Risk Assessment — Pantothenic acid

General information

Chemistry

Pantothenic acid consists of a pantoic acid moiety amide-linked to a ß-alanine subunit. Pantetheine consists of pantothenic acid linked to a ß-mercaptoethylamine group. In living systems, the compound is a component of coenzyme A (CoA), which is composed of 4'-phosphopantetheine linked to adenosine 5'-monophosphate, modified by a 3'-hydroxyl phosphate. 4'-Phosphopantetheine is also found covalently linked to various proteins, particularly those involved in fatty acid metabolism.

Natural occurrence

The active vitamin is present in virtually all plant, animal and microbial cells.

Occurrence in food, food supplements and medicines

The majority of pantothenic acid within foods is present as CoA. Chicken, beef, potatoes, oat cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli and whole grains are reported to be major sources of the vitamin, whilst very high levels are present in royal bee jelly (511 mg/kg) and in the ovaries of tuna and cod (2300 mg/kg). Cooking is reported to destroy 15-50% of pantothenic acid in meats and 37 to 78% of pantothenic acid is lost from vegetables during processing. Breakfast cereals may be fortified with 5-6 mg pantothenic acid/100 g.

Pantothenic acid derivatives sold as supplements or medicines are prepared synthetically as calcium pantothenate or panthenol, which are more stable than pure pantothenic acid. In the UK, dietary supplements generally contain up to 550 mg pantothenic acid; licensed medicines may contain a maximum of 50 mg/day pantothenic acid.

Other sources of exposure

The pantothenic acid derivative, panthenol, is added to some cosmetic products.

Recommended amounts

Dietary reference values for pantothenic acid have not been established in the UK. There is no detectable evidence of pantothenic acid deficiency within the general population, even during pregnancy and lactation. Therefore, human requirements for pantothenic acid are considered to be adequately provided by the diet.

Analysis of tissue levels and pantothenic acid status

Blood, urine or tissue pantothenic acid levels may be measured by yeast or *lactobacillus* assay, or by radio-immunoassay. Assays of pantothenic acid in biological materials other than urine require that the compound be first hydrolysed from CoA.

Brief overview of non-nutritional beneficial effects

It has been claimed that supplementation with pharmacological doses of pantothenic acid may alleviate the symptoms of rheumatoid arthritis and lupus erythematosus.

Function

Pantothenate, usually in the form of CoA-containing species (e.g. acetyl CoA, succinyl CoA), fulfils multiple roles in cellular metabolism and in the synthesis of many essential molecules.

Deficiency

Deficiency of pantothenic acid in humans is extremely rare. Pantothenic acid deficiency has been induced experimentally in human subjects by a diet virtually devoid of the vitamin, or by the administration of a metabolic antagonist (omega-methyl pantothenic acid). Signs and symptoms exhibited by subjects given the antagonist (not all of which were necessarily due to the deficiency) included irritability and restlessness, fatigue, apathy, malaise, sleep disturbance, gastrointestinal complaints (such as nausea, vomiting and abdominal cramps) neurological and other clinical effects such as numbness, paraesthesia, muscle cramps and staggering gait, hypoglycaemia and an increased sensitivity to insulin. Historically, pantothenic acid deficiency has been implicated in the 'burning feet' syndrome experienced by severely malnourished prisoners of war.

Interactions

Reports have indicated a sparing effect of some other vitamins, such as ascorbic acid and other B-vitamins, on pantothenic acid within the body. Biotin and pantothenic acid may share a common carrier-mediated uptake mechanism in the gastrointestinal tract and other tissues, although the physiological relevance of this is unknown. Some earlier reports have suggested that high dietary fat and low dietary protein may exacerbate pantothenic acid deficiency.

Absorption and bioavailability

Pantothenic acid is readily absorbed throughout the gastrointestinal tract. Ingested CoA is hydrolysed within the intestinal lumen, *via* the formation of dephospho-CoA, phosphopantetheine and pantetheine, to pantothenic acid. Uptake of these latter two compounds into intestinal tissues has been demonstrated, and subsequently the enzyme, pantetheinase, can hydrolyse pantetheine to pantothenic acid. Uptake into intestinal cells occurs both by a sodium-dependent active transport mechanism and by passive diffusion. Limited data are available regarding the bioavailability of dietary pantothenic acid. One study found that pantothenic acid in natural foods was approximately 50% bioavailable compared with calcium pantothenate given in a formula diet, as assessed by subsequent urinary excretion of the vitamin.

