

Review of oral vitamin B12 (cobalamin) therapy

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Abstract

Vitamin B12 (cobalamin) deficiency is particularly common in adults and elderlies (>15%). Management of cobalamin deficiency with cobalamin injections is currently well codified, but new routes of vitamin B12 administration (oral and nasal) are being studied, especially oral vitamin B12 therapy for food-cobalamin malabsorption. Three prospective randomized studies, a systematic review by the *Cochrane* group and five prospective cohort studies were found and provide evidence that oral vitamin B12 treatment may adequately treat cobalamin deficiency. The efficacy was particularly highlighted when looking at the marked improvement in serum vitamin B12 levels and hematological parameters, for example hemoglobin level, mean erythrocyte cell volume, reticulocyte count. The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented. Oral cobalamin treatment avoids the discomfort, inconvenience and cost of monthly injections.

Key words: Vitamin B12. Cobalamin. Cobalamin deficiency. Food-cobalamin malabsorption. Biermer's disease. Treatment.

Introduction

Vitamin B12 (cobalamin) is the largest and most complex of all the vitamins. The name vitamin B12 is generic for a specific group of cobalt-containing corrinoids with biological activity in humans. Interestingly it is the only known metabolite to contain cobalt, which gives this water-soluble vitamin its red colour. This group of corrinoids is also known as cobalamins. The main cobalamins in humans and animals are hydroxocobalamin, adenosylcobalamin and methylcobalamin, the last two being the active coenzyme forms [1]. In 1934, three researchers won the Nobel prize in medicine for discovering the lifesaving properties of vitamin B12. They found that eating large amounts of raw liver, which contains high amounts of vitamin B12, could save the life of patients with previously incurable pernicious anemia [2]. To date, management of cobalamin deficiency with vitamin B12 injections is currently well established, but new routes of vitamin B12 administration (oral and nasal) are being studied [3]. This review summarizes the current knowledge on the efficacy of oral cobalamin therapy.

Cobalamin Metabolism and Deficiencies

Vitamin B12 metabolism is complex and is made up of many processes, defects in any one of which can

lead to cobalamin deficiency [1]. The different stages of cobalamin metabolism and corresponding causes of cobalamin deficiency are shown in **Figure 1**. Between 1–5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire gastro-intestinal tract by passive diffusion [4]. This absorption explains the mechanism underlying oral treatment of cobalamin deficiencies. A typical Western diet contributes 3–30 µg of cobalamin per day towards the recommended dietary allowance of 2.4 µg/day for adults [5]. The 5–10 year delay between the onset of vitamin B12 deficiency and the development of clinical symptoms is directly attributable to hepatic stores of cobalamin (>1.5 mg) and the enterohepatic cycle [4].

Cobalamin deficiency (characterized by serum cobalamin levels <150 pmol/L [200 pg/mL] ± serum total homocysteine levels >13 µmol/L) is particularly common in elderly patients (around 2 to 20%), but is often unrecognized or not investigated because the clinical manifestations of cobalamin deficiency are subtle [5]. However, certain complications of cobalamin deficiency, in particular neuropsychiatric and hematological complications are potentially serious and therefore require investigation

in all patients who present with vitamin or nutritional deficiency.

In adult, classic disorders such as nutritional deficiencies or malabsorption are the cause of vitamin B12 deficiency in only a limited number of patients, especially elderly patients [5]. A more common problem is food-cobalamin malabsorption, a disorder characterized by the inability to release cobalamin from food or its binding proteins [6]. However, in this syndrome, the absorption of “unbound” cobalamin (free crystalline) remains within the normal range [7]. The partial nature of this form of malabsorption might produce a more slowly progressive depletion of cobalamin stores compared to that seen with the more complete malabsorption engendered by disruption of intrinsic-factor-mediated absorption, as in Biermer’s disease. This explains why the required treatment dose of oral cobalamin may be lower in food-cobalamin malabsorption than in pernicious anemia [8]. In several recent studies, food-cobalamin malabsorption and Biermer’s disease are the main causes of cobalamin deficiency in adults and elderlies (between 70 to 80%) [7].

Parenteral Vitamin B12 Treatment

The classic treatment for cobalamin deficiency is by parenteral administration — in most countries as intramuscular

injections — in the form of cyanocobalamin and, more rarely, hydroxy or methyl cobalamin [9,10]. Hydroxocobalamin may have several advantages due to better tissue retention and storage [4]. However, the management concerning both the dose and schedule of administration varies considerably between countries [9]. In the USA and UK, doses ranging from 100 to 1,000 µg per month (or every 2-3 months when hydroxocobalamin is given) are used for the duration of the patient’s life [10]. In France, treatment involves the administration of 1,000 µg of cyanocobalamin per day for 1 week, followed by 1,000 µg per week for 1 month, followed by 1,000 µg per month, again, normally for the remainder of the patient’s lifetime [11].

