

PANTOTHENIC ACID: AN OVERVIEW FOCUSED ON MEDICAL ASPECTS

Antonio Sampedro
Javier Rodriguez-Granger
Julian Ceballos
Luis Aliaga

Departamento de Medicina, Facultad de Medicina, Universidad de Granada.
Service of Microbiology, Hospital Universitario Virgen de las Nieves,
Avda. de las Fuerzas Armadas, s/n. Granada

Abstract

Pantothenic acid (vitamin B₅) is a water-soluble B-complex vitamin. It is of biologic importance because of its incorporation into coenzyme A and acyl carrier protein. Coenzyme A is an indispensable cofactor in all living organisms, where it functions in over 70 enzymatic pathways. Most bacteria, plants, and fungi synthesize pantothenic acid; thus, the vitamin is found virtually everywhere in nature. Therefore, a naturally occurring vitamin deficiency in humans does not occur. Several clinical trials have been undertaken in humans using pantothenic acid supplementation in various medical fields. Unfortunately, firm conclusions regarding therapeutic effectiveness cannot be drawn from many of these studies. However, it has been suggested that there is a beneficial effect of pantothenic acid on hyperlipidemia. Cysteamine treatment, a metabolite of the degradation of coenzyme A, has dramatically changed the course of the cystinosis; and clinical trials of this compound are underway in other medical fields. In the last few decades, several studies have pointed out the great interest of the inhibition of the coenzyme A metabolic pathway as an attractive target in developing new antimicrobial agents. Furthermore, recent research on coenzyme A metabolic enzymes has led to the discovery of uniquely non-metabolic roles for both enzymes and their metabolites, thus opening an exciting field of investigation. In the present mini-review, we describe the current understanding of the pantothenic acid medical aspects and provide an overview on future potential therapeutic indications for this vitamin and its metabolic byproducts.

Keywords: Pantothenic acid, pantothenate, vitamin B₅, coenzyme A, cystinosis, new targets for antimicrobials

Introduction

Pantothenic acid (also known as pantothenate or vitamin B₅) is a water-soluble B-complex vitamin (1, 23), that was discovered in 1931 by chemist Roger J. Williams (1893-1988) during his studies on the vitamin B complex (26). Williams observed that an acidic substance was capable of stimulating the growth of strains on yeast *Saccharomyces cerevisiae* (42). In 1933, he named the substance pantothenic acid from the Greek word *panthos*, meaning “from all sides” (42). However, it was given this name because of its widespread presence in food (42). Pantothenic acid was isolated and extracted from liver by Williams and his colleagues in 1939, as an impure substance (about 40% pure). Thus, the initial isolation produced 3g of pantothenic acid from 250kg of sheep liver (26). In 1939, a partial synthesis of pantothenic acid was carried out independently by Williams in Oregon and Conrad A. Elvehjem (1901-1962) in Wisconsin (43). Finally, the synthesis of pantothenic acid was achieved in 1940 by American biochemist, Karl Folkers (1906-1997) and colleagues at Merck and Company in Rawhay, N.J. (38). Therefore, the structure of the pantothenic acid was determined by a stepwise degradation and synthesis (26).

Pantothenic acid is pantoic acid linked with β -alanine through an amide bond (27). Pantothenic acid is of biologic importance because of its incorporation into coenzyme A (CoA) and acyl carrier protein (ACP), on which acetylation and acylation, respectively, and other interactions depend. CoA is an indispensable cofactor in all living organisms, where it functions 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 (1). On the other hand, ACP is an essential component of the fatty acid synthase complex required for fatty acid elongation (1).

Subsequently, only the Dextrorotatory (D) isomer of pantothenic acid –D-pantothenic acid- possesses biologic activity (23). The reactive component of both CoA and ACP is not the pantothenic acid molecule, but rather the sulfhydryl (SH) group donated from cysteine (1). Pantethine is the stable disulfate form of pantetheine. It is the metabolic substrate that constitutes the active part of CoA and ACP (1). Thus, the disulphide form of pantothenic acid –pantethine- is considered to be the most active form of vitamin B₅ because it contains the sulfhydryl-group needed for biological activity in CoA and ACP (1, 23).

However, as D-pantothenic acid becomes relatively unstable, the more stable calcium pantothenate becomes in the form of vitamin B₅. This is usually found in dietary supplements and used basically for study purposes (23).

Biochemistry

Most plants and microorganisms accomplish biosynthesis of pantothenic acid by enzymatically combining pantoic acid with β -alanine. Mammals and some microbes lack the enzyme for this synthetic step, and so, they are unable to synthesize pantothenic acid and need to obtain it from outside (23, 30).

The biosynthesis of CoA from pantothenic acid is an essential and universal pathway in prokaryotes and eukaryotes, and requires cysteine and ATP (23, 27, 30). As it is shown in figure 1, CoA is generated from pantothenate through a series of five synthetic reactions (23, 27, 30). In the synthetic pathway of CoA, pantothenate is first phosphorylated to 4'-phosphopantothenate by the enzyme pantothenate kinase (CoaA). This step is considered the most important control step in the biosynthesis of pantothenate-dependent enzymes and it is subjected to feedback regulation by CoA itself or its thioester derivatives (27, 30). Furthermore, the next step is a condensation reaction with cysteine at the expense of ATP (or CTP in bacteria) yielding 4'-phosphopantothenoylecysteine which is decarboxylated to form 4'-phosphopantetheine. These two reactions are catalyzed by the 4'-phosphopantothenoylecysteine synthase (CoaB) and 4'-phosphopantothenoylecysteine decarboxylase (CoaC) domains of a bifunctional enzyme in prokaryotes (CoaBC). In addition, it is also catalyzed by two distinct proteins in eukaryotes (PPCS and PPCDC) (27,30). 4'-Phosphopantetheine is subsequently converted to dephospho-CoA by phosphopantetheine adenylyltransferase (CoaD), a second rate-limiting reaction in the pathway (27, 30). Afterwards, dephospho-CoA is phosphorylated by dephospho-CoA kinase (CoaE) at the 3'-OH of the ribose to form CoA. The CoaD and CoaE activities are associated with two separate enzymes in prokaryotes and plants, but fused in a bifunctional enzyme which is termed as CoA synthase (COASY), in mammals (27, 30).

