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A Happy, Healthy and Prosperous

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Latest Advancement in Methylcobalamin

Latest Advancement in Methylcobalamin

SANJAY AGRAWAL

Introduction

Vitamin B12, discovered by Karl Folkers in 1948, is available in four related analogs that differ from each other by the chemical group that binds cobalt: cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin¹. Vitamin B12 are important nutrients that are not produced in humans and whose insufficiency is recognized as a worldwide health concern. Hence, intake of this vitamin is necessary either through supplement or in diet. Among all analogs, methylcobalamin is a highly active form of vitamin B12 that is essential for the synthesis of methionine and S-adenosylmethionine². It is also known as mecobalamin or methyl B12 that varies from cyanocobalamin in that it contains cyanide and methyl alkyl bonds³. Substitution of the cyanide side chain with methyl side chain increases the neural uptake of these compounds. This methylcobalamin has an octahedral cobalt (III) core and can be synthesized in laboratory by reducing cyanocobalamin in alkaline solution with sodium borohydride, followed by the addition of methyl iodide. It plays a role in the isomerization of methylmalonyl CoA to succinyl CoA, which is a step in the breakdown of the amino acids valine, isoleucine, threonine, and

fatty acids having an odd number of carbon atoms. It also aids in the maintaining of good health, and its insufficiency causes a variety of major health problems, the most prevalent of which are blood deficiency, depression, irritability, and psychosis. The long-term deficiency of vitamin B12 substance can lead to hyperhomocysteinemia and finally cardiovascular disorder. Hence, methylcobalamin can treat such ailments that are caused due to vitamin B12 deficiency. It is also used to treat diabetic neuropathy, degenerative disorders, the preliminary treatment of amyotrophic lateral sclerosis, nutrition-based diseases such as dementia, and rheumatoid arthritis^{2,4}. Methylcobalamin occurs naturally and found in diet especially non-vegetarian food like fish, meat, egg, etc. Methylcobalamin (MeCbl) is progressively dominating the nutritional formulation industry and is available in India in parenteral, oral, and sublingual forms, alone or in conjunction with other B-group vitamins (multivitamin formulations)⁵. MeCbl formulations (having RDA between 1000 to 5000 mcg which is well above recommended RDA) are widely accessible as health

supplements in the unregulated market across the world. Some of the marketed formulation containing MeCbl are Nurokind Forte Injection, Zatrocob 1500mcg Injection 2ml, Nuromark 1500 Tablet, Zenobal Plus Injection 2ml, Nurokind OD Tab 20s, Nurokind-OD Tab 20s, Cobamet OD 1.5mg Tab, Neuro B Forte Tablet 10s, Mecofol OD Tablet 10s, Nervic OD Tablet 10s, Nuroday 1500mg Injection, etc.

Mechanism of action

Methylcobalamin serves as a cofactor by the enzyme methionine synthase to convert homocysteine to methionine, which further enhances methylation of myelin sheath proteins, increasing their stability, and simultaneously 5-methyltetrahydrofolate (5-methyl THF) is turned into THF⁶. This THF is employed in the synthesis of pyrimidine bases, with an overall contribution of neuroprotection, DNA maintenance, and red blood cell (RBC) generation. Conversion of homocysteine to methionine prevents homocysteine accumulation in tissues and serum, therefore reducing the possibilities of neurological disorders such as depression or brain atrophy and vascular disease⁷. To facilitate

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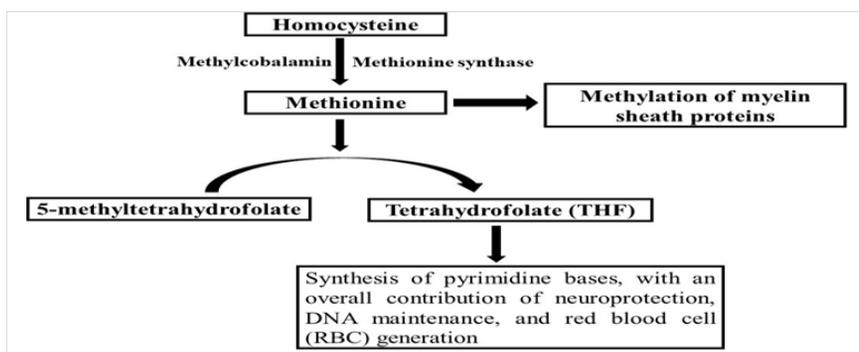


Figure 1. Action Mechanism of Methylcobalamin

optimal absorption, intrinsic factor produced in the stomach must be present throughout the intestinal system. People who are deficient in this factor suffer from vitamin B12 deficits such as pernicious anemia (a gradual and insidious disease that can lead to death). Indeed, elevated homocysteine levels are thought to be vasculotoxic and neurotoxic. Furthermore, methylcobalamin promotes neurite development and prevents neuronal death via the Erk1/2 and Akt signaling pathways⁸. Methylcobalamin is a neurotrophic compound with neuronal tissue selectivity that regulates and regenerates peripheral nerves by up-regulating gene transcription⁹. MeCbl also exerts analgesic activity and based on recent studies, the following are plausible methods through which methylcobalamin exerts analgesic activity: 1. MeCbl increased nerve conduction velocity; 2. MeCbl promoted damaged nerve regeneration, restoring neuromuscular functioning in allodynia and peripheral hyperalgesia; and 3. In neuropathic pain, MeCbl suppressed ectopic spontaneous discharges from peripheral primary sensory neurons¹⁰.