Distribution and metabolism

Absorbed pantothenic acid is transported to body tissues *via* the blood, primarily as bound forms within erythrocytes. Plasma levels do not correlate well with dietary intake. The majority of tissues import pantothenic acid *via* an active sodium co-transport mechanism. Analysis of rat tissues has shown high concentrations of pantothenic acid in the heart and kidneys. CoA is synthesised from pantothenic acid within cells, with the first, and apparently rate-limiting, step catalysed by pantothenate kinase.

Excretion

Catabolism of CoA leads to the formation of pantothenate, which is excreted in the urine. Excretion levels correlate well with dietary intake.

Toxicity

Human data

Case reports and some much earlier non-controlled studies describe a lack of acute or chronic toxic effects of pantothenic acid compounds (calcium or sodium pantothenate, panthenol) at very high doses (approximately 10,000 mg/day in some cases for a number of years), although such levels have been associated with diarrhoea and gastrointestinal disturbances. In more recent, controlled studies (generally carried out to assess the potential benefits of pantothenic acid supplementation in specific subgroups, for example, arthritic patients) no side effects have been reported for pantothenic acid supplementation at levels up to approximately 2000 mg/day, for periods of several days to several weeks. However, the small numbers of participants and short duration of these studies limit the value of the data regarding any potential rare or long-term toxic effects.

One non-blind, non-randomised, non-placebo-controlled trial, designed to investigate the effectiveness of megavitamin therapy in improving the behaviour of 41 children with attention deficit disorder, showed significant increases in serum aspartate transaminase levels (indicative of liver damage) in 17 children after 12 weeks of multivitamin therapy (including doses of calcium pantothenate increasing during the study period to a maximum of 1200 mg/day). This effect may have been associated with the nicotinamide component of the multivitamin supplement, although this could not be confirmed as the vitamins were not given separately.

Animal data

Data regarding the toxicity of pantothenic acid and its commonly-used pharmaceutical forms in experimental animals are limited because of the small numbers of animals used in the studies. In the early 1940's Unna & Greslin reported acute and chronic toxicity tests with D-calcium pantothenate in mice, rats, dogs and monkeys (Unna and Greslin, 1940, 1941). Acute oral LD_{50} values were very high $\geqslant$ 10,000 mg/kg bw, mice and rats), with lethal doses producing death by respiratory failure. An oral dose of 1000 mg/kg bw produced no toxic signs in dogs or in one monkey. Oral dosing (500 or 2000 mg/kg bw/day to rats, 50 mg/kg bw/day to dogs, 200-250 mg/kg bw/day to monkeys) for 6 months produced no toxic signs or weight loss, or evidence of histopathological changes at autopsy. The offspring of rats

supplemented with 500 mg/kg bw/day calcium pantothenate were fed diets supplemented with 500 mg/kg bw/day calcium pantothenate from weaning; no evidence of toxicity or reduced weight gain, or histopathological changes were observed. The available data do not indicate reproductive or developmental toxicity of pantothenic acid or its commonly used pharmaceutical forms.

Carcinogenicity and genotoxicity

Calcium pantothenate, sodium pantothenate and panthenol were not mutagenic in bacterial tests. No *in vivo* genotoxicity or carcinogenicity data have been found.

Mechanism of toxicity

No data have been identified.

Dose response characterisation

No data have been identified.

Vulnerable groups

No vulnerable groups have been identified.

Genetic variations

No genetic variations in the metabolism or effects of pantothenic acid have been identified.

Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

Human studies

Goldman, 1950; Welsh, 1952, 1954

Supplementation of lupus erythematus patients with doses of pantothenic acid of 10,000 mg/day or more led to gastrointestinal signs and symptoms.

