantetheine, are transported to the liver where they are extracted by the hepatocytes and undergo various metabolic reactions. In the liver, some pantethine is reduced to pantetheine and the pantetheine pool in that organ is metabolized to coenzyme A. There appears to be significant first-pass extraction, as well as first-pass metabolism, of pantethine by the liver. There does not appear to be much pantethine circulating in the blood, following ingestion. Coenzyme A itself is catabolized by a number of hydrolytic steps resulting in the production of pantothenate and

cysteamine. There is some evidence that pantethine is more efficiently converted to coenzyme A than is pantothenic acid.

INDICATIONS AND USAGE

Pantethine may favorably affect lipids and protect against cardiomuscular disease. There is evidence, in animal research, that it can inhibit cataract formation. It also exhibits some hepatoprotective effects in animal models. Additionally, it has been shown to protect against a number of toxins, including alcohol. Preliminary research suggests that pantethine may influence various central nervous system and adrenal junctions, but no useful conclusions can yet be drawn from these early investigations. There is no credible evidence that pantethine enhances exercise performance or that it inhibits hair loss and graying of hair.

RESEARCH SUMMARY

Several studies have shown that pantethine can significantly lower levels of both cholesterol and triglycerides. Doses used in these studies have ranged from 600 to 1,200 milligrams daily. In one of these studies, seven children and 65 adults suffering from hypercholesterolemia alone or combined with hypertriglyceridemia achieved significant reductions in total cholesterol, LDL-cholesterol, triglycerides and apo-B, as well as significant increases in HDL-cholesterol and apo-A1. They received 900-1,200 milligrams of pantethine daily for three to six months.

Pantethine has also proved helpful in treating diabetics with dyslipidemia, reducing triglyceride levels by 37% in one study (utilizing 600 milligram daily doses). In general, looking at all studies to date, pantethine typically reduces total cholesterol by 15-25% and triglycerides by 25-40%.

Additionally, there is *in vitro* and clinical evidence that pantethine can help maintain normal platelet functions, favorably affecting platelet lipid composition and cell membrane fluidity. These effects may provide further protection against atherosclerosis.

Animal research indicates that pantethine can inhibit cataract formation. This has been demonstrated in several animal models. Reversal of existing opacities has not been demonstrated. More research is needed to see whether these findings extend to humans.

There is also considerable animal data suggesting that pantethine may have significant hepatoprotective effects. It has demonstrated protection against carbon tetrachloride, halocarbon, autoxidized linoleate, acetaldehyde, ethanol and other hepatotoxins.

There is no evidence that pantethine can prevent hair loss or graying of hair. Similarly there is no evidence that pantethine can enhance athletic performance. A recent study showed that a combination of pantethine, pantothenic acid and allithiamin had no effect on exercise performance.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Pantethine is contraindicated in those hypersensitive to any component of a pantethine-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should avoid the use of pantethine.

The use of pantethine for its possible lipid-lowering effects should only be undertaken under medical supervision.

ADVERSE REACTIONS

Doses up to 1,200 milligrams daily have been well tolerated. There are a few reports of gastrointestinal effects, including nausea and heartburn.

INTERACTIONS

DRUGS

HMG-CoA reductase inhibitors (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin): Concomitant use of pantethine and a HMG-CoA reductase inhibitor may produce additive lipid-modulatory effects.

NUTRITIONAL SUPPLEMENTS

Nicotinic acid: Concomitant use of pantethine and high-dose nicotinic acid may produce additive lipid-modulatory effects.

OVERDOSAGE

There are no reports of pantethine overdosage in the literature.

DOSAGE AND ADMINISTRATION

Single component and combination products (e.g., with pantothenic acid) are available. Possible lipid-lowering dosage typically ranges from 600 to 1,200 milligrams daily, taken in divided doses. See Precautions.

HOW SUPPLIED

Capsules — 500 mg

Sublingual Tablets — 25 mg

LITERATURE

Arsenio L, Bodria P, Magnati G, et al. Effectiveness of long-term treatment with pantethine inpatients with dyslipidemia. *Clin Ther.* 1986; 8:537-545.

Bertolini S, Donati C, Elicio N, et al. Lipoprotein changes induced by pantethine in hyperlipoproteinemic patients: adults and children. *Int J Clin Pharmacol Ther Toxicol.* 1986; 24:630-637.

Bon GB, Cazzolato G, Zago S, Avogaro P. Effects of pantothine on in vitro peroxidation of low density lipoproteins. *Atherosclerosis.* 1985; 57:99-106.

Branca D, Scutari G, Siliprandi N. Pantethine and pantothenate effect on the CoA content of rat liver. *Internat J Vit Nutr Res.* 1984; 54:211-216.

Carrara P, Matturri L, Galbussera M, et al. Pantethine reduces plasma cholesterol and the severity of arterial lesions in experimental hypercholesterolemic rabbits. *Atherosclerosis.* 1984; 53:255-264.

Cighetti G, Del Puppo M, Paroni R, et al. Pantethine inhibits cholesterol and fatty acid syntheses and stimulates carbon dioxide formation in isolated rat hepatocytes. *J Lipid Res.* 1987; 28:152-161.

