Elderly patient may benefit from oral vitamin B12 treatment

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ABSTRACT: The objective of this review is to evaluate the efficacy of oral vitamin B12 treatment in elderly patients, in an evidence based-medicine view. To reach this objective, PubMed data was systematically searched for English and French articles published from January 1990 to July 2008. 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 in elderly patients. The efficacy was particularly well determined on hematological manifestations. Oral vitamin B12 treatment avoids the discomfort, inconvenience and cost of monthly injections.

INTRODUCTION

Vitamin B12 (cobalamin) deficiency is particularly common in the elderly patients (>65 years of age), but is often unrecognized because its clinical manifestations are often subtle; however, they are also potentially serious, particularly from a neuropsychiatric and hematological perspective (1). Management of vitamin B12 deficiency with vitamin B12 injections is currently well codified, but new routes of vitamin B12 administration (oral and nasal) are being studied (2, 3). This review summarizes the current knowledge on the efficacy of oral vitamin B12 treatment in elderly patients, in an evidence based-medicine view. This review was restricted to curative treatment.

REVIEW CRITERIA

PubMed was systematically searched for articles published from January 1990 to July 2008, using the following expressions: “oral vitamin B12 treatment” or “oral cobalamin treatment”. Articles were restricted to those containing human data that were published in English and French languages. Unpublished data from our working group has also been included.

RATIONAL OF ORAL VITAMIN B12 TREATMENT

A typical Western diet contributes 3–30 μg of vitamin B12 per day towards the recommended dietary allowance set by the Food and Nutrition Board of the Institute of Medicine (US) of 2.4 μg/day for adults (4). Cobalamin metabolism is complex and is made up of many processes (Figure 1), defects in any one of which can lead to vitamin B12 deficiency (5). Two main reasons support the rational of oral vitamin B12 treatment (5, 6). First, between 1–5% of free vitamin B12 (or crystalline vitamin B12) is absorbed along the entire intestine by passive diffusion. Second in elderly patients, the main cause of vitamin B12 deficiency is food-cobalamin malabsorption (50-70%), a disorder characterized by the inability to release cobalamin from food or its binding proteins (7, 8). But in this syndrome, the absorption of “unbound” cobalamin (free crystalline) is normal (4, 6). The partial nature of this form of malabsorption might produce a more slowly progressive depletion of cobalamin than does the more complete malabsorption engendered by disruption of intrinsic-factor-mediated absorption. This explains that the required doses of oral cobalamin may be lower in food-cobalamin malabsorption than in pernicious anemia.

CLASSICAL TREATMENT OF COBALAMIN DEFICIENCY

The classic treatment for vitamin B12 deficiency is parenteral administration—in most countries intramuscular injection—of this vitamin (in the form of cyanocobalamin and, more rarely, hydroxy or methyl cobalamin) (1, 9, 10). Hydroxocobalamin may have several
advantages due to a better tissular retention and storage (10). However, traditions concerning both dose and schedule of administration vary considerably (9). In USA and UK, dosages ranging from 100 to 1,000 μg per month (or every 2-3 months when hydroxocobalamin is given) are used during the rest of the patient’s life (9, 10). In France, the 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, normally for the rest of the patient’s life (1).

**ORAL VITAMIN B12 TREATMENT**

Since vitamin B12 is absorbed by intrinsic-factor-independent passive diffusion, daily high-dose (pharmacological dose) oral vitamin B12 (cyanocobalamin) can induce and maintain remissions in patients with megaloblastic anemia (1, 3). In cases of vitamin B12 deficiency other than those caused by nutritional deficiency, alternative routes of vitamin B12 administration have been used in a curative perspective: oral (3, 11) and nasal (12, 13). These other routes of administration have been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections (6, 7). A recent review of Lane et al. has reported preliminary data of the usefulness of oral cobalamin treatment (3). It is to note that to date, oral cobalamin curative treatment accounts for more than 70% of the total vitamin B12 prescribed in Sweden in 2000 (14).

**PROSPECTIVE RANDOMIZED STUDIES**

Two prospective randomized controlled studies comparing oral vitamin B12 versus intramuscular vitamin B12 documented the efficacy of oral vitamin B12 treatment, in a curative perspective (15, 16). 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. 2000 μg per day) (15). 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 (16). 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) (17).

**EVIDENCE-BASED ANALYSIS FROM THE COCHRANE GROUP**

An evidence-based analysis by the Vitamin B12 Cochrane Group supports the efficacy of oral vitamin B12 treatment in a curative objective, with a dose between 1,000 and 2,000 μg given initially daily and then weekly (11). 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) had neurological improvement. 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”. Nevertheless to our knowledge, the effect of oral vitamin B12 treatment in patients presenting severe neurological manifestations has not yet been adequately documented. Thus until this has been done parenteral vitamin B12 therapy is still to be recommended for such patients (10).

**PROSPECTIVE COHORT STUDIES**

Our working group has developed an effective oral curative treatment in elderly patients (presented food-cobalamin malabsorption and pernicious anemia) using crystalline cyanocobalamin (18-22). Our principal studies of oral vitamin B12 treatment (open, not randomized studies) are described in table 1. Our data confirm the previously reported efficacy of oral crystalline cyanocobalamin, especially in food-cobalamin therapy in elderly patients (18-21). All of our 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 doses (i.e. 125–1,000 μg of oral crystalline cyanocobalamin per day) were used. These results were also observed in a documented population of patient presented pernicious anemia (22). Recently, we have 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 (23). These preliminary findings in accordance with the results of Roth’s study, with a median follow up of more than 4 years of oral cobalamin therapy (24).
RECOMMENDATIONS FOR CLINICAL PRACTICE

The procedure for oral vitamin B12 treatment in a curative perspective has not been completely validated yet in real life. To date, as several authors suggest, oral vitamin B12 therapy remains one of "medicine’s best kept secrets" (25). Since loading doses of vitamin B12 far exceed physiologic requirements, clinical responses may result from pharmacologic effects on either cobalamin-related processes or on cellular functions completely unrelated to the known biochemical actions of cobalamin (Figure 1) (10). As a result, blood cobalamin, methylmalonic acid and homocysteine values often fail to predict whether or not a patient will respond to cobalamin therapy (26). Nevertheless, the following can be proposed: ongoing supplementation until associated disorders are corrected (e.g. by halting the ingestion of the offending medication or exogenosis, or by treating H. pylori infection or pancreatic exocrine failure), lifelong administration or, when applicable, sequential administration (6, 7). In elderly patients, a therapeutic schema - including recent data - is proposed in figure 2.

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COMPETING INTERESTS

No author has any conflict of interest.

REFERENCES


Several studies support the efficacy of oral vitamin B12 treatment, particularly on hematological manifestations.