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PERSPECTIVE

Treatment of vitamin B12 deficiency–Methylcobalamine? Cyancobalamine? Hydroxocobalamin?—clearing the confusion

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Vitamin B12 (cyancobalamin, Cbl) has two active co-enzyme forms, methylcobalamin (MeCbl) and adenosylcobalamin (AdCbl). There has been a paradigm shift in the treatment of vitamin B12 deficiency such that MeCbl is being extensively used and promoted. This is despite the fact that both MeCbl and AdCbl are essential and have distinct metabolic fates and functions. MeCbl is primarily involved along with folate in hematopiesis and development of the brain during childhood. Whereas deficiency of AdCbl disturbs the carbohydrate, fat and amino-acid metabolism, and hence interferes with the formation of myelin. Thereby, it is important to treat vitamin B12 deficiency with a combination of MeCbl and AdCbl or hydroxocobalamin or Cbl. Regarding the route, it has been proved that the oral route is comparable to the intramuscular route for rectifying vitamin B12 deficiency.

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Vitamin B12, also known as cyancobalamin (Cbl), is a water-soluble vitamin required for dozens of functions in the body, the prime one being for development and maturation of red blood cells and proper functioning of the nervous system.[1–3] Hence, manifestations of vitamin B12 deficiency are macrocytic anaemia, changes in mood and cognition, hypoesthesia or paresthesias, motor weakness, ataxia, nonspecific gastrointestinal symptoms and so on.[2,3] The factors responsible for deficiency are increased demand, inadequate intake and/or malabsorption.[2,3] Out of these, malabsorption via the enteral route is responsible for the majority of cases.[3] Thereby, parenteral routes, that is, intramuscular, nasal and sublingual, have been traditionally advocated to treat vitamin B12 deficiency.

Methylcobalamine (MeCbl) is a cofactor for the enzyme methionine synthase involved in the production of methionine from homocysteine.[1] In vitamin B12 deficiency, decreased MeCbl leads to the 'folate trap', that is, a functional deficiency of folate.[4] This affects the rapidly dividing cells of the bone marrow, which require increased thymidylate for DNA synthesis, eventually leading to macrocytic anaemia.[2–5]

In India, there has been a flooding of the market with the MeCbl form of vitamin B12. It has been promulgated as the formulation to be preferred for vitamin B12 deficiency. The rationale given is that, as it is an active form of vitamin B12, it is better than cyanocobalamin. However, this is only partly correct.

Vitamin B12 has two active forms, methylcobalamin and adenosylcobalamin (AdCbl), formed as a result of two distinct metabolic cascades.[1,6,7] Their metabolic fates and thereby their functions are also distinct. AdCbl is the major form in cellular tissues stored in the mitochondria. MeCbl is found in the cytosol, and it predominates in blood and in other body fluids.[8]

AdCbl is the cofactor for the enzyme methylmalonyl-CoA mutase that catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA, which is a key component of the tricarboxylic acid pathway of carbohydrate metabolism.[1,3,7,9] In vitamin B12 deficiency, decreased AdCbl leads to a decrease in the conversion of methylmalonyl-CoA to succinyl-CoA with a resultant increase in methylmalonyl-CoA, which disturbs the carbohydrate, fat, amino-acid and urea metabolism and thereby affects the synthesis of neuronal myelin.[10]

Both MeCbl and AdCbl have an important role in the normal development and functioning of the central nervous system, but the role of MeCbl in the functioning of the peripheral nervous system is doubtful.[11–14] Meta-analysis has shown that in cases of diabetic neuropathy, a combination of MeCbl with lipoic acid and MeCbl with prostaglandin E1 is better than MeCbl alone. However, these studies lack a third arm of lipoic acid and prostaglandin E1 alone, and hence whether the beneficial effect of the combination is in fact due to lipoic acid or prostaglandin E1 alone remains an unanswered question.[15,16]

Thus, it is prudent to use Cbl wherever required instead of MeCbl alone in order to address both the neurological and haematopoietic pathways. Concerns have been raised regarding the stability of Cbl. It has also been said that Cbl should not be used in smokers as it has a cyanide moiety and smokers have an excess of thiocyanate in their blood, which can disturb the metabolism of Cbl and increase its excretion.[17] Hydroxocobalamine (HCbl) is the form of vitamin B12 that lacks the cyanide moiety and has a hydroxyl group instead. Thus, HCbl may be a better agent to use in cases of B12 deficiency, especially in smokers.[18,19] Another better option would be to give a combination of the active forms MeCbl and AdCbl.

