

## Oral Cobalamin (Vitamin B12) Therapy: From Empiricism and Personal Experience to Evidence Based Medicine and Perspective of Recommendations and Guideline

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In most countries, the classic treatment for cobalamin deficiency is based on parenteral administration - as intramuscular injections - in the form of cyanocobalamin and, more rarely, hydroxyl- or methylcobalamin [1]. In 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 [2]. In France, treatment involves the administration of 1,000µg of cyanocobalamin per day for 1 week, followed by 1,000 µg per week for 1 month, followed by 1,000µg per month, again, normally for the remainder of the patient's lifetime [3].

However, cobalamin is absorbed by intrinsic factor-independent passive diffusion and daily high-dose (pharmacological dose, of at least 1,000 µg per day) oral vitamin B12 can cure cobalamin deficiency, and may also induce and maintain remission in patients with megaloblastic anemia [4]. In Sweden, curative oral cobalamin treatment accounts for more than 70% of the total vitamin B12 prescribed in Sweden in 2000 [5]. The rationale of this route of administration is avoiding the discomfort, inconvenience and cost of monthly injections of vitamin B12 [6].

Until recent years, prescription of oral cobalamin therapy is primarily based on the knowledge and belief of each practitioner, on empirical data, and in clinical practice, on personal experience [7]. To our knowledge, this modality of vitamin B12 prescription is not taught in most countries in medical schools, absent from the majority of medical textbooks and no international recommendations or guidelines are available.

In 2002, a review by Lane et al. has reported data on the efficacy of oral vitamin B12 treatment and gives to the clinician a few keys on the prescription modality [4]. Since this date, several studies that fulfilled the criteria of evidence based-medicine were published on the efficacy of oral cobalamin therapy [6].

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 [8,9]. Kuzminski et al. [8] 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 higher dose of cobalamin (i.e. 2000 µg per day).

Bolaman et al. [9] 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 1000µg of oral cyanocobalamin therapy

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 [10]. 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 hematological and neurological responses in vitamin B12 deficient patients" [10].

In a randomized, parallel-group, double-blind, dose-finding trial, Eussen et al. [11] 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).

Our working group (CARE B12, Hôpitaux Universitaires de Strasbourg, Strasbourg, France) has developed an effective oral curative treatment in patients presenting with Food-Cobalamin Malabsorption (FCM) and Pernicious Anemia (PA) using crystalline cyanocobalamin [6].

In a first study, we prospectively studied 10 patients with cobalamin deficiency and well-established FCM who received 3000 or 5000 µg of oral crystalline cyanocobalamin once a week for at least 3 months [12]. 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.

We also studied in an open study 10 patients with well-documented cobalamin deficiency related to PA who daily received 1000 µg of oral crystalline cyanocobalamin for at least 3 months [13]. 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;  $p < 0.0001$  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.

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Analysis of several other studies (open, not randomized) we have conducted of this topic show that all of patients who were treated orally corrected their vitamin B12 levels and at least two-thirds corrected their hematological abnormalities [14-16]. Moreover, one-third of patients experienced a clinical improvement on oral treatment. In most cases of FCM a "low" cobalamin dose (i.e. 125-1,000µg of oral crystalline cyanocobalamin per day) was used.

Since the 1990's, at least half of these patients with vitamin B12 deficiency were treated with oral cyanocobalamin, with a dose between 125 and 2,000 µg per day. All of the 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.

Thus, we currently recommend a dose of 1,000 µg per day of oral cyanocobalamin, for life, in case of PA. We recommend 1,000 µg per day of oral cyanocobalamin for 1 month and than 125 to 1,000 µg per day in case of intake vitamin B12 deficiency or FCM [6]. It is to keep in mind that the effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented, both in our experience that in the literature.

In conclusion, we believe that data on the efficacy of vitamin B12 administered orally are numerous enough to propose international consensual recommendations and guideline.

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