Treatment of Vitamin B_{12}–Deficiency Anemia: Oral Versus Parenteral Therapy

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OBJECTIVE: To evaluate the use of oral cyanocobalamin therapy in the treatment of cobalamin (vitamin B_{12})–deficient anemia.

DATA SOURCES: Primary and review articles were identified by MEDLINE search (1966–May 2000) and through secondary sources.

DATA SYNTHESIS: Cobalamin-deficient anemia is among the most common diagnoses in older populations. Cobalamin-deficient anemia may be diagnosed as pernicious anemia, resulting from the lack of intrinsic factor required for cobalamin absorption or as protein malabsorption from the inability to displace cobalamin from protein food sources. Several studies provide evidence that daily oral cyanocobalamin as opposed to monthly parenteral formulations may adequately treat both types of cobalamin-deficient anemias.

CONCLUSIONS: Daily oral cyanocobalamin at doses of 1000–2000 μg can be used for treatment in most cobalamin-deficient patients who can tolerate oral supplementation. There are inadequate data at the present time to support the use of oral cyanocobalamin replacement in patients with severe neurologic involvement.

KEY WORDS: cobalamin, cobalamin deficiency, pernicious anemia, vitamin B_{12}.

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Cobalamin deficiency is commonly observed in older people, with an estimated prevalence of nearly 40%.[1] Oral cyanocobalamin can be a pharmacotherapeutic option for the treatment of cobalamin (vitamin B_{12})– deficient anemia of various etiologies, although it is underused. This is most likely a result of the 1959 US Pharmacopeia Anti-Anemia Preparations Advisory Board, which cautioned against the use of oral therapy for pernicious anemia because of its unpredictable efficacy.[2] Historically, oral cyanocobalamin therapy was perceived as inadequate due to reported low serum cobalamin concentrations in patients taking 100–250 μg/d.[3] Over the course of many years, various published studies[4-9] have shown that this is not always the case. This article reviews the data supporting the use of oral cyanocobalamin for the treatment of all forms of vitamin B_{12}-deficient anemia.

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Pathophysiology

Cobalamin is an important cofactor for synthase and mutase enzymes maintaining methylation reactions in the brain.[10] Its deficiency can result in failure of myelin synthesis and other neurotoxic processes. Cobalamin deficiency classically presents as macrocytic megaloblastic anemia.[11] Patients may have a smooth and beefy red tongue from atrophic glossitis and possible neurologic complications. Frequently, neurologic signs and symptoms precede hematologic abnormalities and include peripheral neuropathy, ataxia, imbalance, upper motor neuronal signs, behavioral abnormalities, and dementia. A patient presenting with these neurologic manifestations may already have irreversible damage to the spinal cord and cerebrum.[12,13] The consequences range from mild paresthesias and numbness to memory loss and frank psychosis.

The daily cobalamin requirement is 2.4 μg/d.[14] Absorption depends on intrinsic factor, which is secreted by the gastric mucosa. Intrinsic factor then binds cobalamin,

forming a complex that is absorbed by the terminal ileum.[11] This mechanism is responsible for approximately 60% absorption of an oral cyanocobalamin tablet.[15] Of particular interest is the observation that approximately 1% of an oral dose of cyanocobalamin is absorbed by simple diffusion independent of intrinsic factor.[14] Absorption by simple diffusion is more than adequate to meet the daily requirements for patients without intrinsic factor when daily oral dosages of 1000 µg are ingested.[16]

Gastric dysfunction leading to food–cobalamin malabsorption is the most prevalent cause of cobalamin deficiency.[17] It may occur in >30% of those with low cobalamin concentrations. Patients with food–cobalamin malabsorption are unable to displace cobalamin from protein food sources. At an acidic pH, pepsin facilitates the transfer of cobalamin from protein food sources.[18] The impairment of this and other unidentified mechanisms for malabsorption may be the result of atrophic body gastritis, gastrectomy, achlorhydria, or pancreatic insufficiency.[11] These patients become deficient in unbound serum cobalamin, but have the functional intrinsic factor necessary for absorption of cobalamin in the small intestine. Nonetheless, these patients can acquire unbound cobalamin from oral or parenteral supplements. Diagnosing this type is more difficult. A Schilling test[19] will provide normal results because it measures the ability to absorb unbound cobalamin through intrinsic factor. Clinical symptoms may take as long as 15 years to manifest following the onset of gastric dysfunction as the reabsorption of biliary cobalamin continues, resulting in a gradual and slow depletion of cobalamin stores.[17]

Pernicious anemia is the second most frequent cause of cobalamin deficiency in the elderly, affecting approximately 1.9% of adults aged >60 years.[11,12,17] The end result of pernicious anemia is a loss of intrinsic factor secretion, therefore impairing the ability to absorb unbound serum cobalamin. An abnormal Schilling test or a positive anti–intrinsic factor antibody can detect this type of anemia. Clinically, pernicious anemia may progress within 5 years because of a failure to both absorb cobalamin and reabsorb biliary cobalamin.

