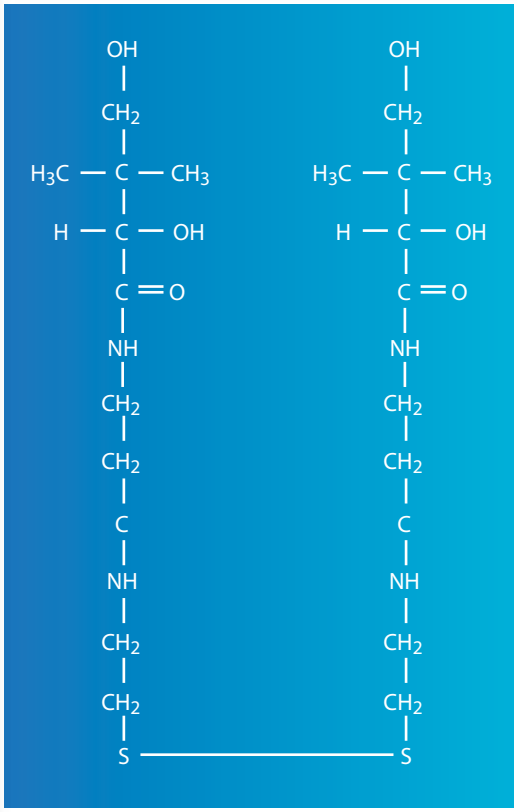
Pantethine Monograph

Introduction

Pantethine is the active, stable form of pantothenic acid (vitamin B5). Oral administration of pantethine has consistently shown a favorable impact on lipid risk factors in individuals with hypercholesterolemia, arteriosclerosis, and diabetes. Pantethine administration has also been shown to favorably affect parameters associated with platelet lipid composition and cell membrane fluidity. Due to its role in the formation of coenzyme A (CoA), pantethine might assist with detoxification of some xenobiotic compounds. Administration also appears to favorably impact adrenal cortex function. In several animal models, preliminary studies have indicated a protective effect against cataract formation.



Biochemistry

Pantethine is the stable disulfate form of pantetheine, the metabolic substrate that constitutes the active part of coenzyme A molecules and acyl carrier proteins (ACP). The reactive component of both CoA and ACP is not the pantothenic acid molecule but rather the sulfhydryl (SH) group donated from cysteine. Although pantothenic acid is commonly known as vitamin B_5, pantethine actually contains the SH molecule required for enzyme activity and provides a more metabolically active form of the vitamin. This SH group is maintained in the catabolic byproducts of pantethine, cysteamine and cystamine, which are currently being researched to determine their various metabolic effects.

Mechanism of Action

The metabolic activity of pantethine is probably due to its role in the synthesis of CoA and ACP. CoA is a cofactor in over 70 enzymatic pathways, including fatty acid oxidation, carbohydrate metabolism, pyruvate degradation, amino acid catabolism, heme synthesis, acetylcholine synthesis, and phase II detoxification acetylation. ACP is an essential component of the fatty acid synthase complex required for fatty acid elongation.

While the exact mechanism of action of pantethine in normalizing parameters associated with dyslipidemia is unknown, several explanations have been proposed. Some authors have suggested pantethine might be capable of directly modulating the action of several enzymes involved in cholesterol synthesis.[1-3]

The efficacy of pantethine in normalizing parameters of dyslipidemia might also be due to its ability to increase CoA levels. Theoretically, if pantethine enhances the formation of CoA, the additional CoA might then combine with free acetyl groups to form acetyl-CoA. The acetyl-CoA could then be directed into the tricarboxylic acid (TCA) cycle or beta-oxidation at the expense of cholesterol formation. The hypothesis also exists that, by supplying the substrate for cystamine formation, pantethine administration indirectly inhibits acetyl-CoA carboxylase, which may be the cause of the increased fatty acid oxidation.[4]

Clinical Indications

Hyperlipidemia

Oral supplementation of pantethine results in a tendency toward normalization of lipid values. Administration of pantethine typically results in a progressive decrease in total cholesterol (TC), triglycerides (TGs), low-density lipoprotein (LDL) cholesterol, and apolipoprotein B (Apo-B) and an increase in high-density lipoprotein (HDL) cholesterol and apolipoprotein A (Apo-A); however, depending on the type of dyslipidemia, results might vary (Table 1).[5-10]

