ADVERSE REACTIONS

Those who are allergic or hypersensitive to bee pollen can develop symptoms, including pruritis, rhinitis, conjunctivitis and bronchospasm and, in some cases, urticaria and anaphylaxis. Two cases of hepatitis have been reported following ingestion of bee pollen for several weeks. Hypereosinophilia, neurologic symptoms (decreased memory, headache) and gastrointestinal symptoms (nausea, abdominal pain, diarrhea) have also been reported following bee pollen ingestion.

OVERDOSAGE

No reported overdosage of bee pollen.

DOSAGE AND ADMINISTRATION

Typical doses used are 1 to 1.5 grams daily in divided doses.

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Benfotiamine

DESCRIPTION

Benfotiamine, chemically, is an analogue of thiamin or vitamin B_1 (See Thiamin). Biochemically, benfotiamine is a precursor of thiamin. In that sense, benfotiamine is a prothiamine, or provitamin B_1. Benfotiamine was synthesized as part of a Japanese research project initiated over 60 years ago, originally led by the Japanese scientist M. Fujiwara and colleagues, whose mission was to discover and develop more bioavailable forms of thiamin for the treatment and prevention of beriberi, as well as for the treatment and prevention of alcoholic polyneuropathy.

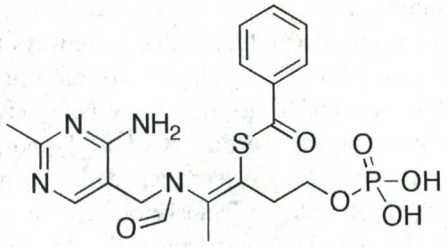
The first compound discovered by these researchers was a disulfide derivative of thiamin, which was isolated from garlic and also found in other members of the allium or onion genus. The compound was named allithiamine and was given the chemical name thiamin tetrahydrofurfuryl disulfide (TTFD). TTFD was found to be more lipophilic than thiamin itself and appeared to have better bioavailability characteristics. Other disulfide derivatives of thiamin were synthesized, and, later, Japanese chemists went on to synthesize S-acyl-thiamin derivatives. One of the derivatives was given the chemical name S-benzoylthiamine monophosphate (BTMP). BTMP is better known by its common name, benfotiamine. Somewhere along the way benfotiamine was classified as a member of the allithiamine family. However, structurally speaking, benfotiamine is quite different from allithiamine. Also, there is no present evidence that benfotiamine is found in garlic or any other member of the allium or onion genus. In fact, to date, there is no evidence that benfotiamine is found naturally.

Along the way the idea was propagated that benfotiamine was significantly more lipophilic than thiamin and that it was perhaps the most bioavailable analogue of thiamin that had been synthesized by the Japanese chemists, much more so even than the disulfide analogues. It was also thought that it was the lipophilic character of a thiamin analogue that promoted greater bioavailability and favored its suitability, over thiamin itself, for therapeutic purposes. Part of this thinking was correct; part was not.

In a recent animal study, it was found that benfotiamine did strongly increase thiamin levels in the blood and liver, better than that found with thiamin itself, but also that very little passed into the brain. Further, physico-chemical data as well as studies with isolated cells strongly suggested that, in contrast to the disulfide derivatives of thiamin, benfotiamine had poor lipophilicity.

Benfotiamine is also known as S-benzoylthiamine monophosphate (BTMP); benzenecarbothioic acid *S*-[-2-[[(4-amino-2-methyl-5-pyrimidinyl)methyl]formylamino]-1-[2-(phosphonooxy)ethyl]-1-propenyl] ester; thiobenzoic acid *S*-ester with N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-N-(4-hydroxy-2-mercapto-1-methyl-1-butenyl)formamide O-phosphate. CAS registry number is 22457-89-2. Its molecular

weight is 466.45, and its molecular formula is $C_{19}H_{23}N_4O_6PS$. Benfotiamine is represented by the following chemical structure.



Benfotiamine

ACTIONS AND PHARMACOLOGY

ACTIONS

Benfotiamine is a precursor of thiamin, or vitamin B_1. Benfotiamine may have antioxidant activity. Benfotiamine may have antiglucotoxic activity, resulting in possible neuroprotective, retinoprotective, cardioprotective and renoprotective activities (see Thiamin for additional actions of thiamin).

