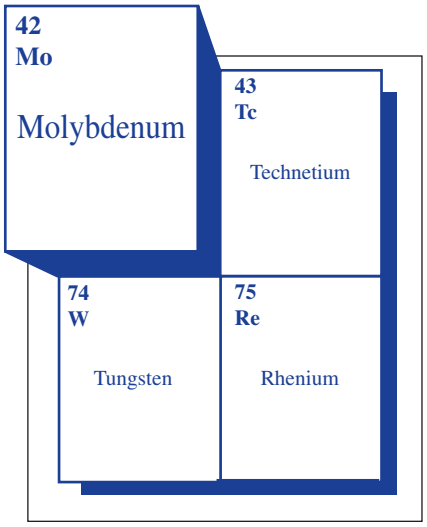

Molybdenum

Introduction

Although molybdenum was first identified as an element over two centuries ago, its biological importance was not appreciated until researchers demonstrated it had a direct role in animal metabolism. Molybdenum has since been identified as an essential trace element for nearly all plants and animals, occurring as a cofactor in three important enzymatic reactions that take place in virtually all forms of life. Clinically, molybdenum deficiency is rare, but inborn errors of metabolism resulting in deficiencies of the molybdoenzymes have been described. Dietary intake of molybdenum is generally sufficient, with legumes such as lentils, beans, and peas being the richest source. Nuts, grains, cauliflower, and leafy vegetables are also good sources, whereas animal products and fruit are low in molybdenum. Molybdenum content of plant-based foods is dependent on the amount of molybdenum in the soil in which they are grown. Molybdenum supplementation may be of therapeutic benefit in patients with molybdoenzyme deficiency, sulfite sensitivity, Wilson's disease, and certain types of cancer, and in those receiving total parenteral nutrition.

Pharmacokinetics

In animals and humans, molybdenum is well absorbed via oral and intravenous routes of administration. Molybdenum research in humans indicates absorption rates range from 70-90 percent (regardless of dosage route), with the highest rates being observed with the highest dietary molybdenum intake.[1,2] Once absorbed, molybdenum peaks in the plasma within 40-60 minutes, is rapidly cleared, and within three hours is excreted in the urine as molybdate. A portion of the absorbed molybdenum is deposited in "slow-turnover" tissue such as the liver, muscle, and bone, while another portion is deposited in "fast-turnover" tissue such as the adrenal glands and gastrointestinal tract. The half-life for molybdenum in slow-turnover tissue has been reported to be 42-74 days, compared to 1.7-2.5 days for fast-turnover tissue.[3] The rapid renal clearance of the majority of ingested molybdenum likely prevents deleterious effects in the event of high intake.

Mechanism of Action

Molybdenum appears to exert its biochemical effects and therapeutic benefit by two mechanisms. Primarily, molybdenum is a cofactor for three important enzymes: xanthine oxidase/dehydrogenase, sulfite oxidase, and aldehyde oxidase. Xanthine oxidase exists *in vivo* mainly as dehydrogenase and was the first enzyme identified as a molybdoenzyme. It is involved in the oxidation of purines and pyrimidines, as well as other nitrogen-containing heterocyclic compounds.[4]

Another molybdoenzyme, aldehyde oxidase, is distinct from other aldehyde-metabolizing enzymes, such as aldehyde dehydrogenases, as it is present only in animal cells and its highest activity is in the liver. Aldehyde oxidase acts on substrates similar to xanthine oxidase/dehydrogenase and, although the exact mechanisms are not known, both appear to play a roll in hepatic detoxification of xenobiotics, certain drugs, estradiol, and progesterone.[5] Aldehyde oxidase deficiency has not been reported in humans.

Perhaps the most important molybdoenzyme in humans is sulfite oxidase. Found in the mitochondrial inter-membrane space, this enzyme oxidizes sulfite to sulfate, the terminal step in the metabolism of sulfur-containing amino acids. In contrast to the other molybdoenzymes, sulfite oxidase has very narrow substrate specificity, catalyzing only this reaction. Deficiencies of this enzyme have been reported in humans and are usually fatal in infancy.[6]

In addition to acting as an enzyme cofactor, molybdenum in the form of tetrathiomolybdate complexes with copper and protein, resulting in decreased copper levels. Because copper is thought to play an important role in angiogenesis and tumor growth, molybdenum in this form may have a preventive effect for certain types of cancer.[7] Due to its copper-chelating mechanism, tetrathiomolybdate has also been shown to be of therapeutic benefit in treating patients with Wilson's disease, a condition characterized by copper toxicity.[8]

Clinical Indications

Sulfite Sensitivity

Sulfite sensitivity is a condition characterized by asthma-like symptoms, including wheezing, chest tightness, coughing, extreme shortness of breath, and even loss of consciousness. Other symptoms include flushing, angioedema, itching, hives, contact dermatitis, swelling of eyes, hands and feet, nausea and diarrhea, and anaphylactic shock.[9,10] The exact cause of sulfite sensitivity is not known, but early studies found that many patients presenting with these symptoms had virtually no detectable blood molybdenum. Normal values are from 10-100 ppb.

