Chapter 139

Methylcobalamin versus Cyanocobalamin

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ABSTRACT

The diagnosis of vitamin B_{12} deficiency can now be supported by the laboratory in view of availability of the facility everywhere to estimate B_{12}. Vitamin B_{12} after absorption from the gut is split into two active forms, methylcobalamin and adenosylcobalamin. The adenosylcobalamin is an important co-factor in synthesis of neuronal lipids. Rationale in administration of methylcobalamin alone in B_{12} deficiency is critically analyzed.

Keywords: Methylcobalamin, methionine synthesis, adenosylcobalamin, methylmalonyl-CoA, succinyl-CoA, neuronal lipids

INTRODUCTION

Methylcobalamin was introduced to the medical profession by the pharma market that methylcobalamin is the active metabolite of cyanocobalamin.

One can as well prescribe directly the active metabolite in place of cyanocobalamin, thereby relieving the patient from the burden of conversion of cyanocobalamin to methylcobalamin and producing faster, better result, etc.

The logic worked very well and the pharma has uncontrolled market for methylcobalamin even 15 years after the molecule introduction. Ironically the basic textbooks of medicine—Davidson's, Harrison's, etc. do not mention methylcobalamin as therapeutic agent even though three editions have come out ever since the molecule is available. Not even there is review of the literature on this molecule in the textbooks, though plenty is available with promoting agencies.

Encephabal, trental (pentoxifylline) are a few other molecules promoted earlier, for ischemic strokes, which were never recommended nor mentioned in the textbooks. These molecules too had honeymoon days, but disappeared quickly from the market because of bogus promotion. Whereas methylcobalamin continues to enjoy supermarket and it is tagged to every other molecule like pregabalin, statins, antidepressants, so on so forth.

It is most appropriate time to revisit B_{12} metabolism and to take a second look before prescribing methylcobalamin.

METABOLISM OF COBALAMIN

Cobalamin or vitamin B_{12} is a member of corrin family, known as hydroxocobalamin in United Kingdom and as cyanocobalamin in the United States of America.[1] Vitamin B_{12} is essential for cellular DNA synthesis and hence contributes to functions of various tissues of the body, formation of myelin sheath, more so the rapidly dividing and proliferating cellular systems such as blood and gastric epithelium.[2,3] Up to 40–50% of serum corrins may be physiologically inactive B_{12} analogs. These analogs serve no useful function and may compete with B_{12} for serum B_{12} binding capacity. The archetypical analog, cobinamide, is not bound by the primary binding protein specific for ileal B_{12} uptake.

Human body does not synthesize cobalamin. The only source is food of animal origin—meat, fish and dairy products.

INDIAN SCENARIO

Dietary cobalamin deficiency arises in vegetarians who do not touch meat, fish, egg and cheese. The largest group in the world consists of Indian vegetarians.[1,4] Millions of Indian vegetarians are at risk of cobalamin deficiency on nutritional basis. Subnormal serum cobalamin levels are found in 50% of randomly selected young Indian vegetarians, but the deficiency usually does not progress to megaloblastic anemia since the diet of most vegans is not totally lacking cobalamin and the enterohepatic circulation of cobalamin is intact. Dietary cobalamin deficiency may also arise rarely in nonvegetarian individuals who exist on grossly inadequate diets because of poverty or psychiatric disturbance.

Daily requirement of vitamin B_{12} is 1–3 micrograms. Human stores are 2–3 milligrams which is sufficient for 2–3 years even if vitamin B_{12} supply is completely cut off.[1]

ABSORPTION

The ingested cobalamin is released from the dietary protein complexes by the digestive enzymes, forms cobalamin—intrinsic factor complex and gets absorbed at the distal ileum.[3,5] Part of it enters enterohepatic circulation.[1] Some amount of cobalamin is also derived from the sloughed intestinal cells (some source of vitamin B_{12} for veganins).