Clark JI, Livesey JC, Steele JE. Delay or inhibition of rat lens opacification using pantethine and WR-77913. *Exp Eye Res.* 1996; 62:75-84.

Congdon NT, West ST, Duncan DT, et al. The effect of pantethine and ultraviolet-B radiation on the development of lenticular opacity in the emory mouse. *Curr Eye Res.* 2000; 20:17-24.

Donati C, Barbi G, Cairo G, et al. Pantethine improves the lipid abnormalities of chronic hemodialysis patients: results of a multicenter clinical trial. *Clin Nephrol.* 1986; 25:70-74.

Donati C, Bertieri RS, Barbi G. [Pantethine, diabetes mellitus and atherosclerosis. Clinical study of 1045 patients]. [Article in Italian]. *Clin Ter.* 1989; 128:411-422.

Friberg G, Pande J, Ogun O, Benedek GB. Pantethine inhibits the formation of high-Tc protein aggregates in gamma B crystallin solutions. *Curr Eye Res.* 1996; 15:1182-1190.

Gaddi A, Descovich GC, Noseda G, et al. Controlled evaluation of pantethine, a natural hypolipidemic compound, in patients with different forms of hyperlipoproteinemia. *Atherosclerosis.* 1984; 50:73-83.

Galeone F, Scalabrino A, Giuntoli F, et al. The lipid-lowering effect of pantethine in hyperlipidemic patients: a clinical investigation. *Curr Ther Res.* 1983; 34:383-390.

Gensini GF, Prisco D, Rogasi PG, et al. Changes in fatty acid composition of the single platelet phospholipids induced by pantethine treatment. *Int J Clin Pharm Res.* 1985; 5:309-318.

Hayashi H, Kobayashi A, Terada H, et al. Effect of pantethine on action potential of canine papillary muscle during hypoxic perfusion. *Jap Heart J.* 1985; 26:289-296.

Hiramatsu N, Kishida T, Hamano T, Natake M. Effects of dietary pantethine levels on contents of fatty acids and thiobarbituric acid reactive substances in the liver of rats orally administered varying amounts of autoxidized linoleate. *J Nutr Sci Vitaminol (Tokyo).* 1991; 37:73-87.

Hoffman B, Lang A, Ostermann G, et al. Effect of pantethine on platelet functions *in vitro*. *Curr Ther Res.* 1987; 41:791-801.

Iida J, Nishimura K, Ukei S, Azuma I. Macrophage activation with pantethine and pantetheine-4'-phosphate. *Int J Vitam Nutr Res.* 1985; 55:405-411.

Kumerova AO, Silova AA, Utno Lia. [Effect of pantethine on post-heparin lipolytic activity and lipid peroxidation in the myocardium]. [Article in Russian]. *Biull Eksp Biol Med.* 1991; 111:33-35.

Maggi GC, Donati C, Criscuoli G. Pantethine: a physiological lipomodulating agent in the treatment of hyperlipidemias. *Curr Ther Res.* 1982; 32:380-386.

Nagiel-Ostaszewski I, Lau-Cam CA. Protection by pantethine, pantothenic acid and cystamine against carbon tetrachloride-induced hepatotoxicity in the rat. *Res Commun Chem Pathol Pharmacol.* 1990; 67:289-292.

Prisco D, Rogasi PG, Matucci M, et al. Effect of pantethine treatment on platelet aggregation and thromboxane A_2 production. *Curr Ther Res.* 1984; 35:700-706.

Vecsei L, Alling C, Widerlov E. Comparative studies of intracerebroventricularly administered cysteamine and pantethine in different behavioral tests and on brain catechols in rats. *Arch Int Pharmacodyn Ther.* 1990; 305:140-151.

Watanabe A, Hobara BS, Kobayashi M, et al. Lowering of blood acetaldehyde but not ethanol concentrations by pantethine following alcohol ingestion: different effects in flushing and nonflushing subjects. *Alcoholism: Clin Exper Res.* 1985; 9:272-276.

Webster MJ. Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. *Eur J Appl Physiol.* 1998; 77:486-491.

Wittwer CT, Graves CP, Peterson MA, et al. Pantethine lipomodulation: evidence for cysteamine mediation *in vitro* and*in vivo*. *Atherosclerosis.* 1987; 68:41-49.

Yoon SB, Kajiyama K, Ogura R. [Effect of pantethine on adriamycin-induced cardiotoxicity]. [Article in Japanese]. *Kurume Igakkai Zasshi.* 1982; 45:598-606.

Pantothenic Acid

TRADE NAMES

Pantothenic acid is available generically from numerou manufacturers. Branded products include: Panto-250 (Bio Tech Pharmacal).

DESCRIPTION

Pantothenic acid, a member of the B-vitamin family, is a essential nutrient in human nutrition. It is sometimes referre to as vitamin B_5. Pantothenic acid is involved in a number biological reactions, including the production of energy, th catabolism of fatty acids and amino acids, the synthesis fatty acids, phospholipids, sphingolipids, cholesterol ar steroid hormones, and the synthesis of heme and th neurotransmitter acetylcholine. It also appears to be involve in the regulation of gene expression and *in signal transdu* tion. Roger J. Williams, the discoverer of pantothenic ac and a scientist who pioneered the use of nutrients for th prevention and treatment of disease, thought that pantothen