MECHANISM OF ACTION

Benfotiamine is a provitamin of thiamin (prothiamin or provitamin B_1) and is converted to thiamin intracellularly. It is more bioavailable than is thiamin and it strongly increases thiamin levels in the blood and the liver when administered orally, but appears to have little effect on thiamin levels in the brain.

Benfotiamine was demonstrated to have direct antioxidative action and to prevent oxidative DNA damage *in vitro*. Benfotiamine prevented oxidative stress induced by the mutagen 4-nitroquinoline-1-oxide (NQO), known to form 8-hydroxydeoxyguanosine via reactive oxygen species (ROS), the uremic toxin indoxyl sulfate, and the peptide hormone angiotensin II. (Angiotensin II induces oxidative stress via its activation of NAD(P)H oxidase.) This was shown in a human embryonic kidney cell line, an epithelial rat kidney cell line and an epithelial porcine kidney cell line. Cell-free experiments also showed a direct antioxidant effect of benfotiamine. Oxidative damage induced by angiotensin II was completely prevented by benfotiamine. The exact mechanism of action of the antioxidant effect is unclear.

Although D-glucose is of utmost importance in cellular metabolism, glucose itself can be quite toxic to tissue when levels are higher than normal. The most serious complications of diabetes—diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy—peripheral vascular disease and cardiovascular disease are caused to a great degree by the toxicity (glucotoxicity) to tissue of high levels of D-glucose. Microvascular and macrovascular pathologies underlie all of these diabetic complications. Since thiamin plays a number of vital roles in the metabolism of glucose, it was thought that benfotiamine may have some therapeutic benefit in the prevention and treatment of these diabetic complications. Preliminary studies suggest that it may.

One of the major questions in pathophysiology is how all the diverse microvascular and macrovascular pathologies result from the toxic effects of elevated D-glucose levels. There are four hypotheses: by increased polyol pathway flux, by increased advanced glycation end products (AGEs) formation, by activation of protein kinase C (PKC) isoforms and by increased hexosamine pathway flux.

The first enzyme in the polyol pathway is aldose reductase. Aldose reductase catalyzes the reduced nicotanimide dinucleotide phosphate (NADPH)-dependent reduction of a wide variety of carbonyl compounds, including glucose. When D-glucose levels are high, aldose reductase reduces D-glucose to the sugar alcohol sorbitol. In the process, NADPH levels are lowered, sorbitol is oxidized to fructose via the enzyme sorbitol dehydrogenase and nicotinamide adenine dinucleotide (NAD+) is reduced to reduced nicotinamide dinucleotide (NADH). This leads to an increase in the cytosolic NADH:NAD ratio, which inhibits activity of the enzyme glyceraldehydes-3-phospate dehydrogenase (GAPDH) and increases the concentration of triose phosphate. Increased triose phosphate may increase concentrations of both methylglyoxal, one of the major precursors of advanced glycation end products (AGEs), and diacylglycerol (DAG). Elevated DAG may activate PCK isoforms (see below for further discussion).

AGEs are found in increased amounts in diabetic retinal blood vessels and renal glomeruli. In fact, the most important measure of long-term glucose control is the measurement of serum hemoglobin A1c. Hemoglobin A1c is glycated hemoglobin. The history of the discovery of AGEs goes back to the early 1900s and to the food chemist Louis-Camille Maillard. In 1912, Maillard described a chemical reaction that occurs with foods and which to a great extent imparts various flavors to foods. The reaction is now called the Maillard reaction or the browning reaction. The Maillard reaction is a nonenzymatic reaction that occurs when aldehydes, ketones and reducing sugars (eg, D-glucose) condense with the amino groups of proteins, peptides or amino acids. These reactions may impart flavor to foods but they do little worthwhile when they occur in the body. It is the Maillard or browning reaction that produces AGEs. Hemoglobin A1c was the first example that nonenzymatic reactions, specifically the Maillard reaction, can occur physiologically.