Oral Vitamin B12 Treatment

Since cobalamin is absorbed by intrinsic factor-independent passive diffusion, daily high-dose (pharmacological dose, of at least 1,000 µg per day) oral vitamin B12 (cyanocobalamin) can induce and maintain remission in patients with megaloblastic anemia [3,12]. In cases of cobalamin deficiency other than those caused by nutritional deficiency, alternative routes of cobalamin administration have been used with good effect such as via the oral [3,8] and nasal passages [13,14]. These other routes of

administration have been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections [8]. A review by Lane *et al.* has reported preliminary data of the efficacy of oral vitamin B12 treatment [3]. It is to note that to date, curative oral cobalamin treatment accounts for more than 70% of the total vitamin B12 prescribed in Sweden in 2,000 [15]. Moreover, three studies that fulfilled the criteria of evidence based-medicine supported the efficacy of oral cobalamin therapy [16-18].

Randomized Controlled Studies

Two prospective randomized controlled studies comparing oral vitamin B12 *versus* intramuscular vitamin B12 treatment documented the efficacy of oral vitamin B12 as a curative treatment [16,17] (*Table 1*). Kuzminski *et al.*, in a prospective randomized trial including 38 patients, reported improvement of hematological parameters and vitamin B12 levels (mean value: 907 pg/mL), after 4 months of oral cyanocobalamin therapy using a much higher dose (i.e. 2,000 µg per day) [16]. Bolaman *et al.*, in a prospective randomized trial of 60 patients, also reported significant improvement of hematological parameters and vitamin B12 levels (mean improvement: +140.9 pg/mL), after 3

months of daily 1000 µg of oral cyanocobalamin therapy (*Table 1*) [17].

An evidence-based analysis by the *Vitamin B12 Cochrane Group* supports the efficacy of oral vitamin B12 as a curative treatment, with a dose between 1,000 and 2,000 µg initially prescribed daily and then weekly [18]. In this analysis, serum vitamin B12 levels increased significantly in patients receiving oral vitamin B12 and both groups of patients (receiving oral and intramuscular treatment) showed an improvement in neurological symptoms. The *Cochrane Group* concludes that daily oral therapy “may be as effective as intramuscular administration in obtaining short term haematological and neurological responses in vitamin B12 deficient patients” [18]. Nevertheless to our knowledge, the effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented. Thus until this has been studied, parenteral cobalamin therapy is still to be recommended for such patients [8].

In a randomized, parallel-group, double-blind, dose-finding trial, Eussen *et al.* showed that the lowest dose of oral cyanocobalamin required to normalize mild cobalamin deficiency is more than 200 times the recommended dietary allowance of approximately 3 µg daily (i.e. >500 µg per day) [19].

Other Not Randomized Studies

Our working group (*Groupe d'Etude des CAREnce vitamine B12 – CARE B12*) has developed an effective oral curative treatment in patients presenting with food-cobalamin malabsorption and pernicious anemia using crystalline cyanocobalamin [20-24]. In a first study, the *CARE B12* group prospectively studied 10 patients with cobalamin deficiency and well-established food-cobalamin malabsorption who received 3,000 or 5,000 µg of oral crystalline cyanocobalamin once a week for at least 3 months [20]. After 3 months of treatment, all patients had increased hemoglobin levels (mean increase of 1.9 g/dL; 95% confidence interval: 0.9 to 3.9 g/dL; $p < 0.01$ compared with baseline), and decreased mean erythrocyte cell volume (mean decrease of 7.8 fL; 95% confidence interval: 0.9 to 16.5 fL; $p < 0.001$). However, 2 patients had only minor, if any, responses. Serum cobalamin levels were increased in all 8 patients in whom it was measured.

Table 2 describes the other studies conducted on oral vitamin B12 treatment (open, not randomized studies) by the *CARE B12* group [20-24]. Analysis of these data confirms the previously reported efficacy of oral crystalline cyanocobalamin, particularly in food-cobalamin

malabsorption and in elderly patients [20-23]. All of the patients who were treated orally corrected their vitamin B12 levels and at least two-thirds corrected their hematological abnormalities. Moreover, one-third of patients experienced a clinical improvement on oral treatment. In most cases of food-cobalamin malabsorption a “low” cobalamin dose (i.e. 125–1,000 µg of oral crystalline cyanocobalamin per day) was used.