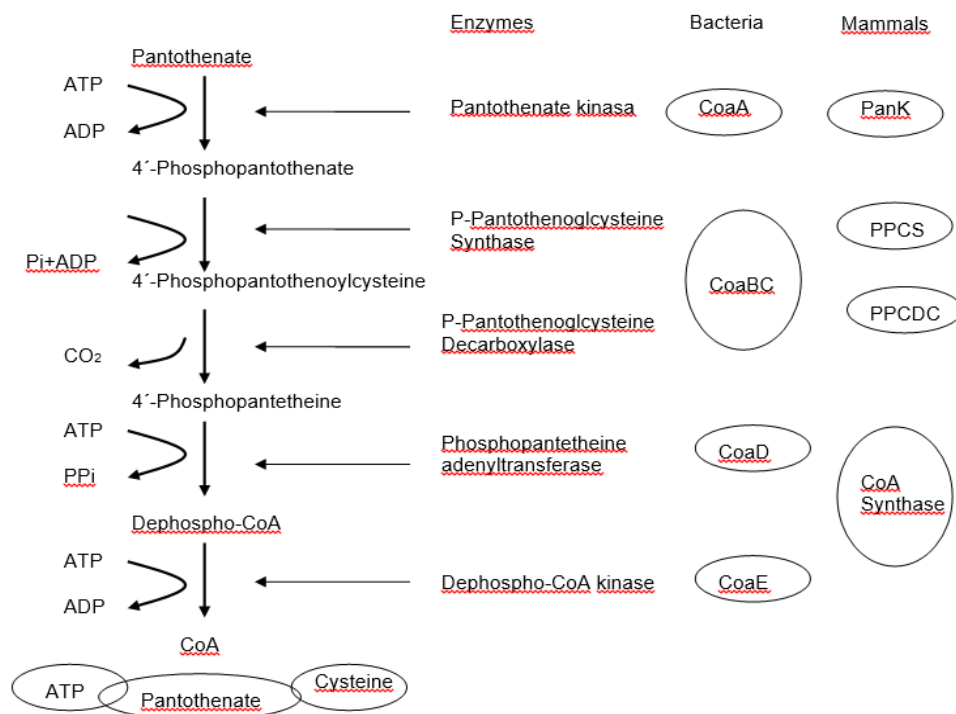
In bacteria, the nomenclature for the biosynthetic enzymes is CoaA, CoaBC (bifunctional enzyme), CoaD and CoaE for each of the steps previously discussed and presented in figure 1. In mammals, the corresponding biosynthetic enzymes are PanK, PPCS, PPCDC, and COASY, encompassing phosphopantetheine adenylyltransferase and dephospho-CoA kinase as a unique enzyme.

CoA accounts for a large proportion of cellular pantothenic acid, although ACP also contains the pantothenic acid molecule (23). However, the synthesis of ACP has not yet been elucidated completely (23).

CoA catabolism occurs as the reverse of the biosynthetic pathway except that 4'-phosphopantetheine is converted to pantetheine followed by conversion to pantothenic acid by the pantetheinase enzyme (27, 32). In the metabolic pathway, CoA is desphosphorylated at the 3' position of ribose to

form dephospho-CoA. Dephospho-CoA is then degraded to 4'-phosphopantetheine and 5'-AMP. Therefore, dephosphorylation of 4'-phosphopantetheine forms pantetheine. In the final step of the metabolic pathway, pantetheine is hydrolyzed into pantothenic acid and cysteamine by the enzyme, pantetheinase (also called vanin). In addition, pantothenic acid generated during the CoA degradation is recycled for another biosynthesis of CoA or is excreted intact in urine, where it can be measured using a *Lactobacillus plantarum* assay or a radionmunoassay (12).

Fig. 1. CoA biosynthetic pathway and its key players in bacteria and mammals: ATP, adenosine triphosphate; ADP, adenosine diphosphate; CO₂, carbon dioxide; PPi, pyrophosphate.



Sources and dietary intake

Animals and some microbes lack the capacity to synthesize pantothenate and are totally dependent on the uptake of exogenous pantothenic acid. However, most bacteria such as *Escherichia coli*, plants, and fungi synthesize pantothenic acid, and as such pantothenate is found virtually everywhere in biology (27, 30). Pantothenic acid is found both free and conjugate in virtually all plant and animal cells (12). However, data on the pantothenic acid content of food are very limited. Chicken, beef, potatoes, oats, tomato products, liver, kidney, peanuts, almonds, yeast, egg yolk, broccoli, cheese, lobster, and whole grains are reported to be the major sources of pantothenic acid (12, 23). Also, royal bee jelly and ovaries of tuna

and cod have very high levels of pantothenic acid (12). Others such as meats, vegetables, milk, and fruits also contain moderate amounts of pantothenic acid (30). Processing and refining grains produce a loss of pantothenic acid content (12). Ordinary cooking does not cause excessive losses of pantothenic acid (12). However, freezing and canning of vegetables, fish, meat, and dairy products has been shown to decrease the pantothenic acid content of foods (12).