Absorption and Bioavailability

Since, cyanocobalamin is cost effective and synthetically produced, it is found in most B12 supplements. According to some studies, human body absorbs around 49% of a 1-mcg dosage of cyanocobalamin somewhat better than 44% of the same quantity of methylcobalamin¹¹. Another research comparing the two types found that three times as much cyanocobalamin was eliminated through urine, indicating that methylcobalamin may be better kept inside the body. However, for utilizing B12 in the body, the

liver must first remove the cyanide molecule and attach a methyl group to generate methylcobalamin, the physiologically active, tissue-ready version. Hence, it has been predicted that direct supply of methylcobalamin can surpass this first phase. However, some research suggests that differences in bioavailability between the two forms may be insignificant and that absorption could be influenced by factors such as age and genetics¹².

The Merck index which is even referred as encyclopedia of chemicals says that the methylcobalamin is soluble in alcohol but insoluble in acetone, chloroform, and ether and can be given orally, parenterally, or intranasally¹³. There is also tentative evidence that unbound B12 can be actively absorbed at faster rates through the membranes beneath the tongue than through passive diffusion in the digestive system, especially when paired with an absorption enhancer. Methylcobalamin forms a complex with an intrinsic factor that is absorbed in the distal ileum. Its absorption is facilitated by a highly specialized receptor-mediated transport mechanism and have a half-life of six days¹⁴. RDA for vitamin B12 for adults is 2.4 µg/day, and guidelines suggest that 10% to 30% of persons over the age of 50 frequently have B12 malabsorption syndromes, resulting in absorption rates as low as 1% of the ingested B12¹⁵. As a result, those adults would need to consume 240 µg of B12 to absorb at least 2.4 µg. FSSAI banned methylcobalamin through the gazette passed in 2016 but products were later approved by scientific committee of FSSAI in December 2019, but no amended gazette was issued in this regard. Further development was made when on December 26, 2021, FSSAI

clarified that it had mentioned all vitamin B12 derivatives, including methylcobalamin, under the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Foods, and Novel Foods) Regulations, 2016 via an amendments gazette notification on September 16, 2021¹⁶.

Administration of methylcobalamin also improves the clinical and psychological profile of individual with autism as proved by study performed by Corejova, A. and his co-workers¹⁷. MeCbl (daily at 500 µg dose to autistic children and young adults during a 200-day period) treatment gradually improved the overall clinical and psychological status, with the highest impact in the social domain, followed by the cognitive, behavioral and communication characteristics. In 2018, Kaji, R. and his co-workers performed a study to determine the effect of ultra-high dose (25 or 50 mg) of methylcobalamin in amyotrophic lateral sclerosis¹⁸. It was determined that ultra-high dose methylcobalamin did not demonstrate substantial effectiveness in the entire group, this medication may prolong survival and slow symptom development without causing serious adverse effects. Similarly, Xu performed a randomized phase III clinical trial, G. et. al. in 2018 in which they did local administration of methylcobalamin for subcutaneous ophthalmic herpetic neuroglia (SOHN)¹⁹. They observed that pain levels were lowered in all groups but were higher in the LM (local injection) group when compared to intramuscular (IM) treatment. Clinically substantial pain reduction (>30%) was observed in 91% of LM patients,

a higher proportion than in the systemic groups (66% IM group, 57% OM group). This study found that local injection of methylcobalamin relieves SOHN pain more effectively than systemic treatment. A review of multiple clinical trials using methylcobalamin alone or in conjunction with other B vitamins discovered that it also provided overall symptomatic improvement of neuropathy symptoms. MeCbl is a light-sensitive compounds that should be kept in sealed cartons until it is ready for use. The prescribed amount of methylcobalamin is 500 mcg three times day or 1500 mcg daily for the highest bioavailability and absorption²⁰.

Conclusion

Methylcobalamin, active form of vitamin B12 is an essential dietary requirement especially found in non-vegetarian foods. Intake of this vitamin that has been included in various marketed formulations helps us to treat several diseases such as diabetic neuropathy, autism, amyotrophic lateral sclerosis, and ophthalmic herpetic neuroglia. MeCbl serves as cofactor in conversion of homocysteine to methionine which is finally converted to tetrahydrofolate (THF). This THF is employed in the synthesis of pyrimidine bases, DNA maintenance, and red blood cell (RBC) generation. Furthermore, methylcobalamin promotes neurite development and prevents neuronal death via the Erk1/2 and Akt signaling pathways. Although both methylcobalamin and cyanocobalamin are an important form of vitamin B12, but as body requires MeCbl form for active absorption it can be concluded as better form. FSSAI banned methylcobalamin through its official gazette in 2016 but recently approved it via an

amendments gazette notification on September 16, 2021. RDA recommended for vitamin B12 for adults is 2.4 µg/day, but most of marketed formulation have much higher value than this. Several clinical trials suggest that taking methylcobalamin in such higher amount produce no significant side-effects. Hence, it can be concluded that methylcobalamin is an important and more effective form of vitamin B12.

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