A review article in *Nutrition Research* best summarizes the data on the use of pantethine for hyperlipoproteinemia.[11] McRae included 28 human trials published from 1981-1991 (22 from Italy) with a total of 646 hyperlipidemic subjects averaging 52.8 years. The mean daily dose of pantethine was 900 mg/day and the average study length was 12.7 weeks. Mean percent decreases from months 1 through 4 were evaluated for TC, LDL- and HDL-cholesterol, and TGs. After compiling both quantitative and qualitative data for adverse reactions, the rate was 1.4 per 100 subjects with the majority being mild gastrointestinal complaints. McRae summarizes by stating: "Pantethine, a naturally occurring physiological compound, offers an effective therapeutic option in treating patient populations with total serum cholesterol levels greater than 200 mg/dL and/or serum triacylglycerol levels greater than 150 mg/dL. However, the full benefit of pantethine may not be attained until at least four months from the commencing of supplementation." Table 2 illustrates the changes in lipids from months 1-4.[11]

Vascular Complications in Diabetes

Pantethine administration has been shown to favorably affect parameters associated with platelet lipid composition and cell membrane fluidity.[12,13] In diabetic patients, composition of platelets is characterized by a derangement in a wide variety of lipid concentrations and a higher microviscosity than in healthy platelets. Administration of pantethine is reported to normalize these values of fatty acids to control levels and result in a concomitant reduction in hyperaggregation.[14,15]

Malaria Complications

A mouse model study mimicking cerebral malaria indicated that pantethine may provide significant protection from malaria-associated neurological syndrome.[16] After seven days of an injection of *Plasmodium berghei* ANKA (PbA), infected mice experienced normal signs and symptoms of cerebral malaria including ataxia, convulsions, and death. Within one day of injection of 30 mg pantethine, PbA-infected mice had similar characteristics of the non-infected controls. Complete protection from cerebral malaria complications was

Table 1. Pantethine's Reported Impact on Lipid Parameters in Patients with Frederickson's Type IIa, IIb, and IV Dyslipidemia

Type	Pantethine's Impact
IIa	decreased total cholesterol decreased LDL-cholesterol decreased VLDL-cholesterol decreased triglycerides decreased Apo-A increased HDL-cholesterol increased Apo-A
IIb	decreased total cholesterol decreased LDL-cholesterol decreased VLDL-cholesterol decreased triglycerides decreased Apo-B increased HDL-cholesterol increased Apo-A
IV	mixed results with total cholesterol mixed results with LDL-cholesterol decreased VLDL-cholesterol decreased triglycerides decreased Apo-B mixed results with HDL-cholesterol

Table 2. Percent Change in Lipids from Months 1-4

Lipid	Change from Baseline			
	Month 1	Month 2	Month 3	Month 4
TC	↓ 8.7%	↓11.6%	↓12.6%	↓ 15.1%
LDL	↓10.4%	↓15.2%	↓17.7%	↓ 20.1%
TGs	↓14.2%	↓15.8%	↓23.7%	↓ 32.9%
HDL	↑ 6.1%	↑ 7.8%	↑10.7%	↑ 8.4%

avoided when mice were given 5 mg pantethine eight days prior to the PbA infection. This study attributed the action of pantethine to its ability to modify platelet function, and hence decrease blood-brain barrier permeability and alter microparticle release by endothelial cells. The authors hypothesize that all these actions were directly or indirectly linked to the disulfide bonds in pantethine and their ability to influence various thio-dependent mechanisms.[16]

Cataract Protection

In several animal models, preliminary studies have indicated pantethine can inhibit cataract formation.[17-19]

Impact on Adrenal Function

Pantethine appears to exert a positive influence on some indicators of adrenal function. Administration of pantethine to 20 individuals with a variety of clinical conditions was reported to buffer the increase in 24-hour urinary 17-hydroxycorticosteroids and plasma 11-hydroxycorticosteroids stimulated by a loading dose of adrenocorticotropic hormone.[20]

Depression

Studies have indicated that antidepressant medications may have a positive effect by increasing central brain-derived neurotrophic factor (BDNF) levels.[21,22] Cysteamine and cystamine, natural metabolites of pantethine, have been shown to have neuroprotective effects in Huntington's disease (HD) mice by raising central BDNF levels. Injections of cystamine or cysteamine have also raised serum BDNF in both HD and wild-type mice.[23]

Side Effects and Toxicity

Although digestive disturbances have occasionally been reported in the literature, the majority of researchers have commented on the complete freedom from side effects experienced by individuals taking pantethine.

Dosage

The most common oral dosage used in the treatment of dyslipidemia is 300 mg three times per day.

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