The U.S. Institute of Medicine Food and Nutrition Board regularly updates dietary guidelines that defines the quantity of each micronutrient that is “adequate to meet the known nutrient needs of practically all healthy persons” (12). These Recommended Dietary Allowances (RDA) were revised between 1998 and 2001 (12). As it was stated in this revision, due to lack of suitable data, an Estimated Average Requirement and thus a RDA for pantothenic acid in humans of any age cannot be established (12). Therefore, the available information on pantothenic acid can only be used to support the adequacy of the Adequate Intake (AI), which is the amount to prevent a deficiency state of the vitamin (12). The usual pantothenic acid intake is 4 to 7mg/day, as reported in small groups of adolescents and adults of various ages (12). There is no evidence suggesting that this range of intake is inadequate. Thus, the approximate midpoint -5mg/day- is set as the AI for adults. The AIs in other age groups have been usually calculated by extrapolating from adult values (Table 1).

Except during pregnancy and lactation, there is no basis for determining a separate recommendation based on gender. Thus, the AIs for men and women are the same (12). Curiously, a study reported that pantothenic acid levels in blood and urine were significantly lower in females using oral contraceptives (9 women) compared with four females who does not (29).

Some studies have shown that certain subsets of the population might consume insufficient pantothenate in their diets (23,24). However, it is possible that intestinal flora contributes to overall vitamin B₅ status in humans (23). Intestinal bacteria would produce enough pantothenate to ward off signs of a deficiency state in humans (23). However, the contribution of bacterial synthesis to body pantothenic acid levels or fecal losses in humans has not been quantified (12).

Whole blood and urine concentrations of pantothenate are indicators of status (12). Although, it is theoretically possible that erythrocyte concentrations are a more accurate representation of status than whole-blood concentrations because of the contribution of serum pantothenic acid to the latter, no clear advantage of using erythrocyte values has been shown (12). However, plasma or serum levels are not considered to be accurate for measuring pantothenate status (12).

- Table 1. Adequate Intake of pantothenic acid in humans according to life stage groups, modified from Dietary Reference Intakes: Vitamins (U.S. Food and Nutrition Board, released June 12, 2000).

Stage Group	Adequate Intake (mg/dl)
Infants	
0 – 6 mo	1.7
7 – 12 mo	1.8
Children	
1 – 3 y	2
4 – 8 y	3
9 – 13 y	4
Adolescents	
14 – 18 y	5
Adults	
19 - > 70 y	5
Pregnancy	
(any age)	6
Lactation	
(any age)	7

Deficiency

As a consequence of the ubiquitous nature of pantothenic acid, a naturally occurring vitamin deficiency in humans either does not occur or has not been recognized (27). Presumably even in very poor diets, other vitamin deficiencies are limiting factors before pantothenic acid deficiency causes definite trouble (23). Actually, our knowledge about pantothenic acid deficiency in man comes from some studies on the burning-feet syndrome, a disorder which is considered as a natural deficiency state (6, 17). Consequently, this is in addition with the investigations inducing pantothenate deficiency in healthy volunteers feeding on a devoid diet of pantothenic acid, along with the administration of vitamin antagonists (3, 19, 20, 39).

In the Spanish Civil War and among malnourished prisoners held by the Japanese in the South of Pacific during the World War II, common complaints were numbness and burning pain in the feet (12, 26). Patient's condition was reported to improve by adding rice Polishings and yeast to their diet, although not cured completely. Thus, this finding suggested that a deficiency of some vitamin B-complex factor was responsible for the disease (17, 26). The underlying nutritional disorder was attributed to the deficiency of pantothenic acid, riboflavin, nicotinic acid, thiamine, or some combinations (26). Pantothenic acid deficiency is now often considered to be responsible for these symptoms (12, 26) on the basis of the report by Gopalan in 1946 (17). Here, the symptoms were remedied with calcium

pantothenate supplementation, but not when other B-complex vitamins were administered. However, a later controlled trial carried out in 56 patients from a rural area of Sri Lanka did not support these findings.

In the mid-to late 1950s, internists William Bean and Robert Hodges and their colleagues at the University of Iowa produced experimental pantothenic acid deficiency in man by the administration of a vitamin antagonist in combination with a deficient pantothenic acid diet (3, 19, 20, 39). These studies were undertaken in a few healthy volunteers. After taking the drug omegamethylpantothenic acid (a pantothenate kinase inhibitor) along with a partly synthetic diet deficient in pantothenate, serious clinical symptoms appeared within a few weeks. The triad of fatigue (including apathy and malaise), headache, and weakness was the most consistent finding. Other symptoms included emotional lability, impaired motor coordination, paresthesias, burning sensations of the hands and feet, muscle cramps, and gastrointestinal disturbance such as nausea, vomiting and abdominal cramps. Some subjects had tachycardia, orthostatic hypotension, and fluctuations in arterial blood pressure. In some individuals, upper respiratory infections were common, while in others, they were not. One subject who had many infections had a decrease in gamma globulins, but in other subjects, they were normal. Furthermore, other lab abnormalities included a reduction in urinary 17-ketosteroids, a loss of the eosinopenic response to ACTH, abnormal glucose tolerance, and increased sensitivity to insulin (3, 19, 20). Secretion of gastric hydrochloric and pepsin was also reduced in these subjects (39).