The absorbed inert form of cobalamin is converted into two important active forms.[5,6] One is methylcobalamin—involved in maturation of red blood corpuscles. The second active form is adenosylcobalamin involved in healthy myelination and neuronal integrity.[1,5]

Methylcobalamin is the co-factor for methionine syntheses. Methylation of homocysteine to methionine requires methylcobalamin and five methyl tetrahydrofolate.[1] Briefly, methylcobalamin enters into folic acid metabolism for formation of methionine from homocystine which is essential for effective erythropoiesis.[1] Methylcobalamin deficiency leads to folate trap resulting in megaloblastic anemia.

The second active form, adenosylcobalamin is the co-factor for the enzyme methylmalonyl-CoA mutase. It is present in mitochondria.[1]

Isomerization of methylmalonyl-CoA to succinyl-CoA (essential for synthesis of neuronal lipids to form myelin) requires

adenosylcobalamin.[1,6] Deficiency of adenosylcobalamin leads to accumulation of large amount of methylmalonyl-CoA resulting in synthesis and incorporation of nonphysiological fatty acids into neuronal lipids, causing, demyelination, axonal degeneration and neuronal death leading to neurological complications.[5,6] In case of spinal cord damage the values of vitamin B_{12} are very low even in the absence of anemia.[7]

From above it is obvious that hematological complications are due to abnormality in methylcobalamin pathway and neurological complications are due to abnormality in adenosylcobalamin pathway.

But, it may be noted, there is no single isolated disease of methylcobalamin deficiency or isolated disease of adenosylcobalamin deficiency existing. What existing is the disease due to cobalamin deficiency, recommending methylcobalamin for neurological complications of vitamin B_{12} deficiency is irrational and difficult to substantiate?

For cobalamin or vitamin B_{12} deficiency only cobalamin is to be recommended but not methylcobalamin alone.

CAUSES OF COBALAMIN DEFICIENCY

The common cause in the western world is lack of intrinsic factor (IF),[5,6] where as it is a very rare cause in India.

Broadly the two main causes of cobalamin deficiency in India are—nutrition lacking in vitamin B_{12} due to large section of Indian society adopting vegetarianism, secondly malabsorption due to various diseases mentioned in **Tables 1 and 2**.

OUR EXPERIENCE

Out of 28 case studies more than 50% were traditional vegetarians. Six persons happened to be on vegetarian food even though traditionally not vegetarians. Two cases were on carbamazepine (anemia) and two other cases on metformin (anemia and neurological features) for long time. One case happened to be hyperthyroidism and another case rheumatoid arthritis (associated autoimmune disorders). Most of the cases presented with neurological manifestations. Three cases among vegetarians presented with hemolytic anemia—mild icterus. All the above cases received cyanocobalamin only but not methylcobalamin.

TABLE 1 | Common causes in India

- Inadequate intake (nutrition)
- Malabsorption

A. Defective release of cobalamin from food
- Gastric achlorhydria
- Partial gastrectomy
- Drugs blocking acid secretion (PPI)

B. Inadequate production of IF
- Total gastrectomy

C. Disorders of terminal ileum
- Tropical and nontropical sprue
- Intestinal resection
- Granulomatous diseases

D. Competition for cobalamin
- Bacteria (blind loop syndrome)

E. Drugs
- Colchicines, neomycin, metformin carbamazepine

TABLE 2 | Rarer causes of cobalamin deficiency in India

- Pernicious anemia[9]
- Congenital absence or functional abnormality of IF
- Regional enteritis
- Neoplasm
- Selective cobalamin malabsorption
- Fish tapeworm infection
- Transcobalamin II deficiency
- Congenital enzyme defects

DATA OF A FEW CASES

Vitamin B_{12} normal levels in serum—211-946 pg/ml are mentioned [interfaced chemiluminescence immunoassay (CLIA)] in **Table 3**.