The General Practitioner Research Group, 1980

This randomised, double-blind, placebo-controlled study was carried out to assess the effects of high-dose pantothenate supplementation in alleviating symptoms of arthritis. A total of 47 (31 completed the trial) patients were treated with calcium pantothenate (total daily dose – 500 mg on days 1-2, 1000 mg on days 3-5, 1500 mg on days 6-9, 2000 mg from day 10 onwards) and 47 (34 completed the trial) with placebo for a period of 8 weeks. The patients were suffering from a variety of arthritides, including 27 patients with rheumatoid arthritis. The authors stated that '... no side effects were recorded in 43 patients (91%) on calcium pantothenate as compared to 37 (79%) on placebo.'

Animal studies

Unna & Greslin, 1940, 1941

These were reports of sub-chronic toxicity studies of D-calcium pantothenate in rats, dogs and monkeys (strains not specified). Young rats (10 males and 10 females per group) were fed doses of 50 or 200 mg/day (approximately 500 or 2000 mg/kg bw/day) D-calcium pantothenate, for 190 days. Growth and development were normal and did not differ significantly from those of a control group fed a standard diet. The authors reported that autopsies at the end of the feeding period did not reveal any gross or microscopic changes in the organs (not specified). Six adult dogs and 4 monkeys were fed 50 mg/kg bw/day and 1000 mg/day (approximately 200-250 mg/kg bw/day) D-calcium pantothenate, respectively, for periods of 6 months. None of the animals showed any toxic signs or weight loss during the supplementation period, and again the authors reported that histopathological examination at the end of the supplementation period did not reveal any changes.

Exposure assessment

Total exposure/intake:

Food	Mean: 5.4 mg/day (1990 NDNS) 97.5th percentile: 9.7 mg/day
Supplements	up to 550 mg/day (Annex 4)
Estimated maximum intake	9.7 + 550 = 560 mg/day

No potential high intake groups were identified.

Risk assessment

The available toxicological data on pantothenic acid are limited. However, case reports and some earlier, uncontrolled human studies suggested a lack of acute or chronic toxic effects of pantothenic acid compounds (calcium or sodium pantothenate, panthenol) at very high doses (approximately 10,000 mg/day, in some cases for a number of years). However, doses at such levels have been associated with diarrhoea and gastrointestinal disturbances. In more recent, controlled studies, no side effects have been reported with pantothenic acid supplementation at levels up to approximately 2000 mg/day, for periods varying from several days to several weeks. These studies were generally designed to assess the potential benefits of pantothenic acid supplementation in specific subgroups, for example patients suffering joint disease.

Data regarding the toxicity of pantothenic acid and its commonly-used pharmaceutical forms in experimental animals are also limited. However, doses of 500 and 2000 mg/kg bw/day in rats and 200-250 mg/kg bw/day in dogs and monkeys, given in the diet for periods of six months, were not associated with adverse effects.

ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data from human or animal studies to establish a Safe Upper Level for pantothenic acid.

There are relatively few human data available on the oral toxicity of pantothenic acid from controlled trials. The limited available data have not identified target organ toxicity and the adverse effects that were noted were transient. The apparent low toxicity of pantothenic acid is supported by the available animal data. The General Practitioner Research Group study suggests that doses of 2000 mg pantothenic acid/day are without effect, although this study investigated relatively few individuals, suffering from a variety of clinical conditions (rheumatoid arthritis, osteoarthritis, gout and spondylitis). Adverse effects were not a primary outcome measure, and though the authors specifically noted the absence of side effects in fewer placebo than treated individuals, the method by which these data were collected and the specific nature of the side effects noted are not discussed. An uncertainty factor of 10 is applied to allow for inter-human variability because of the small numbers of individuals involved, of which one third failed to complete the study, and the incomplete investigation of possible adverse effects. Based on these data, for guidance purposes only, a supplemental daily intake of 200 mg (equivalent to 3.3 mg/kg bw/day for a 60 kg adult), in addition to that present in the diet, would not be expected to produce adverse effects in the general population. Assuming a maximum dietary intake of 10 mg/day, this would equate to a total intake of 210 mg/day, or 3.5 mg/kg bw/day for a 60 kg adult.

References

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