AGEs can arise from many sources: the auto-oxidation of glucose to glyoxal, the fragmentation of glyceraldehydes-3-

phosphate and dihydroxyacetone phosphate to methylglyoxal, among others. The dicarbonyls react with amino groups of intercellular and extracellular proteins to form AGEs via the Maillard reaction, which consists chemically of Schiff base formation leading to an Amadori derivative. Production of intracellular AGE precursors results in damage to cells and tissues, mainly by increasing oxidative stress. Recently, receptors for AGEs have been identified and called RAGEs, or receptors for advanced glycation end products. Association of AGEs with AGE receptors can either cause further havoc to tissue or neutralize the AGEs, depending on the type of receptor the AGEs bind to. The coupling of AGEs with certain receptors may cause the induction of severe oxidative stress. There is much ongoing research in AGEs and RAGEs

Shunting of excess D-glucose into the hexosamine pathway might also contribute to the severe manifestations of diabetic complications. In this pathway, fructose-6-phosphate is diverted from glycolysis to provide substrates to biochemical reactions that require UDP-N-acetylglucosamine, including proteoglycan synthesis and the formation of O-linked glycoproteins. Basically, activation of the hexosamine pathway by elevated D-glucose levels may result in many changes in both gene expression and protein function, which together contribute to the pathogenesis of diabetic complications.

The PKC family is comprised of at least 11 isoforms, nine of which are activated by the lipid second messenger diacylglycerol (DAG). Elevated levels of D-glucose in cells increase the amount of DAG in microvascular cells and in the retinal and renal glomeruli of diabetic animals. It does this by increasing *de novo* DAG synthesis from the glycolytic intermediate, dihydroxyacetone phosphate. Increases in DAG are thought to lead to activation of PKC, mainly the beta isoform of PKC. Activation of PKC-beta is thought to mediate retinal blood flow and renal blood flow abnormalities.

It is thought that each of the four different pathogenic mechanisms discussed above may reflect a single hyperglycemia-induced process—the overproduction of the reactive oxygen species superoxide by the mitochondrial electron transport chain. Much more research is necessary to establish this most interesting hypothesis.

Benfotiamine has been demonstrated to block three of the four pathways of hyperglycemic damage discussed above—the hexosamine pathway, the DAG-PKC pathway and the advanced glycation end products pathway. These studies were performed both *in vitro* in endothelial cells and *in vivo* in rats with experimental diabetic retinopathy. Benfotiamine was found to prevent diabetic retinopathy in the rats.

As a result of the reduced ability of glyceraldehyde-3-phosphate dehydrogenase to process upstream metabolites, the AGE pathway, the DAG-protein kinase C pathway and the hexosamine pathway are activated. Recently, it has been reported that benfotiamine blocks these pathways by activating the pentose phosphate pathway enzyme transketolase. Transketolase is a major enzyme in the pentose phosphate pathway, catalyzing the reaction of ribose-5-phosphate and xylulose-5-phosphate to glyceraldehyde-3-phosphate and sedoheptulose-7-phosphate. Transketolase requires cocarboxylase or thiamin diphosphate, the active form of thiamin, for its activity.

PHARMACOKINETICS

There is still much we don't know about the pharmacokinetics of benfotiamine. What follows is our present state of knowledge.

Benfotiamine is absorbed from the lumen of the small intestine, either intact as the monophosphate or dephosphorylated by intestinal alkaline phosphatase (found at the brush border of the small intestine) to S-benzoylthiamin. If benfotiamine is not dephosphorylated, then S-benzoylthiamin phosphate enters the circulation and is transported to various tissues, but especially to the liver. Once within the cells, benfotiamine is dephosphorylated to S-benzoylthiamin, the thiazole ring is formed and thiamin is produced. If the dephosphorylation step takes place in the intestine, then S-benzoylthiamin enters the cells, the thiazole ring is formed and thiamin is made. Recent evidence suggests that benfotiamine is dephosphorylated by brush border alkaline phosphatase before it enters the bloodstream. Intracellular thiamin is metabolized to thiamin monophosphate (TP, TMP), thiamin diphosphate (TDP, cocarboxylase) and thiamin triphosphate (TTP). Thiamin is phosphorylated directly to thiamin diphosphate by thiamin diphosphokinase, and thiamin diphosphate is dephosphorylated to thiamin monophosphate via thiamin diphosphatase. Approximately 80% of thiamin in blood is present in erythrocytes as TPP.

It is of interest to compare the pharmacokinetics of benfotiamine with that of thiamin itself. Thiamin is absorbed from the lumen of the small intestine—mainly the jejunum—by active transport and passive diffusion mechanisms. At lower amounts, absorption from the small intestine is by an active, carrier-mediated process that is energy-dependent as well as sodium-dependent. Passive diffusion occurs with higher amounts of thiamin. Absorption of thiamin appears to be limited by a saturable rate-limiting transport mechanism. Only a small percentage of a high dose of thiamin is absorbed. Benfotiamine does not appear to be subject to the rate-limiting transport mechanism. Thiamin is transported by the portal circulation to the liver and by the systemic circulation to various tissues in the body. The transport of

thiamin into erythrocytes appears to occur by facilitated diffusion; it enters other cells by an active process. Total thiamin content in the adult body is about 30 milligrams. Thiamin and its metabolites are mainly excreted by the kidneys.