However, we have to emphasize the small number of individuals included and the considerable variation in clinical manifestations among them particularly in relation to these studies. Moreover, the clinical symptoms were unspecific and some artefacts were introduced in the experiment due to the nature of the experimental plan. For example, subjects were isolated in a ward during the experiment and fed by a gastric tube. These conditions may explain some of the emotional alterations that the individuals suffered. In addition, one cannot rule out that some of these symptoms were not adverse side effects of the administered drug. Finally, prompt and complete recovery did not always follow pantothenic acid administration. Improvement of the paresthesias and muscle weakness usually followed the administration of the vitamin, but fatigue and some degree of irritability persisted.

Calcium hopantenate has a structural formula similar to that of pantothenic acid and is obtained by substituting the β -alanine moiety of pantothenic acid for gamma aminobutyric acid (GABA). So, it has a GABAergic effect on the central nervous system. Since 1978, this drug has been available only in Japan for the treatment of diminished reactivity in

organic brain diseases of children and adults. This compound is also a pantothenic acid antagonist, with a potency of three times higher than that of omega-methyl pantothenic acid (33).

Between 1983 and 1985, eleven Japanese children, aged between 9 months and 10 years, suffered from Reye-like syndrome during calcium hopantenate therapy, and seven of them died (33). The duration of administration of hopantenate was varied, ranging from 15 days to 15 months (median: 160 days) and the dosage from 0.5 to 3g per day. Noda et al. (33) have reported three additional senile patients who developed fatal Reye-like syndrome coincident with treatment of hopantenate for 120 to 124 days, at a dose of 33 to 58mg/kg/d. Serum levels of pantothenic acid was measured in one patient and low levels was found. On the basis of these data, the authors speculated with the possibility that the pathogenesis of the Reye-like syndrome could be due to pantothenic acid deficiency produced by calcium hopantenate.

Finally, Leonardi et al., in their excellent and exhaustive review article on coenzyme A, pointed out that extremely low CoA resulting from pantothenate deficiency, either in animals models and humans, is associated with hypoglycemia, increased sensitivity to insulin, elevated serum triglycerides, and hepatic steatosis (consistent with an inability to degrade fatty acids) (27).

Medical aspects

Several clinical trials have been undertaken in humans using pantothenic acid supplementation and its derivatives in various medical fields, such as hyperlipedemia, obesity, acne vulgaris, alopecia, hepatitis A, lupus erythematosus, osteoarthritis, rheumatoid arthritis, and wound healing (1, 21, 23). Unfortunately, a firm conclusions regarding therapeutic effectiveness cannot be drawn from many of these studies, given the nonrandomized design, statistical biases, confounding variables, and small sample size of participating patients.

Moreover, specific cysteamine treatment has dramatically changed the course of cystinosis (21). Furthermore, recent research on CoA metabolic enzymes has led to the discovery of uniquely non-metabolic roles for both enzymes and their metabolites, opening a broad field of investigation (32).

Hyperlipidemia

The effects of pantethine on the treatment of hyperlipoproteinemia have been investigated in numerous studies. Pantethine is a dimer of pantothenic acid linked by a disulfide cystamine (see biochemistry). McRae has reviewed 28 clinical trials from the literature on this topic, which provided a pooled population of 646 hyperlipidemic patients (31). All but 6

of these investigations were conducted in Italy (31). Only 4 of the 28 published studies used a randomized double-blind study design, and only one of these was controlled with placebo (31). Oral supplementation of pantethine resulted in a tendency toward normalization of lipid values during a study period of 4 months (1, 23, 31). Only one study out of these 28 clinical trials showed results in 9 and 12 months (31). Administration of pantethine resulted in a progressive decrease in total cholesterol, triglycerides, and low-density lipoprotein cholesterol, along with an increase in high-density lipoprotein cholesterol (31), as shown in table 2. However, the doses used of pantethine ranged from 300 and 600mg twice daily. The most common dosage administration was 300mg 3 times a day (31). The mechanism of the action of pantethine in normalizing parameters associated with dyslipidemia is unknown, although one can assume it to be secondary to the increased levels of intracellular pantothenate coenzymes (1). However, two recent papers have not confirmed these data in North American people (13, 35). Thus, future randomized, double-blind, and placebo-controlled trials with longer intervention are needed to clarify the possible therapeutic effect of pantethine on lipids. This is because some methodological shortcomings and narrow regional population are involved in these investigations (31).

A reduction in very low-density lipoprotein cholesterol and apolipoprotein A has also been reported in patients treated with pantethine (1, 21). No studies have investigated whether pantothenic acid has lipid-lowering effects.

Table 2. Percentage mean change from baseline for serum lipids at months 1 through 4 (31).
↑: Increase. ↓: Decrease

	1 st month	2 nd month	3 rd month	4 th month
Total serum cholesterol				
cholesterol	↓ 8.7%	↓11.6%	↓12.6%	↓15.1%
Low-density lipoprotein	↓10.4%	↓15.2%	↓17.7%	↓20.1%
cholesterol				
High-density lipoprotein	↑ 6.1%	↑ 7.8%	↑10.7%	↑ 8.4%
cholesterol				
Triglycerides	↓14.2%	↓15.8%	↓23.7%	↓32.9%

Platelets

Extrinsic factors, such as the plasma lipids, play a major role in the regulation of the platelet lipid pattern (21). The platelet membrane lipids modulate certain important platelet functions, such as platelet aggregation and thromboxane A₂ synthesis. Therefore, a number of investigations have been performed on the effects of pantethine treatment on the platelet

function. It has been shown that oral treatment with pantethine led to significant decrease in the total cholesterol and the total phospholipids not only in the plasma, but also in the platelets, without any change in their ratio (21). The effects of pantethine on the membrane platelet composition may influence the fluidity of the cell membranes (1, 21). Thus, it has been suggested that pantethine supplementation might prevent atherogenesis in man through its effect on serum lipid profile and platelet aggregability (21).