The aforementioned results were also observed in a documented population of patients presenting with Biermer's disease (**Table 2**) [24]. The *CARE B12* group studied in an open study 10 patients with well-documented cobalamin deficiency related to pernicious anemia who daily received 1,000 µg of oral crystalline cyanocobalamin for at least 3 months. After 3 months of treatment, serum cobalamin levels were increased in all 9 patients in whom it was measured (mean increase of 117.4 pg/mL; $p < 0.0000003$ compared with baseline). Eight patients had increased hemoglobin levels (mean increase of 2.45 g/dL; $p < 0.01$). All 10 patients had decreased mean erythrocyte cell volume (mean decrease of 10.4 fL; $p < 0.003$). Three patients experienced clinical improvements.

Recently, the *CARE B12* group had also documented the long-term efficacy of oral cobalamin treatment, with a median follow up of 2.5 years, in a population of 22 patients (**Table 2**) (*personal communication* [25]). These preliminary findings are in accordance with the results of Roth's study, with a median follow up of more than 4 years on oral cobalamin therapy [26]. The *CARE B12* group also documented in a small study (10 patients) the relative efficacy of oral cyanocobalamin treatment on cognitive functions (Mini Mental State Examination score) (**Table 2**) (*personal communication* [27]).

Since the 1990's, at least half of the patients followed in the University Hospital of Strasbourg (Strasbourg, France) with well-documented cobalamin deficiency were treated with oral cyanocobalamin, with a dose between 125 and 2,000 µg per day [20-29]. In the Department of Internal Medicine in the aforementioned institution (>500 patients with a documented cobalamin deficiency, median age 71 years), food-cobalamin malabsorption accounts for about 60–70% of the cases of cobalamin deficiency in elderly patients, whereas Biermer's disease accounted for only 15–25%. All of these patients who were treated orally corrected their vitamin B12 levels and at least 80%

corrected their hematological abnormalities. Moreover, half of the patients experienced a clinical improvement on oral treatment. It is to note that the patients presenting with severe neurological manifestations were usually excluded by our team for the oral vitamin B12 treatment. In the experience of the *CARE B12* group, oral cobalamin treatment avoids the discomfort, inconvenience and cost of monthly injections.

Conclusions

In conclusion, the experience of the *CARE B12* group and the present analysis support the use of oral cobalamin therapy in clinical practice. This group recommend a dose of 1,000 µg per day of oral cyanocobalamin for life in case of Biermer's disease (**Table 3**). In case of intake deficiency or food-cobalamin malabsorption, the *CARE B12* group recommend 1,000 µg per day of oral cyanocobalamin for 1 month and then 125 to 1,000 µg per day, until the cobalamin deficiency cause is corrected. The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

However, the recommendation of oral vitamin B12 as a definitive treatment has not yet been fully validated in current

clinical practice. To date, several authors suggest that oral vitamin B12 therapy remains one of “medicine’s best kept secrets” [30]. Nevertheless, the following can be proposed: ongoing supplementation is needed until any associated disorders are corrected (e.g. by halting the ingestion of the offending medication or exogenous, or by treating *H. pylori* infection or pancreatic exocrine failure) [8,29]. This may result in lifelong administration or, when applicable, sequential administration.

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Competing interests

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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Table 1: Prospective randomized studies of oral vitamin B12 treatment.

Study characteristics (number of patients)	Therapeutic modalities	Results	
Prospective randomized controlled study (n = 38)	Oral crystalline cyanocobalamin: 2,000 µg per day, during at least 4 months	<ul style="list-style-type: none"> - The mean pretreatment values for serum cobalamin, methylmalonic acid, and homocysteine were, respectively, 93 pg/mL, 3,850 nmol/L, and 37.2 µmol/L in the oral group and 95 pg/mL, 3,630 nmol/L, and 40.0 µmol/L in the parenteral therapy group. After 4 months of therapy, the respective mean values were 1,005 pg/mL, 169 nmol/L, and 10.6 µmol/L in the oral group and 325 pg/mL, 265 nmol/L, and 12.2 µmol/L in the parenteral group. The higher serum cobalamin and lower serum methylmalonic acid levels at 4 months posttreatment in the oral group <i>versus</i> the parenteral group were significant, with $p < 0.0005$ and $p < 0.05$, respectively - Correction of hematological and neurological abnormalities was prompt and indistinguishable between the 2 groups 	[16]
Prospective randomized open-label study (n = 60)	Oral crystalline cyanocobalamin: 1000 µg p.o. once daily for 10 days (p.o. group) or cobalamin i.m.: 1,000 µg once daily for 10 days (i.m. group). After 10 days, both treatments were administered once a week for 4 weeks, and after that, once a month for life	<ul style="list-style-type: none"> - The mean serum vitamin B12 concentration increased significantly from day 0 to 90 ($p < 0.001$). - In the p.o. group, at days 30 and 90, all hematological parameters changed significantly versus day 0 (mean hemoglobin levels increased [both $p < 0.001$]; mean corpuscular volume decreased [both $p < 0.001$]; mean white blood cell count increased [day 30, $p < 0.01$; day 90, $p < 0.001$]; and mean platelet count increased [both $p < 0.001$]). Reticulocytosis was observed in all patients. These hematological parameters and the recovery patterns were similar between the 2 groups - Neurological improvement was detected in 78% in the p.o. group and 75% in the i.m. group at day 30 	[17]