Pertinent serum markers for cobalamin-deficient anemia include serum cobalamin, methylmalonic acid (MMA), and homocysteine. Serum cobalamin concentrations are frequently used to diagnose cobalamin-deficient anemia, yet this may be insufficient for a diagnosis in some cases. Clinically significant cobalamin deficiency has been found in 2.9% of patients with serum cobalamin concentrations >200 pg/mL,[20] and as many as 2.5% of healthy subjects who are not anemic will have low serum cobalamin concentrations.[21] MMA and homocysteine serum concentrations have been markedly elevated in most patients with cobalamin-deficient anemia; they may be more sensitive markers than serum cobalamin concentrations.[11]

Literature Review

The effectiveness of oral cyanocobalamin is supported by the cumulative results of various studies in patients lacking intrinsic factor. The 100–200 µg daily dose was shown to be adequate in most patients, but low circulating cobalamin concentrations were occasionally observed.[4-9] A 300–500 µg daily dose has produced satisfactory responses, but due to individual variability in absorption, borderline cobalamin concentrations are possible.[4,16] The 1000-µg daily dose has produced successful long-term results in all patients studied.[7,15,16]

Interestingly, the study of oral cyanocobalamin therapy dates back to 1968, when Berlin et al.[16] described 64 cobalamin-deficient patients (55 with pernicious anemia and 9 with malabsorption) who were prescribed oral cyanocobalamin 500 or 1000 µg daily. Sixty-one patients completed 36 months of therapy, 44 completed 48 months, and 17 patients completed 60 months of oral therapy. After 2 months of treatment, 562 serum cobalamin values were obtained from the 64 patients so as to strictly evaluate compliance and serum B_{12} response (all patients discontinued oral therapy 3 d prior to blood sample measurements to avoid temporary peaks in serum B_{12} concentrations). Only 40 values were <150 pg/mL, and 6 values were <100 pg/mL. The number of patients from whom these values were obtained was not mentioned.

Generally, the lower recorded readings were attributed to early months of treatment in patients who were relapsing. Repeated low serum concentrations of cobalamin were found only in patients taking 500 µg of cyanocobalamin daily. After 2 months, mean serum cobalamin values in the entire sample were within normal range (>150 pg/mL), and all patients demonstrated clinical and hematologic remission. No adverse effects were reported in any patients. Six patients had cyanocobalamin therapy discontinued to determine the length of time it would take for them to deplete their cobalamin stores; 4 patients completed 33 months of therapy, 1 completed 28 months, and 1 completed 19 months when therapy was discontinued. All patients (including 2 with pernicious anemia) had normal serum cobalamin concentrations without hematologic or neurologic complications after 4 months of discontinuation. This study did not provide specific results or the number of patients from each dosing group. Both groups were presented together. No statistical evaluations were presented in this study; however, it did demonstrate successful use of oral cyanocobalamin 1000 µg/d for maintenance therapy in all types of cobalamin-deficient anemia, with no adverse effects.[16]

In 1970, it was noted that oral cyanocobalamin use greatly increased in Sweden.[22] In fact, approximately 80% of cyanocobalamin costs in Sweden are now accounted for by oral preparations. Oral therapy is currently used by 40% of patients requiring cobalamin replacement in Sweden.[3] These utilization patterns of oral cyanocobalamin therapy do not appear to extend internationally.

Kuzminski et al.[15] conducted a randomized, controlled study comparing oral with intramuscular cyanocobalamin for treatment of cobalamin deficiency. This study included 33 patients with various causes of cobalamin deficiency, including pernicious anemia, atrophic gastritis, drug-in-

duced, ileal resection, gastric stapling, and dietary deficiencies. At baseline, all patients had serum cobalamin concentrations <160 pg/mL (normal 200–900) and elevations in serum MMA, total homocysteine, or elevations of both metabolites >3 standard deviations above the mean in normal controls. Subjects were randomized to receive oral cyanocobalamin 2000 µg/d or intramuscular cyanocobalamin 1000 µg on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 for a total of 4 months. Four patients in each group experienced neurologic symptoms. Eighteen patients received oral cyanocobalamin, and 15 patients received intramuscular cyanocobalamin. Mean serum ± SD cobalamin concentrations were significantly higher at 2 months (643 ± 328 vs. 306 ± 118 pg/mL; $p < 0.001$) and at 4 months (1005 ± 595 vs. 325 ± 165 pg/mL; $p < 0.0005$) in the oral cyanocobalamin group. Intramuscular cyanocobalamin produced a more rapid decline in serum MMA concentrations at 1 month ($p < 0.001$). Interestingly, MMA concentrations rebounded to higher concentrations with intramuscular cyanocobalamin at 2 and 4 months than with oral administration ($p < 0.05$), possibly reflecting superior efficacy for maintenance therapy with oral administration. Homocysteine concentrations also decreased in most patients in the oral and intramuscular groups over 4 months without a statistical difference noted in either group at any time. Neurologic symptoms improved in 2 of the 4 patients in each group, and completely cleared in the other 2 patients in each group at 4 months; no timetable was provided specifying how rapidly the improvement occurred. This was a very small study, but it clearly demonstrated that oral cyanocobalamin had equal, if not superior, efficacy in the long-term treatment of cobalamin deficiency of various etiologies.