The most common serious complication of *Plasmodium falciparum* infection in man is cerebral malaria, with a case fatality rate of 20 to 50% (14). The pathogenesis of cerebral malaria is currently viewed in relation to the process of sequestration of parasitized erythrocytes in the cerebral microvasculature (14). Among other pathogenic mechanisms, the process is accompanied by platelet and endothelial cell activation (14). An investigation has shown that infected mice with *P. berghei* did not develop the cerebral syndrome when pantethine was administered (34). The protection was associated with down-regulation of platelet responsiveness and impairment of endothelial cell activation (34). In this experiment, parasite development was unaffected by panthetine, as infected mice who escaped from cerebral malaria died of high parasitemia (34). Unfortunately, neither this nor any other experimental malaria model provides a reliable representation of human cerebral malaria (14).

Cystinosis

For now, therapy of cystinosis relies on the aminothioliol cysteamine (4, 5, 16, 44). Cystinosis is a rare autosomal recessive disorder with an estimated incidence of 1 case per 100,000 to 200,000 live births (16). It is caused by mutations in the gene CTNS, and is mapped to chromosome 17p13, which encodes cystinosin, a lysosomal cystine transporter (5, 16, 44). However, defects in this transporter lead to the accumulation of intralysosomal cystine crystals and widespread cellular destruction. The predominant pathological finding in cystinosis is the presence of cystine crystals in almost all cells and tissues, including the conjunctivae, corneas, liver, spleen, lymph nodes, kidneys, thyroid, intestines, rectal mucosa, muscle, brain, macrophages, and bone marrow (5, 16). The disease is manifested as a multisystem disorder that affects the kidney (Fanconi syndrome, renal failure), the eyes, muscles, central nervous system, lungs, and various endocrine organs. Nevertheless, kidney involvement remains the earliest and foremost clinical characteristic of the disorder.

The mainstay of cystinosis therapy is oral cysteamine bitartrate (trade name Cystagon[®], Mylan Pharma, USA), an aminothioliol that can lower intracellular cystine content by 95% (16, 44). Consequently, cysteamine is administered in four divided doses; but newly long-acting, enteric-coated

formulations are available (called RP103) by Raptor Pharmaceutical Corp. (USA), which can be administered twice a day (4, 5). The mechanism of intralysosomal cystine depletion involves entry of cysteamine into the lysosomal compartment through a specific transporter, and a disulfide reaction with cystine, resulting in the equimolar generation of a cysteine-cysteamine molecule and a molecule of cysteine. Both compounds can exit lysosomes via “system c” transporters, bypassing the defective cystinosis pathway (5, 16, 44). In well-treated children, cysteamine has proven efficacy in delaying renal glomerular deterioration, enhancing growth, and preventing hypothyroidism (4, 5, 16, 44). Corneal cystine crystals do not dissolve with oral cysteamine therapy, but do respond to the administration of cysteamine eye drops (5). Therefore, the U.S. Food and Drug Administration (FDA) has approved a formulation for this purpose.

Approximately 14 percent of patients are unable to tolerate cysteamine therapy because of nausea and vomiting (5). Intracellular cysteamine is produced by the action of the enzyme pantetheinase on pantetheine. Pantethine, the disulfide dimer of pantetheine, was proven in the treatment of four cystinotic children (45). Thus, pantethine is non-toxic and more palatable than cysteamine. The authors concluded that pantethine had less efficacy than cysteamine to deplete leukocytes from cystine; and therefore, it should only be considered in cases of cysteamine intolerance (45).

Miscellaneous Medical Uses

An open-label study included one hundred patients with acne to be treated with high doses of pantothenic acid (10g/day in four divided doses) for eight weeks or longer. The authors reported that the disease was usually controlled by eight weeks in cases of moderate severity (23). A recent paper has indicated that the administration of a pantothenic acid-based dietary supplement in healthy adults with facial acne lesions reduced total facial lesion after 12 weeks of supplementation (2.2g/day of pantothenic acid) (46).

A study used pantothenic acid at a dose of 100mg/day for 4-5 months to treat diffuse alopecia in women. No beneficial effects could be demonstrated (23).

One hundred obese patients of Chinese descent were treated with pantothenic acid (10 g/day in four divided doses) along with a calorie restricted diet. The authors noted an average weight loss of 1.2 Kg per week and no side effects were observed (23).

A randomized, double-blind, and placebo-controlled study compared the effect of pantothenic acid and L-cysteine in the treatment of osteoarthritis of the knees. Thus, no difference was observed either subjectively or objectively between the two groups (23).

By the early 1960s, the effects of intramuscular daily injection of calcium-D-pantothenate into patients with rheumatoid arthritis were tested (2). The authors reported temporary alleviation of symptoms and no uniform success.

The efficacy of panthenol for pediatric post-tonsillectomy pain and wound healing has been evaluated (45). Panthenol (synonyms: D-panthenol or dexpanthenol) is a stable alcoholic analogue of pantothenic acid. Postoperative administration of panthenol significantly accelerated the wound healing process and reduced tonsillectomy-related complaints, independently of the surgical technique used. The mechanism(s) of the action of panthenol for these effects remains elusive (7).

The effect of oral supplementation of 1.5g/day each of D-pantothenic acid and L-cysteine on exercise performance was examined in eight healthy male volunteers aged 22.9 ± 1.4 years (41). The conclusion of this study was that “acute feeding with pantothenate and cysteine does not alter muscle CoA content and consequently does not affect muscle fuel metabolism or performance during exercise in humans”.