INDICATIONS AND USAGE

Benfotiamine, synthesized in the 1960s as an analogue and precursor of thiamin (vitamin B_1), has been reported to have greater bioavailability than thiamin itself and so has been postulated to have efficacy in various thiamin-related deficiencies and disorders. There is *in vitro* and *in vivo* experimental animal data, as well as some clinical data, suggesting that benfotiamine may be helpful in relieving inflammatory and neuropathic pain and especially diabetic neuropathy. There is also the suggestion in some research that benfotiamine might be beneficial in some hemodialysis patients, possibly reducing cancer risk in those patients. On the other hand, a recent study has called into question the mode of action through which benfotiamine was thought to achieve these benefits and, in so doing, has also questioned the extent to which some of the observed benefits are real.

RESEARCH SUMMARY

There have been many reports in the literature that benfotiamine is of benefit in diabetes. Among the more recent reports was one in which the researchers concluded that benfotiamine blocks three major pathways of hyperglycemic damage. They showed that through this blockage benfotiamine was able to prevent experimental diabetic retinopathy. They hypothesized that the substance might thus be useful in preventing the development and progression of diabetic complications generally. In an *in vitro* study of human endothelial progenitor cells (EPCs), another group of researchers demonstrated that benfotiamine can help correct hyperglycemic impairment of EPC differentiation into mature, healthy endothelial cells. Benfotiamine's ability to counteract glucose toxicity was again seen as an indication of the substance's ability to help curb diabetic damage generally. In a mouse study, benfotiamine was said to activate glucose metabolism and insulin synthesis in adult bone marrow-derived, insulin-producing cells and thus to prevent glucose toxicity resulting from high concentrations of blood glucose in diabetes mellitus. In a rat study, benfotiamine was reported to relieve inflammatory and neuropathic pain in both diabetic and nondiabetic animals.

A recent clinical test sought to determine whether benfotiamine could prevent some of the postprandial endothelial dysfunction that is a characteristic of diabetes. Thirteen people with type 2 diabetes were given a three-day trial of benfotiamine (1,050 mg per day) and challenged with a hyperglycemic diet. By several measures, the researchers concluded that benfotiamine had significantly prevented both macrovascular and microvascular endothelial dysfunction and oxidative stress in these subjects challenged with a meal rich in advanced glycation end products ages.

A still more recent study, this one related to hemodialysis, was inspired in part by the finding in prior studies that benfotiamine reduces AGEs, as noted above in the diabetes work. This is relevant to hemodialysis patients since they often suffer from thiamin (vitamin B_1) deficiency and accumulation of uremic toxins, including the glycation products. In this research, which comprised two related studies, the research concluded there were indications that benfotiamine helped prevent DNA damage in the peripheral blood lymphocytes of these patients. They speculated, based on some of their findings, that the benefits observed might have been due to a benfotiamine antioxidative effect. They further concluded that benfotiamine might, through this reduction of genomic damage, decrease the higher risk of cancer that dialysis patients experience.

Given the broad range of studies reporting positive effects from benfotiamine over a long period of research, it would seem unlikely that the substance is entirely without clinical merit, but one recent study has rejected one of the most important assumptions of the prior research and has thus called into question the validity of some of the positive conclusions of the earlier reports. This group reported that, contrary to all prior claims, there is little or no evidence that benfotiamine has bioavailability superior to the disulfide analogues. They reported that it is only slightly soluble in water under physiologic conditions and cannot be dissolved at all in some lipids. They claimed that it does not penetrate most cell membranes and that it could not be more effective than any of the other thiamin precursors in preventing or treating diabetic pathology. In their animal study, these researchers observed elevated levels of thiamin in peripheral tissues induced by benfotiamine but no elevation whatever in the brain. Thus they rejected the idea that benfotiamine could be helpful in central nervous system disorders. These researchers acknowledged the findings of others that benfotiamine exerts direct antioxidant effects but stated that it is not clear in what way, if any, this might have an impact on diabetic complications.