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As far as the route of administration is concerned, studies have shown that high-dose oral and intramuscular regimens are comparable with regard to recovery from B12 deficiency.[20–22] The suggested regimen for the oral route is about 2000 μg of CoA daily, followed by weekly and then monthly.[20] The duration of treatment would depend on the cause of deficiency and other factors; for example, in the case of pernicious anaemia it would be lifelong.

To summarize, the preferred formulation for vitamin B12 deficiency should be a combination of the active forms of vitamin B12, MeCbl and AdCbl, or HCbl/Cbl. In case of the oral route, about 500–750 μg of each, MeCbl and AdCbl, would be required. A lower quantity may be required via the parenteral route. Only in the rare genetic disorders of conversion of vitamin B12 to its active coenzyme forms are the active forms to be used exclusively by the parenteral route.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Gherasim C, Lofgren M, Banerjee R. Navigating the B(12) road: assimilation, delivery, and disorders of cobalamin. *J Biol Chem* 2013; **288**: 13186–13193.
2 Brito A, Hertrampf E, Olivares M, Gaitán D, Sánchez H, Allen LH *et al.* [Folate, vitamin B12 and human health]. *Rev Med Chil* 2012; **140**: 1464–1475.
3 O'Leary F, Samman S. Vitamin B12 in health and disease. *Nutrients* 2010; **2**: 299–316.
4 Stover PJ. Physiology of folate and vitamin B12 in health and disease. *Nutr Rev* 2004; **62**: S3–S12 (discussion S13).
5 Tsukerman ES, Pomerantseva TI, Poznanskaia AA, Korsova TL, Klement'eva IV. Effect of methylcobalamin and adenosylcobalamin on the process of hematopoiesis and vitamin B12 exchange in experimental phenylhydrazine-induced anemia in rabbits. *Vopr Med Khim* 1989; **35**: 106–111.
6 Randaccio L, Geremia S, Demitri N, Wuerges J. Vitamin B12: unique metalorganic compounds and the most complex vitamins. *Molecules* 2010; **15**: 3228–3259.
7 Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. *Br J Haematol* 2010; **148**: 195–204.
8 Cooper BA, Rosenblatt DS. Inherited defects of vitamin B12 metabolism. *Annu Rev Nutr* 1987; **7**: 291–320.
9 Marsh ENG, Meléndez GDR. Adenosylcobalamin enzymes: theory and experiment begin to converge. *Biochim Biophys Acta* 2012; **1824**: 1154–1164.
10 Yudkoff M. Disorders of organic acid metabolism. In: Siegel G, Agranoff B, Albers R *et al.* (eds). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, 6th edn. Lippincott-Raven: Philadelphia, PA, USA, 1999.
11 Hall CA. Function of vitamin B12 in the central nervous system as revealed by congenital defects. *Am J Hematol* 1990; **34**: 121–127.
12 Castillo Lancellotti C, Tur Marí JA, Uauy Dagach R. Effect of folate and related nutrients on cognitive function in older people; systematic review. *Nutr Hosp* 2012; **27**: 90–102.
13 Morris MS. The role of B vitamins in preventing and treating cognitive impairment and decline. *Adv Nutr* 2012; **3**: 801–812.
14 Zhang Y-F, Ning G. Mecobalamin. *Expert Opin Investig Drugs* 2008; **17**: 953–964.
15 Xu Q, Pan J, Yu J, Liu X, Liu L, Zuo X *et al.* Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. *Diabetes Res Clin Pract* 2013; **101**: 99–105.
16 Deng H, Yin J, Zhang J, Xu Q, Liu X, Liu L *et al.* Meta-analysis of methylcobalamin alone and in combination with prostaglandin E1 in the treatment of diabetic peripheral neuropathy. *Endocrine* 2014; **46**: 445–454.
17 Linnell JC, Smith AD, Smith CL, Wilson J, Matthews DM. Effects of smoking on metabolism and excretion of vitamin B12. *Br Med J* 1968; **2**: 215–216.
18 Freeman AG. Cyanocobalamin-a case for withdrawal: discussion paper. *J R Soc Med* 1992; **85**: 686–687.
19 Freeman AG. Hydroxocobalamin versus cyanocobalamin. *J R Soc Med* 1996; **89**: 659.
20 Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A *et al.* Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev* 2005; CD004655.
21 Carmel R. How I treat cobalamin (vitamin B12) deficiency. *Blood* 2008; **112**: 2214–2221.
22 Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon K *et al.* *Oral Vitamin B12 versus Intramuscular Vitamin B12 for Vitamin B12 Deficiency*. John Wiley and Sons, Ltd. for The Cochrane Collaboration, 2009. Available from http://summaries.cochrane.org/CD004655/oral-vitamin-b12-versus-intramuscular-vitamin-b12-for-vitamin-b12-deficiency (cited 11 June 2014).