Recently, cysteamine has been used in the treatment of non-alcoholic fatty liver disease in children with promising results (5). Moreover, some experimental and clinical data support the usefulness of cysteamine in the treatment of patients with Huntington Disease. Thus, a randomized, controlled, and double-blind multicenter phase II-III trial using RP103 cysteamine formulation is currently underway (5). In addition, some animal studies have suggested that cysteamine might also be beneficial in the treatment of Parkinson’s disease, as well as in certain neuropsychiatric disturbances, such as schizophrenia and major depressive disorders (5).

Finally, during the last few decades, the inhibition of the metabolism of CoA is being extensively investigated in relationship to its potential antimicrobial effect. A breakthrough discovery was the molecular cloning of genes encoding CoA biosynthetic pathway enzymes (27,30), of the pantothenate kinases in particular. These enzymes have been divided into four groups based on their amino acid sequences, i.e., prokaryotic type I, II, and III CoaAs and eukaryotic PanK (27). Type I and III CoaAs are widely distributed among bacteria, while the type II CoaA is limited to staphylococci. The requirement for CoA in numerous metabolic bacterial processes and the diversity amongst the structure of pantothenate kinase in bacteria and mammals have made these enzymes an attractive drug targets for the development of novel antimicrobial agents (27,30). Pantothenamides, and amides derived from pantothenic acid, are substrates of the key rate-limiting enzyme pantothenate kinase (CoaA). N-pentylpantothenamide (N5-Pan) and N-heptylpantothenamide (N7-Pan) are the prototypes of pantothen. However, only Gram-positive bacteria are sensitive to pantothenamide at

pharmaceutically realistic concentrations (22). In addition, they have also been shown to possess activity against fungi and malaria parasites (22). It was thought that the mechanism of action of pantothenamides was the formation of CoA analogs that lead to the transfer of an inactive 4'-phosphopantothenamide moiety to ACP, which is the first step in the bacterial type II route of fatty acid synthesis (10,22,28). However, the precise mechanism by which pantothenamides act to inhibit bacterial viability is not yet completely resolved, because pantothenate supplementation do not revert this effect (22). However, two recent papers have shown that the antibacterial (22) and anti-malaria (37) activities of pantothenamides might be increased through the inactivation of the enzyme pantetheinase.

Another compound, the antibiotic CJ-15,801 was discovered by Sugie et al. at Pfizer Laboratories in 2001, from the fermenting cultures of a *Sematosporium* sp. fungus (40). Structural analysis showed the compound resembles pantothenic acid, with the notable exception of a *trans*-substituted double bond in the β -alanine moiety. CJ-15,801, like pantothenamides, selectively inhibits the growth of *Staphylococcus aureus* and the intraerythrocytic growth stage of the malaria parasite *Plasmodium falciparum* (40). The basis for CJ-15,801's unique antimicrobial specificity may also be based on the type-specificity of their pantothenate kinases, both of which have been characterized as type II enzymes (40). Van der Westhuyzen et al. have demonstrated that CJ-15,801 acts as an antimetabolite against staphylococci using the first enzyme of the CoA biosynthesis to enter the pathway, after which it inhibits the second CoA biosynthesis enzyme, phosphopantothenoylcysteine synthase, by forming a tight-binding inhibitor *in situ* (40). This mode of action is reminiscent of the sulphonamide antibiotics, which block folic acid biosynthesis using a similar strategy.

Pantothenol is an alcoholic analogue of the pantothenic acid, which is widely used in health-care and cosmetic industries (see below). Pantothenol has been reported to reduce the activities of type I and II CoaAs, with a more potent effect being observed on the type II CoaA than on the type I CoaA. By contrast, the type III CoaA is not inhibited by pantothenol (9). Thus, pantothenol has been shown to markedly inhibit the phosphorylation activity of pantothenate kinases *in vitro* of *Escherichia coli* and staphylococci (9). The growth of *Mycobacterium tuberculosis* is also inhibited by pantothenol (25). At the same time, Saliba et al. showed that pantothenol inhibited the *in vitro* growth of *Plasmodium falciparum* (36). The authors speculated that the mechanism might involve the competition with pantothenate, inhibiting the activity of the parasite's pantothenate kinase.

Therefore, the antimicrobial properties of the inhibitors of the metabolism of the CoA are an exciting and promising field of research.

Tolerable upper intake level and adverse side effects

Tolerable Upper Intake Level (UL) is the maximum level of daily nutrient intake that is likely to pose no adverse health risks (12). The UL represents total intake from food, water, and supplements. However, there is no sufficient scientific evidence on which to base a UL for pantothenic acid (12). Evidence available from clinical studies using high doses of pantothenic acid indicates that intake considerably in excess of 5mg do not represent a health risk for the general population (23).

On the other hand, the existing clinical studies on pantothenic acid were not designed to monitor and assess side effects. Thus, information of the adverse effects on human is limited. The most commonly reported side effect is mild transient gastrointestinal disturbance such as nausea, heartburn, and diarrhea (1, 23, 31). Adverse effects typically do not occur until doses exceed 1 gram daily (23). In doses of 10g/day, diarrhea is reported to occur. Furthermore, there has been one case report of eosinophilic pleuropericardial effusion in a patient taking 300mg/day of pantothenic acid in combination with 10g/day of biotin for two months. Hence, the condition was resolved after the vitamins were stopped (11).

