Methylcobalamin

Use

Methylcobalamin has been used as a supplement in patients with vitamin B_{12} deficiency and in those with diabetes and other neuropathies. Although use in dementia is advocated, aside from correcting deficiencies, clinical trials are limited.

Dosing

The Dietary Reference Intake (DRI, also known as Recommended Daily Allowance [RDA]) for vitamin B_{12} is 2.4 mcg/day.

Clinical trials with specific dosage recommendations for methylcobalamin are lacking. Dosage is based on recommended dosages for vitamin B_{12}. High dosages of methylcobalamin (1,500 mcg/day orally) have been used in limited studies.

Contraindications

None identified.

Pregnancy/Lactation

Compatible at usual dosages.

Interactions

Medicines considered to reduce the absorption of vitamin B_{12} include alcohol, aminosalicylic acid, chloramphenicol, colchicine, metformin, neomycin, and proton pump inhibitors.

Adverse Reactions

Vitamin B_{12} at dosages found in foods or from supplements is well tolerated. GI effects from methylcobalamin may include anorexia, diarrhea, headache, nausea, and vomiting.

Toxicology

Specific toxicological studies are lacking. Vitamin B_{12} has a long history of safe use even at high dosages.

Source

Vitamin B_{12} is obtained from animal products (eg, meat, fish, shellfish, poultry, eggs, milk, milk products). Tempeh, made from fermented soybeans, contains the beneficial bacteria responsible for producing vitamin B_{12}. Commercial forms of methylcobalamin are produced in the laboratory through the conversion of cyanocobalamin.

History

Early empirical work on the structure and function of cobalamins as coenzymes was conducted using vitamin B_{12}-dependent bacteria in the 1950s. Prior to this date, Addison anemia (pernicious anemia) had been described and the involvement of intrinsic factor was recognized through experiments involving regurgitated raw meat. The discovery of liver as a treatment for pernicious anemia in the 1920s led to the Nobel Prize in Medicine, and in 1948 Karl Folkers and Alexander Todd identified cobalamin as the active principle in liver.

Chemistry

Methylcobalamin is the methyl form of cobalamin obtained from hydroxycobalamin, either by chemical manipulation in the laboratory or in the body as a natural process. Cyano- and hydroxocobalamin are considered the storage or transport forms of cobalamin, while methylcobalamin and deoxyadenosylcobalamin are the active forms involved in enzymatic reactions. Methylcobalamin is involved specifically in the normal metabolism of folate and the consequent maintenance of normal homocysteine serum levels.

The 4 cobalamins collectively are often referred to as vitamin B_{12}, and are essential cofactors in the bone marrow and myeloid cells where the replication of chromosomes and cellular division occurs.

Uses and Pharmacology

Vitamin B_{12} deficiency

The prevalence of vitamin B_{12} deficiency among elderly Americans is thought to be about 20%. Dietary deficiency of vitamin B_{12} can result from poor diets or among strict vegetarians who choose not to consume any animal products. A lack of stomach acid occurs in elderly patients and among people taking proton pump inhibitors, leading to poor digestion of the vitamin from animal products. People with a lack of intrinsic factor (also known as pernicious anemia), as well as those with severe GI disorders with impaired small intestine function (eg, Crohn disease) or those who have undergone gastric bypass surgery may also be deficient in vitamin B_{12}.

The deficiency can lead to subtle cognitive and neurologic changes, as well as to more severe anemia and dementia. Neonatal development may also be impaired in infants breastfed by mothers who have a vitamin B_{12} deficiency.

Animal data

Specific data on the correction of methylcobalamin deficiencies in animals is lacking.

Clinical data

Vitamin B_{12} deficiency can be corrected with the administration of cobalamin. Usually either cyano- or hydroxocobalamin is used to restore normal levels. Clinical trials specifically evaluating methylcobalamin supplementation are lacking. However, there is no reason to suggest lack of efficacy, and reports exist of therapeutic efficacy of methylcobalamin.

Neuropathy

Animal data

In animal models of vitamin B_{12}-related neuropathy, ultra-high dose methylcobalamin (500 mcg/kg) resulted in regeneration of motor neurons.

Clinical data

Limited clinical trials have evaluated the effect of supplemental methylcobalamin on diabetic peripheral neuropathy, as well as neuropathy associated with renal disease. Subjective measures were reported to have improved.