Clearly, more research is needed and warranted to try to resolve some of these conflicting findings and shed further light on the mode of action through which benfotiamine may confer some health benefits.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Benfotiamine is contraindicated in those allergic to any component of a benfotiamine-containing product.

PRECAUTIONS

The use of benfotiamine for the support of any medical condition must be discussed with one's physician before starting supplementation.

ADVERSE REACTIONS

Oral benfotiamine is well tolerated at doses up to 600 milligrams daily or higher. There are rare reports of transient headaches.

INTERACTIONS

DRUGS

None known.

NUTRITIONAL SUPPLEMENTS

No known interactions.

FOODS

None known.

HERBS

No known interactions.

OVERDOSAGE

No reports.

DOSAGE AND ADMINISTRATION

Benfotiamine supplements have been recently introduced into the U.S. dietary supplement marketplace. Typical capsules contain 50 mg and 150 mg of benfotiamine, and those using this supplement take from one to four capsules daily (150 mg to 600 mg). However, doses that high need to be discussed with ones physician.

Benfotiamine has been available in Japan since 1961 and is marketed under the trade name Biotamin. Among other reasons, the Japanese take Biotamin (benfotiamine) for hearing disorders and alcohol-related neuropathy, sciatica and other painful nerve conditions. However, its most common use is the prevention and treatment of vitamin B_1 deficiencies.

Benfotiamine has been marketed in Germany since 1978 as 50 mg pills under the trade name Milgamma Mono. In Germany, it is considered a drug and is available in pharmacies without a prescription. Typical daily oral doses range from 50 mg to an authorized maximum of 900 mg. Milgamma Mono ((benfotiamine) is used to prevent and treat vitamin B_1 deficiencies. It is also used to treat painful nerve problems. In about 30 years of use in Germany, there have been only about ten reports of adverse events related to the use of Milgamma Mono, and those have mainly been transient headaches.

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Bentonite

DESCRIPTION

Bentonite is occasionally used in nutritional supplements as a source of trace minerals. It is a type of clay, the major constituent of which is a hydrated aluminum silicate called montmorillonite. Minor constituents found in bentonite include calcium, magnesium and iron. Bentonite is found in certain areas of the United States and Canada. Wyoming bentonite, found in Wyoming and South Dakota, contains sodium and is composed of alternating layers of aluminum oxide and silicon dioxide. It is also known as sodium montmorillonite. Bentonite found in Mississippi is known as calcium montmorillonite.

Bentonite absorbs water readily to form highly viscous suspensions or gels. Bentonite itself is practically insoluble in water. Because of its water-absorbing property, bentonite has been used as a bulk laxative and is used in the pharmaceutical industry as a suspending and stabilizing agent, as well as an adsorbent or clarifying agent. A derivative of bentonite is used to block urushiols from the skins. Urushiols are the etiological factors causing contact dermatitis from poison ivy, poison oak and poison sumac. Bentonite itself may bind to some toxins, such as paraquat, by adsorbing them.

ACTIONS AND PHARMACOLOGY

ACTIONS

Bentonite may be a delivery form of small amounts of certain trace minerals and small amounts of magnesium and calcium. It may also bind to some toxins, such as pesticides.

MECHANISM OF ACTION

Certain toxins, such as paraquat, may be adsorbed by bentonite.

PHARMACOKINETICS

Little is reported on the pharmacokinetics of bentonite. Following ingestion, there is probably very little to no absorption of bentonite from the gastrointestinal tract, and it is excreted in the feces. Small amounts of trace minerals and small amounts of calcium and magnesium may be absorbed.

INDICATIONS AND USAGE

It is claimed that bentonite binds to a number of toxins and thus renders them harmless. There is some evidence of this effect in animal studies.

RESEARCH SUMMARY

Bentonite has been shown to protect against the effects of aflatoxins in broiler chickens and rats but did not alleviate locoweed toxicosis in rats. Bentonite has also been shown to prevent high radiocesium levels in animal products. Clinical trials are lacking.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Bentonite is contraindicated in those who are hypersensitive to any component of a bentonite-containing product. It is also contraindicated in those whose gastrointestinal tract is not anatomically intact.

PRECAUTIONS

Pregnant women, nursing mothers and the elderly should avoid using bentonite.

Those who do use bentonite should ingest plenty of fluid (water, juice) concomitantly in order to avoid possible intestinal obstruction.

Bentonite should not be used concomitantly with drugs or nutritional supplements.