Panthenol, the alcoholic analogue of pantothenic acid, is widely used in a variety of cosmetics, topical medical, over-the-counter, and in photoprotective products (22, 23, 28, 37). Because of its moisturizing and conditioning properties, it is mainly used in hair preparations. Nevertheless, it is also added to other products. Allergic contact dermatitis caused by panthenol is considered to be rare, but has been occasionally reported following the use of medications, moisturizers, and sunscreens (8, 15, 18).

Pantothenic acid has an FDA Use-in-Pregnancy category A rating for doses at or below Adequate Intake. What this means is that “well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in the later trimester)” for doses at or below this level (23). Higher doses of pantothenic acid have a Pregnancy category C rating (23). Cysteamine is also classified as a Pregnancy category C drug (5). That is to say that “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite the potential risks”.

Conclusion

Pantothenic acid is a naturally occurring physiological compound, which offers potential effective therapeutic actions on diverse clinical conditions. The proper role of pantothenic acid in the therapeutic armamentarium is still challenging to proper answer. In light of the potential therapeutic benefit of pantothenic acid and its derivatives and the lack of

adverse reactions, there is a need to address the issue of treatment with this compound. Since cysteamine has been useful in the treatment of cystinosis, it is possible that other clinical conditions may benefit the treatment with this compound. In our opinion, pantothenic acid (and its derivatives) deserves much more attention than it has received now.

References:

- Anonymous (2010). Pantethine monograph. *Altern Med Rev* 15:279-282.
- Barton-Wright EC, Elliot WA (1963). The pantothenic acid metabolism of Rheumatoid Arthritis. *Lancet* 282:862-863.
- Bean WB, Hodges RE, and Daum K (1955). Pantothenic acid deficiency induced in human subjects. *J Clin Invest* 34:1073-1084.
- Bertholet-Thomas A, Bacchetta J, Tasic V, and Cochat P (2014). Nephropathic cystinosis: a gap between developing and developed nations. *N Engl J Med* 370:1366-1367.
- Besouw M, Masereeuw R, van den Heuvel L, and Levtschenko E (2013). Cysteamine: an old drug with new potential. *Drug Discov. Today* 18:785-792.
- Bibile SW, Lionel NDW, Dunuwille R, and Perera G (1957). Pantothenol and the burning feet syndrome. *Br J Nutr* 11:434-439.
- Celebi S, Tepe C, Yelken K, and Celik O (2013). Efficacy of dexpanthenol for pediatric post-tonsillectomy pain and wound healing. *Ann Otol Rhinol Laryngol* 122:464-467.
- Chin MF, Hughes TM, and Stone NM (2013). Allergic contact dermatitis caused by panthenol in a child. *Contact Dermatitis* 69:321-322.
- Chohnan S, Murase M, Kurikawa K, Higashi K, and Ogata Y (2014). Antimicrobial activity of pantothenol against staphylococci possessing a prokaryotic type II pantothenate kinase. *Microbes Environ* 29:224-226.
- Choudhry AE, Mandichak TL, Broskey JP, Egolf RW, Kinsland C, Begley TP, Seefeld MA, Ku TW, Brown JR, Zalacain M, and Ratnam K (2003). Inhibitors of pantothenate kinase: novel antibiotics for Staphylococcal infections. *Antimicrobial Agents Chemother* 47:2051-2055.
- Debourdeau PM, Djezzar S, Estival JL, Zammit CM, Richard RC, and Castot AC (2001). Life-threatening eosinophilic pleuropericardial effusion related to vitamins B5 and H. *Ann Pharmacother* 35:424-426.
- Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998) 10. Pantothenic Acid. National Academies Press 357-373. <http://www.nap.edu/catalog/6015.html>
- Evans M, Rumberger JA, Azumano I, Napolitano JJ, Citrolo D, and Kamiya T (2014). Pantethine, a derivative of vitamin B5, favorably alters total, LDL and non-HDL cholesterol in low to moderate cardiovascular risk subjects

- eligible for statin therapy: a triple-blinded placebo and diet-controlled investigation. *Vasc Health Risk Manag* 10:89-100.
- Fairhurst RM, and Wellems TE (2010). *Plasmodium* species (Malaria). In: Mandell GL, Bennett JE, Dolin R (ed) Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th edn. Churchill Livingstone Elsevier, Philadelphia, pp 3437-3462.
- Fernandes S, Macias V, Cravo M, Amaro C, Santos R, and Cardoso J (2012). Allergic contact dermatitis caused by dexpanthenol: report of two cases. *Contact Dermatitis* 66:159-162.
- Ghal WA, Thoene JG, and Schneider JA (2002). Cystinosis. *N Engl J Med* 347:111-121.
- Gopalan C (1946). The 'burning-feet' syndrome. *Indian Med Gaz* 81:22-26.
- Gulec AI, Albayrak H, Uslu E, Baskan E, and Aliagaoglu C (2014). Pustular irritant contact dermatitis caused by dexpanthenol in a child. *Cutan Ocul Toxicol* (Epub ahead of print). Doi: 10.3109/15569527.2014.883405.
- Hodges RE, Ohlson MA, and Bean WB (1958). Pantothenic acid deficiency in man. *J Clin Invest* 37:1642-1657.
- Hodges RE, Bean WB, Ohlson MA, and Bleiler R (1959). Human pantothenic acid deficiency produced by omega-methyl pantothenic acid. *J Clin Invest* 38:1421-1425.
- Horvath Z, and Vecsei L (2009). Current medical aspects of pantethine. *Ideggyogy Sz* 62:220-229.
- Jansen PAM, Hermkens PHH, Zeeuwen PLJM, Botman PNM, Blaauw RH, Burghout P, Van Galen PM, Mouton JW, Rutjes FPJT, and Schalwijk J (2013). Combination of pantothenamides with vanin inhibitors as a novel antibiotic strategy against Gram-positive bacteria. *Antimicrobial Agents Chemoter* 57:4794-4800.
- Kelly GS (2011). Pantothenic acid. *Altern Med Rev* 16:263-274.
- Kolahdooz F, Spearing K, and Sharma S (2013). Dietary adequacies among South African adults in rural KwaZulu-Natal. *PLoS One* 8:e67184. Doi: 10.1371/journal.pone.0067184.
- Kumar P, Chhibber M, and Surolia A (2007). How pantothenol intervenes in coenzyme: A biosynthesis of *Mycobacterium tuberculosis*. *Biochem Biohys Res Commun* 361:903-909.
- Lanska DJ (2012). The discovery of niacin, biotin, and pantothenic acid. *Ann Nutr Metab* 61:246-253.
- Leonardi R, Zhang Y, Rock CO, and Jackowski S (2005). Coenzyme A: back in action. *Prog Lipid Res* 44:125-153.
- Leonardi R, Chohnan S, Zhang Y-M, Virga KG, Lee RE, Rock CO, and Jackowski S (2005). A pantothenate kinase from *Staphylococcus aureus* refractory to feedback regulation by coenzyme A. *J Biol Chem* 280:3314-3322.