For people with this condition, avoiding sulfite exposure is very difficult as sulfites are ubiquitous in food and beverages, including wine, beer, and soft drinks. Many people, although not severely sulfite sensitive, will exhibit the "red-wine stuffy nose" after drinking just a single glass of red wine. Others get a characteristic alcohol flush on the face and neck when drinking red wine, beer, or hard liquor.[11] Anecdotal reports indicate oral molybdenum supplementation can alleviate these symptoms.

Sulfites are frequently used as food preservatives for meat, fish, salad bar items, and dehydrated fruits and vegetables. They are also added to foods to preserve color, flavor, and ascorbic acid and carotene content. Most pickled and vinegar-containing foods contain sulfites. Because it is not always required that sulfites be listed on food information labels, avoiding them is difficult. Ironically, sulfites are present in the form of bisulfites in many drugs used to relieve symptoms of respiratory distress, bronchospasm, and gastrointestinal spasm due to asthma and allergies.[12] Airborne sulfur dioxide is difficult to avoid and levels are particularly high in polluted urban air and in the vicinity of coal- or oil-burning plants. Patients with sulfite sensitivity and asthma are particularly susceptible to insult in this environment because they have lower tolerance thresholds than people without the condition.[13]

Case reports indicate exposure to sulfites can exacerbate asthma symptoms. A 53-year-old female asthmatic requiring numerous asthma medications to control her symptoms was found to have a urinary sulfite (a marker of sulfite oxidase deficiency) of 10-20 ppm (reference range = 0 ppm). Over a three-month period, the patient was treated with 250 mcg IV molybdenum twice weekly, gradually working up to 750 mcg for the last four injections. Urinary sulfite levels were reduced to 2-6 ppm, wheezing decreased significantly, and the patient was able to discontinue theophylline and prednisone; dosages of two inhaler medications were reduced by 50 percent.[14] In a second case, a 68-year-old man with a 30-year history of asthma was treated with IV molybdenum for 90 days. His urinary sulfite value decreased from 30-40 ppm to 3-7 ppm, while organic urinary sulfate increased from 14 percent to 30 percent, indicating improved sulfite metabolism.[15]

Molybdenum Cofactor Deficiency

Molybdenum cofactor (moco) is a term used to denote a complex consisting of a central molybdenum molecule, two dithiolates, and molybdopterin. Moco is synthesized in a four-step process and a defect at any step results in a loss of all moco enzyme activities.[16] Moco deficiency is an autosomal recessive disease characterized by the loss of both xanthine dehydrogenase and sulfite oxidase activity. A deficiency of sulfite oxidase results in impaired metabolism of sulfur-containing amino acids and is responsible for the severe clinical abnormalities associated with this disease. This usually fatal condition presents shortly after birth with seizures, myriad neurological symptoms, mental retardation, and ocular lens subluxation.[17] Currently, no proven therapy is available, although case reports indicate IV molybdenum can reduce urinary sulfite levels.[14,15] Due to the rarity of molybdenum cofactor deficiency and the fact it is often fatal in infancy, effectiveness of oral or IV molybdenum therapy has not been confirmed. In theory, it should help correct a sulfite oxidase deficiency and make presentation of this disease less severe.

Research in an animal model has shown that a biosynthetic moco precursor is effective in reducing the symptoms of moco deficiency. Unfortunately, due to the instability of moco and its short half-life,[18] large-scale production of the precursor for therapeutic use is not currently possible. Research in this arena continues;[19,20] the gene locus for the mutation causing this disease has been identified[21] and prenatal genetic testing can identify individuals at risk.[22]

Total Parenteral Nutrition and Molybdenum Deficiency

In 1981, a case report of a 24-year-old man with a 12-year history of Crohn's disease demonstrated the negative effects of 18 months of total parenteral nutrition (TPN). The young man had undergone numerous small bowel resections, resulting in short bowel syndrome and nutrient malabsorption, as evidenced by intolerance to certain amino acids in the TPN. During the final six months of TPN administration, the patient developed tachycardia, rapid breathing, severe headaches, night blindness, nausea, and vomiting, which progressed to lethargy, disorientation, severe generalized edema, and coma within 48 hours after presentation. Laboratory results revealed high plasma methionine, low serum uric acid, and elevated urinary thiosulfate. Based on these results, molybdenum deficiency was considered likely and ammonium molybdate was added to the TPN solution at a dose of 300 mcg daily. The patient's clinical symptoms resolved rapidly and he exhibited no further intolerances to amino acid solutions as long as molybdenum was added to the TPN. This patient apparently had a deficiency of both sulfite oxidase and xanthine oxidase/dehydrogenase, induced by the lack of molybdenum in the TPN solution.[23]

