Oral cobalamin therapy: It may be perhaps time to propose international recommendations?

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Vitamine B12 administrée par voie orale : peut-être est-il temps d’édicter des recommandations ?

In most countries, the classic treatment for cobalamin (vitamin B12) deficiency is based on parenteral administration - as intramuscular injections - in the form of cyanocobalamin and, more rarely, hydroxyl- or methylcobalamin [1]. The rationale for this practice is that theoretically no absorption of vitamin B12 can be realized orally in pernicious anemia (PA).

In the USA and UK, doses ranging from 100 to 1000 μg per month (or every 2 to3 months when hydroxocobalamin is given) are used for the duration of the patient’s life [2]. In France, treatment involves the administration of 1000 μg of cyanocobalamin per day for 1 week, followed by 1000 μg per week for 1 month, followed by 1000 μg per month, again, normally for the remainder of the patient’s lifetime [3].

In all healthy individuals or patients, cobalamin is however absorbed by intrinsic factor-independent passive diffusion (at least 1%) and daily high-dose (pharmacological dose, of at least 1000 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].

Historically, the Swedish team (Berlin’s team) was the first to routinely propose oral cobalamin therapy to cure vitamin B12 deficiency [6]. The rational of this route of administration is avoiding the discomfort, inconvenience and cost of monthly injections of vitamin B12 [7].

Moreover, in recent years, food-cobalamin malabsorption (FCM) has been found to be the leading cause of cobalamin malabsorption, especially in elderly patients. In our experience, this
syndrome accounted for 60 to 70% of cases of cobalamin deficiency in elderly patients [8]. To date, in practice, FCM is characterized by cobalamin deficiency in the presence of sufficient food-cobalamin intake and a normal Schilling test ruling out malabsorption or PA (diagnosis of exclusion). Thus, in this syndrome, patients can absorb “unbound” cobalamin through passive diffusion and also through intrinsic factor mechanisms, the latter being by definition intact [9].

Until recent years, prescription of oral cyanocobalamin therapy is primarily based on the knowledge and belief of each practitioner, on empirical data (derived from the Swedish experience), and in clinical practice, on personal experience [4,7]. 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 guideline 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 cyanocobalamin therapy [7].

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 [10,11]. 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 higher dose of cobalamin (i.e. 2000 µg per day) [10].

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 [11].

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 1000 and 2000 µg initially prescribed daily and then weekly [12]. 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” [12].

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) [13].

In an other randomized, parallel-study, in patients with subtle vitamin B12 deficiency, Favrat et al. report that oral vitamin B12 treatment normalized the metabolic markers of vitamin B12 deficiency [14]. In this study, a 1-month daily treatment with 1000 µg oral vitamin B12 was not sufficient to normalize the deficiency markers for four months, and treatment had no effect on hematological signs of B12 deficiency.

Our working group (CARE B12, hôpitaux universitaires de Strasbourg, Strasbourg, France) has developed an effective oral curative treatment in patients presenting with FCM and PA using crystalline cyanocobalamin [7].

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 [15]. 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 minimal, 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 [16]. After 3 months of treatment, serum cobalamin levels were increased in all 9 patients in whom it was measured (mean increase of 117.4 µg/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; µg0.003). Three patients experienced clinical improvements.

Analysis of several other studies (open, not randomized) we have conducted of this topic shows that all of patients who were treated orally corrected their vitamin B12 levels and at least two-thirds corrected their hematological abnormalities [17–20]. Moreover, one-third of patients experienced a clinical improvement on oral treatment. In most cases of FCM a “low” cobalamin dose (i.e. 125–1000 µg of oral crystalline cyanocobalamin per day) was used.

Our last study confirms the efficacy and safety of oral cyanocobalamin therapy (between 125 to 1000 µg per day) in 31 patients with FCM (n = 20) and PA (n = 11) [20]. After 3 months of therapy, the serum cobalamin levels have significantly increased in all the patients, with a mean of +161.6 ± 79.3 µg/mL in the FCM group (µg0.00005) and +136.7 ± 67.4 pg/mL in the PA group (µg0.0001). Hematological parameters have been normalized in 90% of the patients, independently of the cause of the cobalamin deficiency. Only 1 patient presented an urticarial reaction.
TABLE 1
Take home message and recommendations for oral cobalamin treatment

<table>
<thead>
<tr>
<th>Pernicious anemia</th>
<th>Intake deficiency and food-cobalamin malabsorption</th>
</tr>
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<tbody>
<tr>
<td>Oral administration</td>
<td>Cyanocobalamin: 1000 μg per day for life&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>1000 μg per day for 1 month</td>
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<tr>
<td></td>
<td>than 125 to 1000 μg per day, until the cobalamin deficiency cause is corrected&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parenteral administration (intramuscular)</td>
<td>Cyanocobalamin</td>
</tr>
<tr>
<td></td>
<td>1000 μg per day for 1 week</td>
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<td></td>
<td>than 1000 μg per week for 1 month</td>
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<tr>
<td></td>
<td>than 1000 μg per each month, for life</td>
</tr>
<tr>
<td></td>
<td>than 1000 μg per each 1 or 3 months, until the cobalamin deficiency cause is corrected</td>
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<td></td>
<td>(1000 to 2000 μg per day for at least 1 to 3 months in case of severe neurological manifestations)</td>
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<td></td>
<td>(1000 μg per day for at least 1 to 3 months in case of severe neurological manifestations)</td>
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<sup>1</sup>The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

Since the 1990’s, at least half of our patients with vitamin B12 deficiency were treated with oral cyanocobalamin, with a dose between 125 and 2000 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. In our experience, only two of our patients had a cutaneous eruption (minor allergic reaction) related to the excipients used in pharmaceutical preparation.

In conclusion, we believe that data on the efficacy and safety of vitamin B12 administered orally are numerous enough to propose recommendations for this modality of treatment. In 2012, (10 years after the review of Lane et al. [4]), it’s perhaps time to incorporate it in the international guidelines and reference textbooks. Otherwise, this treatment modality will remain “the best kept secret in medicine” [21].

In this context, we (take home message) currently recommend a dose of 1000 μg per day of oral cyanocobalamin, for life, in case of PA. As you see in the (table 1), we recommend 1000 μg per day of oral cyanocobalamin for 1 month and than 125 to 1000 μg per day in case of intake vitamin B12 deficiency or FCM [7]. However, 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 2012, it’s perhaps time to propose international recommendations...

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References