- Lewis CM, and King JC (1980). Effect of oral contraceptive agents on thiamine, riboflavin, and pantothenic acid status in young women. *Am J Clin Nutr* 33:832-838.
- Lopez Martinez D, Tsuchiya Y, and Gout I (2014). Coenzyme A biosynthetic machinery in mammalian cells. *Biochem Soc Trans* 42:1112-1117.
- McRae MP (2005). Treatment of hyperlipoproteinemia with pantethine: a review and analysis of efficacy and tolerability. *Nutr Res* 25:319-333.
- Nitto T, and Onodera K (2013). The linkage between Coenzyme A metabolism and inflammation: roles of pantetheinase. *J Pharmacol Sci* 123:1-8.
- Noda S, Umezaki H, Yamamoto K, Araki T, Murakami T, and Ishii N (1988). Reye-like syndrome following treatment with the pantothenic acid antagonist, calcium hopantenate. *J Neurol Neurosurg Psychiatry* 51:582-585.
- Penet MF, Abou-Hamdan M, Coltel N, Cornille E, Grau GE, De Reggi M, and Gharib B (2008). Protection against cerebral malaria by the low-molecular-weight thiol pantethine. *Proc Natl Acad Sci USA* 105:1321-1326.
- Rumberger JA, Napolitano J, Azumano I, Kamiya T, and Evans M (2011). Pantethine, a derivative of vitamin B(5) used as a nutritional supplement, favorably alters low-density lipoprotein cholesterol metabolism in low- to moderate-cardiovascular risk North American subjects: a triple-blinded placebo and diet-controlled investigation. *Nutr Res* 31:608-615.
- Sabila KJ, Ferru I, and Kirk K (2005). Provitamin B₅ (pantothenol) inhibits growth of the intraerythrocytic malaria parasite. *Antimicrobial Agents Chemother* 49:632-637.
- Spry C, Macuamule C, Lin Z, Virga KG, Lee RE, Strauss E, and Sliba KJ (2013). Pantothenamides are potent, on-target inhibitors of *Plasmodium falciparum* growth when serum pantetheinase is inactivated. *PLoS One* 8:e54974. Doi: 10.1371/journal.pone.0054974.
- Stiller ET, Harris SA, Finkelstein J, Keresztesy JC, and Folkers K (1940). Pantothenic acid. VIII. The total synthesis of pure pantothenic acid. *J Am Chem Soc* 62:1785-1790.
- Thornton GHM, Bean WB, and Hodges RE (1955). The effect of pantothenic acid deficiency on gastric secretion and motility. *J Clin Invest* 34:1085-1091.
- Van der Westhuyzen R, Hammons JC, Meier JL, Dahesh S, Moolman WJA, Pelly SC, Nizet V, Burkart MD, and Strauss E (2012). The antibiotic CJ-15,801 is an antimetabolite which hijacks and then inhibits CoA biosynthesis. *Chem Biol* 25:559-571.
- Wall BT, Stephens FB, Marimuthu K, Constantin-Teodosiu D, Macdonald IA, and Greenhaff PL (2012). Acute pantothenic acid and cysteine supplementation does not affect muscle coenzyme A content, fuel selection, or exercise performance in healthy humans. *J Appl Physiol* 112:272-278.

Williams RJ, Lyman CM, Goodyear GH, Truesdail JH, and Holaday D (1933). "Pantothenic acid", a growth determinant of universal biological occurrence. *J Am Chem Soc* 55:2912-2927.

Williams RJ (1939). Pantothenic acid-a vitamin. *Science* 89:486.

Wilmer MJ, Emma F, Levtchenko EN (2010). The pathogenesis of cystinosis: mechanisms beyond cystine accumulation. *Am J Physiol Renal Physiol* 299:F905-F916.

Wittwer CT, Gahl WA, Butler JD, Zatz M, and Thoene JG (1985). Metabolism of pantethine in cystinosis. *J Clin Invest* 76:1665-1672.

Yang M, Moclair B, Hatcher V, Kaminetsky J, Mekas J, Chapas A, and Capodice J (2014). A randomized, double-blind, and placebo-controlled study of a novel pantothenic acid-based dietary supplement in subjects with mild to moderate facial acne. *Dermatol Ther (Heidelb)* 4:93-101.