Wilson's Disease

Wilson's disease is characterized by copper accumulation and toxicity resulting in liver and brain damage and neurological complications. Currently, there are three commercially available anti-copper agents but all three of them are somewhat unsatisfactory.[24,25] Tetrathiomolybdate (TM) was developed by George Brewer, MD, at the University of Michigan, and is proving to be a safe and effective alternative. Brewer et al have conducted several trials using TM to treat copper toxicity in Wilson's disease patients.[26-29]

TM works differently than other anti-copper agents in that it forms a strong complex with copper and protein. If given orally with food, TM complexes with food proteins and copper, rendering copper unavailable for absorption. If given away from food, TM is absorbed into the bloodstream where it complexes with copper and albumin. The copper complex is non-toxic because it cannot be taken up by cells. With TM therapy, further copper toxicity is stopped within 1-2 weeks.[29] Although all Brewer et al studies have shown benefit, the most recent study involved the largest number of patients. In an open-label trial, 55 untreated Wilson's disease patients presenting with neurological complications were given 120-410 mg oral TM daily for eight weeks; patients were followed for three years. Only two of 55 patients (4%) worsened neurologically during the eight weeks of TM therapy, compared to a rate of 50-percent neurological deterioration in patients treated with penicillamine. Because higher doses of TM are no more effective than low doses, 120 mg TM daily is currently recommended.[29]

Cancer

Due to TM's copper-reducing and antiangiogenic properties, it has been investigated as a potential therapeutic agent for several types of cancer. Numerous animal and *in vitro* studies using human cancer cell lines have demonstrated TM's effectiveness at inhibiting angiogenesis.[30-33]

Two clinical trials have demonstrated the effectiveness of oral TM in cancer patients. In the earlier trial, researchers theorized that oral TM would achieve a mild copper deficiency and subsequently impair neovascularization in metastatic solid tumors. Eighteen patients with metastatic cancer were given 90, 105, or 120 mg TM daily in six divided doses. Six patients were enrolled at each dose level, with the treatment goal to lower copper levels to 20 percent of baseline without inducing anemia. Patients were followed up to 17 months. Of the 18 patients, 14 achieved targeted copper deficiency without anemia and six (33%) of those experienced stabilization of disease without progression; two patients even experienced a disappearance of some lung lesions. The optimal dose was determined to be 120 mg TM daily and was associated with no toxicity.[34]

In a phase II clinical trial, 15 patients with advanced kidney cancer were given 40 mg oral TM three times daily and 60 mg at bedtime. As in the previous study, the goal was to reduce copper without inducing anemia. Thirteen of 15 patients achieved targeted copper levels and were available for evaluation. Four of 13 patients (31%) had stable disease for at least six months (median 34.5 weeks) during copper depletion.[35]

Eight additional phase II studies of TM for various cancers are underway.[32]

In addition to tetrathiomolybdate therapy, studies have demonstrated oral molybdenum (ammonium molybdate) supplementation in rats at a dose of 10 mg/L drinking water increased xanthine oxidase levels and decreased the incidence of mammary carcinogenesis.[36]

The only published human trial using oral molybdenum (other than TM) to prevent or decrease cancer incidence was conducted in Linxian, China. Because the soil in this region is low in molybdenum and other minerals, dietary intake is low. People in this region have a 100-times greater incidence of stomach and esophageal cancer than people in the United States (10 times greater than in other areas of China). Adding 30 mcg molybdenum (form not specified) daily to the diet of residents in this area did not decrease gastroesophageal cancer incidence over a five-year period, but the dosage used was very low.[37] It is not clear whether higher dosages might have been beneficial.

Nutrient-Nutrient Interactions

High molybdenum intake (dietary or supplemental) may interfere with copper absorption and likewise, high copper intake may interfere with molybdenum absorption.[38,39]

Drug-Nutrient Interactions

Although high doses of molybdate have been shown to inhibit acetaminophen metabolism in rats,[40] it is not known if this occurs in humans at clinically relevant doses.

Warnings and Contraindications

Patients with gout should use care when supplementing with molybdenum. High doses (10-15 mg daily) have been associated with elevated levels of uric acid and a gout-like syndrome. This is likely due to molybdenum complexing with copper in the kidneys, making it unavailable to aid in uric acid elimination.[41] Patients on long-term dialysis should also use caution in supplementing with molybdenum; since the main excretion route is impaired, molybdenum accumulates and has been associated with dialysis-related arthritis.[42]

Safety and Toxicity

Molybdenum toxicity is rare due to its rapid renal clearance after absorption. Dosages up to 1,500 mcg daily for 24 days did not result in elevated blood or urinary levels of molybdenum.[1]

Dosage

Molybdenum supplements are generally available in one of several forms: sodium molybdate, ammonium molybdate, molybdenum picolinate, molybdenum citrate, and molybdenum aspartate. Although all forms of supplemental molybdenum

appear to be well absorbed, research using oral dosages is limited. Therefore, an exact dosage for conditions such as sulfite sensitivity has not been established. Supplementation with oral molybdenum covers a wide range of dosages from 50 mcg-6.0 mg daily in divided doses. The most effective therapeutic dosages for TM appear to be 120-150 mg daily.

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