Table 2: Cohort studies of oral vitamin B12 treatment conducted at the University Hospital of Strasbourg, France (*adapted from [8]*).

Study characteristics (number of patients)	Therapeutic modalities	Results	
Open prospective study of vitamin B12 deficiency related to food-cobalamin malabsorption (n = 10)	Oral crystalline cyanocobalamin: 650 µg per day, during at least 3 months	<ul style="list-style-type: none"> - Normalization of serum vitamin B12 levels in 80% of the patients - Significant increase in Hb levels (mean of 1.9 g/dL) and decrease of mean ECV (mean of 7.8 fL) - Improvement of clinical abnormalities in 20% of the patients - No adverse effect 	[20]
Open prospective study of low vitamin B12 levels not related to pernicious anemia (n = 20)	Oral crystalline cyanocobalamin: between 1000 µg per day during at least 1 week	<ul style="list-style-type: none"> - Normalization of serum vitamin B12 levels in 85% of the patients - No adverse-effect 	[22]
Open prospective study of vitamin B12 deficiency related to food-cobalamin malabsorption (n = 30)	Oral crystalline cyanocobalamin: between 1000 and 250 µg per day, during 1 month	<ul style="list-style-type: none"> - Normalization of serum vitamin B12 levels in 87% of the patients - Significant increase of Hb levels (mean of 0.6 g/dL) and decrease of ECV (mean of 3 fL); normalization of Hb levels and ECV in 54% and 100% of the patients, respectively - Dose effect - effectiveness dose of vitamin B12 ≥500 µg per day - No adverse-effect 	[21]
Open prospective study of low vitamin B12 levels not related to pernicious anemia (n = 30)	Oral crystalline cyanocobalamin: between 1000 and 125 µg per day during at least 1 week	<ul style="list-style-type: none"> - Normalization of serum vitamin B12 levels in all patients with at least a dose of vitamin ≥250 µg per day - Dose effect - effectiveness dose of vitamin B12 ≥500 µg per day - No adverse-effect 	[23]
Open prospective study of low vitamin B12 levels related to pernicious anemia (n = 10)	Oral crystalline cyanocobalamin: 1000 µg per day, during at least 3 months	<ul style="list-style-type: none"> - Significant increase of serum vitamin B12 levels in 90% of the patients (mean of 117.4 pg/mL) - Significant increase of Hb levels (mean of 2.45 g/dL) and decrease of ECV (mean of 10.4 fL) - Improvement of clinical abnormalities in 30% of the patients 	[24]
Cohort study of low vitamin B12 levels mainly related to food-cobalamin malabsorption (n = 22)	Oral crystalline cyanocobalamin: 650 µg per day, during a median of 2.5 years	<ul style="list-style-type: none"> - Normalization of serum vitamin B12 levels in 95% of the patients - Significant increase of Hb levels (mean of 1.1 g/dL) - Improvement of clinical abnormalities in 20% of the patients 	[25]
Cohort study of patients with cognitive alteration related to low vitamin B12 levels mainly related to food-cobalamin malabsorption (n = 10)	Oral crystalline cyanocobalamin: 1,000 µg per day, during a week, than 1,000 µg per week, during a moth, and 1,000 µg per month, during at least 3 months	<ul style="list-style-type: none"> - Increase of MMSE score during the treatment ($p < 0.06$) 	[27]

Hemoglobin = Hb. Erythrocyte cell volume = ECV. MMSE = Mini Mental State Examination.

Table 3: Expert opinion recommendations for oral vitamin B12 treatment.