Reversal of moderate cognitive impairment (dementia) with oral methylcobalamin, but not hydroxocobalamin, was reported in an 83-year-old female despite B_{12} levels being within normal limits. Therapy was inspired by the VITACOG trial and consisted of daily oral methylcobalamin (3,000 mcg) and folic acid (1,200 mcg). Two months later, her Mini Mental State Examination improved from 14 to 29 and her body mass index improved from 17.1 to 22.6 kg/m^2.

The American Academy of Neurology (AAN) updated practice guideline for mild cognitive impairment (2018) states that insufficient evidence is available to support or refute the use of homocysteine-lowering B vitamins, including vitamin B_{12}, in patients with mild cognitive impairment (Very Low Level, Class II).

Other uses

Animal studies and clinical data suggest a role for vitamin B_{12} parenteral therapy in the care of the critically ill, especially in shock; however, clinical trials are lacking and information specifically regarding methylcobalamin is lacking.

A systematic review showed little evidence supporting vitamin B_{12} supplementation to reduce the risk of diabetes or cardiovascular disease. A 2013 meta-analysis that included 15 studies and 1,106 diabetic patients found combination therapy for 2 to 4 weeks with intravenous (IV) alpha lipoic acid 300 to 600 mg/day plus IV methylcobalamin 500 to 1,000 mg/day to be superior to methylcobalamin monotherapy for improving nerve conduction. Similarly, combination therapy with prostaglandin E1 (10 or 20 mcg IV), methylcobalamin (500 to 1,500 mcg IV/intramuscularly [IM]) plus lipoic acid (300 or 600 mg/day IV) significantly improved nerve conduction velocity compared with combination therapy without the lipoic acid in a 2015 meta-analysis of 18 randomized clinical trials (N = 1,410) involving patients with diabetic peripheral neuropathy.

Limited information suggests methylcobalamin may play a role in immune modulation and in cancer.

Methylcobalamin has been used in clinical studies to reduce serum homocysteine levels.

A Cochrane systematic review and meta-analysis of antioxidants for male subfertility identified 1 double-blind, randomized, parallel study that administered vitamin B_{12} (N=396); however, the lack of useable data prevented its inclusion in the meta-analysis. Japanese men with abnormal sperm count or motility received mecobalamin at a dose of either 1,500 or 6,000 mcg/day for 12 weeks. No statistically significant difference was observed in sperm parameters compared to placebo.

Dosing

The DRI of vitamin B_{12} is 2.4 mcg. The FDA has set the Daily Reference Value (DRV) at 6 mcg.

Methylcobalamin 1,000 mcg IM 3 times a week for 2 weeks followed by weekly doses was reported to reverse neuropsychiatric symptoms in 1 case study.

Clinical trials evaluating the effect of methylcobalamin in diabetic neuropathy have used dosages of saline 2,500 micrograms in 10 mL injected intrathecally and oral methylcobalamin 500 mcg taken 3 times a day. Trials in patients with renal failure-associated neuropathy utilized daily dosages of oral methylcobalamin 1,500 mcg for 6 months.

Methylcobalamin is at least as bioavailable as cyano- and hydroxycobalamin.

Pregnancy / Lactation

In pregnant women the recommended intake of vitamin B_{12} increases to 2.6 mcg/day to meet the needs of the developing fetus. Supplementation with methylcobalamin may improve the nutritional status of pregnant women but data from clinical trials is lacking. No reports linking high doses of vitamin B_{12} with maternal or fetal complications have been found.

Interactions

Information on interactions caused by methylcobalamin supplementation is lacking. Certain medicines are considered to reduce the absorption of vitamin B_{12} including alcohol, aminosalicylic acid, chloramphenicol, colchicine, metformin, neomycin, and proton pump inhibitors.

Most antibiotics, methotrexate, or pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic blood assays.

Adverse Reactions

Vitamin B_{12} at dosages found in foods, or from supplements is well tolerated. GI effects from methylcobalamin may include anorexia, nausea, vomiting, and diarrhea. Headache has been reported.

Toxicology

Specific toxicological studies are lacking. Vitamin B_{12} (as cyanocobalamin or hydroxocobalamin) has a long history of safe use even at high doses (cyanocobalamin 1 mg IM at weekly intervals for 1 month, followed by monthly injections for 6 months). At usual doses, the cobalt and cyanide content are not considered to be toxicologically relevant.

Hydroxocobalamin is used at 5 g doses in the management of cyanide poisoning.

A study conducted in rats in the 1950s suggested vitamin B_{12} might exert tumor-promoting effects, while another study suggested reduced survival rates among rats with Walker carcinosarcoma treated with methyl- and cyanocobalamin.