COBALAMIN MALABSORPTION IN ELDERLY

Due to inadequate hydrochloric acid and digestive enzymes in the persons aged above 65 years, the cobalamin bound to meat is not split effectively.[1,8] Experimentally it is found in these groups when crystalline cobalamin was administrated orally, the cobalamin levels measured were normal. Slight elevation of homocystine is an indicator to suspect vitamin B_{12} deficiency in the elderly.

Elderly person needs vitamin B_{12} supplementation as there is no efficient splitting of vitamin B_{12} due to impaired digestive functions. The choice of route of administration is parenteral as most of the times B_{12} deficiency is due to malabsorption and/or nutritional deficiency.

SUMMARY AND CONCLUSION

Why cobalamin only to be given but not methylcobalamin?

- There is no disease described in human body where conversion of inactive cobalamin to active methylcobalamin is impaired. So there is absolutely no necessity to use methylcobalamin in place of cobalamin.
- There is no isolated disease of methylcobalamin deficiency.
- Methylcobalamin has little effect on neurological complications due to vitamin B_{12} deficiency.
- When cobalamin deficiency is diagnosed only cobalamin to be given so that patient gets both methylcobalamin and adenosyl cobalamin, thereby both hematological and neurological abnormalities can be corrected simultaneously.
- Finally the costs of cobalamin are less than Rs. 10/- for single dose whereas methylcobalamin is 510 times more without dual benefits.

MESSAGES

- Let us familiarize basics before we go beyond basics.
- Be not the first when the new is tried, nor yet the last to lay the old aside.

TABLE 3 | Case study of vitamin B_{12} deficiency

S. No	Year of presentation	Age and sex vegetarian/ nonvegetarian (Veg/NV)	Presentation	Additional investigation	Vitamin B_{12} levels pg/ml
1.	May 2002	F-34 VEG	Fatigability, gait ataxia, Romberg's positive	----------	97
2.	Jun 1998	F-50 VEG	Polyarthritis— headache	Anti-CCP negative RA negative	145
3.	Aug 2007	M-70 VEG	COPD anemia	Hb% 6.2 g	92
4.	Jun 2009	M-40 NV	Speech disturbance gait ataxia,	Hb% 8.6 g	184
5.	Jun 1995	F-25 NV	Anemia CHF	Hb% 6.4 g	80 Jan-2010
6.	Feb 2010	F-40 NV	Fatigability	Hb% 6.4 g macrocytosis, mega polys	134
7.	Feb 2007	M-20 NV	Parasthesias of extremities and hyperpigmentation of knuckles	----------	190
8.	Jul 1995	M-45 NV	Anemia, epilepsy, on carbamazepine	Hb% 4.6 g macrocytosis hypersegmented polys	76-FeB_{10}
9.	Aug 1996	F-50 VEG	Anemia and syncope	Hb% 6.0 g	137
10.	Apr 2010	M-54 VEG	A symptomatic (Wife-B_{12} Def.)	Homocysteine-27 µmol/L	125
11.	Jun 2010	M-31 NV	Easy fatigability, parasthesias of extremities	----------	137
12.	May 2010	M-46 VEG	Gait disturbance	----------	61
13.	May 2010	F-44 NV	Polyarthralgia	Hyperthyroidism— 10 years	85
14.	Jun 2010	F-36 VEG	Bil. brachial neuralgia	MRI C5C6 Disk degeneration	167
15.	Dec 2011	F-20 NV	Seizure disorder	On carbamazepine 5 years	182
16.	Jan 2012	M-32 VEG	Jaundice, anemia	Indirect hyperbilirubinemia	96
17.	Feb 2012	M-60 VEG	Parasthesias of extremities	DM on metformin	156
18.	Aug 2012	M-60 VEG	Symmetrical sensory neuropathy	DM on metformin	164

Abbreviations: CCP, Cyclic citrullinated peptide; RA, Rheumatoid arthritis; COPD, *Chronic obstructive pulmonary disease*; Hb, Hemoglobin; CHF, Congestive heart failure; MRI, Magnetic resonance imaging; DM, Diabetes mellitus

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