	Pernicious anemia	Intake deficiency and food-cobalamin malabsorption
Parenteral administration (intramuscular)	<p>Cyanocobalamin:</p> <ul style="list-style-type: none"> - 1,000 µg per day for 1 week - than 1,000 µg per week for 1 month - than 1,000 µg per each month, for life <p>(1,000 to 2,000 µg per day for at least 1 to 3 months in case of severe neurological manifestations)</p>	<p>Cyanocobalamin:</p> <ul style="list-style-type: none"> - 1,000 µg per day for 1 week - than 1,000 µg per week for 1 month - than 1,000 µg per each 1 or 3 months, until the cobalamin deficiency cause is corrected <p>(1,000 µg per day for at least 1 to 3 months in case of severe neurological manifestations)</p>
Oral administration	<p>Cyanocobalamin:</p> <p>1,000 µg per day for life[±]</p>	<p>Cyanocobalamin:</p> <ul style="list-style-type: none"> - 1,000 µg per day for 1 month - than 125 to 1,000 µg per day, until the cobalamin deficiency cause is corrected[±]

[±]: The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

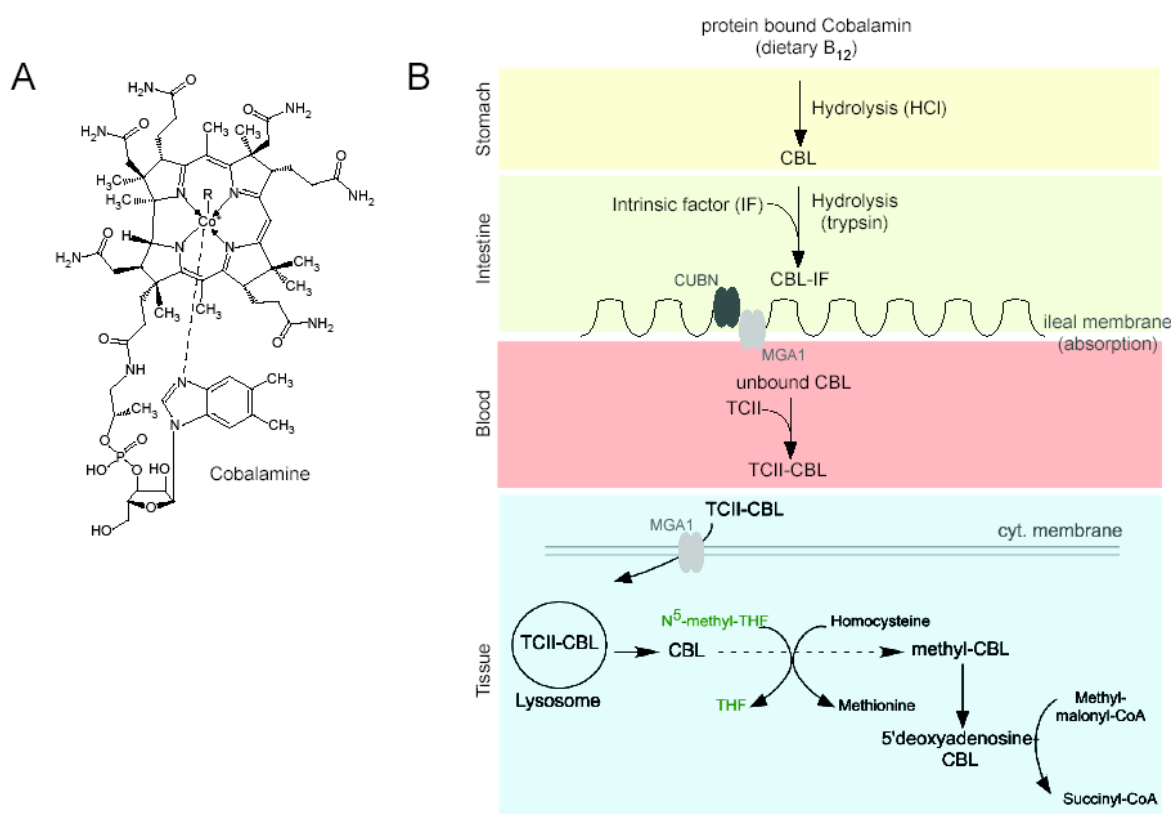


Figure 1: Structure (A) and metabolism of the vitamin B12 (B). The metabolic journey of cobalamin (cbl) from nutrient intake to its intestinal absorption. Endocytic receptors and proteins responsible for vitamin B12 intestinal absorption include cubilin (CUBN), amnionless (AMN), receptor-associated protein and megalin (MGA1). The membrane megalin/transcobalamin II (TCII)-receptor complex allows the cellular uptake of cbl. Lysosomal-mediated degradation of TCII and subsequent release of free-cbl is essential for vitamin B12 metabolic functions. MS, methonine synthase; THF, tetrahydrofolate; MTHFR, methylene tetrahydrofolate reductase; MCM, methylmalonyl CoA mutase [1,5].