Three different oral forms of vitamin B_{12} (cyanocobalamin, hydroxycobalamin, methylcobalamin) were studied[23] in 8 patients with cobalamin deficiency due to pernicious anemia (4 patients) or postgastrectomy megaloblastic anemia (4 patients). Patients were given 1500 µg/d of one of the forms of cobalamin replacement therapy. Baseline serum cobalamin concentrations ranged from 39 to 170 pg/mL (normal 249–983). MMA was measured in 5 patients and elevated in all measured (normal <10 mg/d). All 8 patients exhibited clinical neurologic manifestations of cobalamin deficiency such as paresthesia, numbness, and impaired mental status. Six patients tested positive for either anti-intrinsic factor or antiparietal cell antibody, resulting in either inhibition of intrinsic factor or a lack of intrinsic factor formation, respectively. This study lasted for 1 year. Clinical improvement was noted as early as 3–4 days; neurologic impairments disappeared after 1–2 months in all patients. This study had a very small sample size, lacked a comparison group with intramuscular cyano-cobalamin, and did not provide statistical analyses. The question remains whether intramuscular cyanocobalamin would have resulted in more rapid clinical improvement in these patients who had neurologic complications.

Verhaeverbeke et al.[24] conducted a prospective, open-label study to evaluate the response to oral cobalamin therapy of patients with food–cobalamin malabsorption. Patients with pernicious anemia were excluded from this study (they were diagnosed using the Schilling test or by measuring anti-intrinsic factor or antiparietal cell antibodies). Ninety-four patients aged >70 years with cobalamin serum concentrations <220 pg/mL (normal 220–950) were included in the study. Serum cobalamin concentrations were evaluated before therapy, after 10 days, and after 1 month. Cyanocobalamin was administered at a dose of 100 µg/d. Follow-up data were available for 88 patients after 10 days and 44 patients after 1 month. Serum concentrations of cobalamin increased from a mean ± SD of 146.5 ± 35.6 pg/mL on day 0 to 271.5 ± 95.5 pg/mL at 10 days, then increased to 371.2 ± 285.4 pg/mL ($p < 0.001$) after 1 month. The normalization of serum cobalamin occurred after 10 days in 69% of patients and after 1 month in 88% of patients. The study did not include a control group of intramuscular therapy, so no comparisons can be made.

Presently, many clinicians are unaware of the efficacy of oral cobalamin and its potential place in the therapy of cobalamin-deficient anemia. Lederle[25] conducted a study to investigate physician awareness of oral cyanocobalamin in the US. The study used a survey provided to medical internists in 1989 and again in 1996. The survey asked for a description of cyanocobalamin regimens used by the respondents rather than asking about oral cyanocobalamin directly. A 68% response rate was acquired in 1989 and a 69% response rate in 1996. The percentage of respondents who reported ever using oral cyanocobalamin to treat pernicious anemia rose from 0% in 1989 to 19% in 1996 ($p < 0.001$). The percentage of respondents aware of the efficacy of oral cyanocobalamin also increased significantly from 4% in 1989 to 29% in 1996 ($p < 0.001$). Overall, the investigators observed that 71% of medical internists in 1996 still believe that sufficient quantities of cobalamin cannot be absorbed when administered orally.

Factors to Consider

Although oral cobalamin maintenance therapy is appropriate for many patients, factors such as cost, compliance, and physiologic differences must be considered. The only contraindications to oral therapy are having the inability to take medications by mouth and diarrhea or vomiting. While some patients have difficulty taking tablets or are opposed to taking an increased number of oral medications, injections can be very painful in patients with less muscle mass, such as older adults. Furthermore, on rare occasions, infections can result at the site of injection.

Cost

The average wholesale price (AWP) for one hundred 1000-µg oral tablets is approximately $4.00.[26] Although the AWP for a 1000-µg intramuscular cyanocobalamin injection is approximately $0.11, the physician visit for an injection will cost between $20 and $30, and home-nurs-

ing service will cost between $60 and $100 per injection. Many older and frail patients cannot afford home-nursing care to administer their injection and may have transportation limitations, making repeat physician visits difficult. Oral replacement enables office visits twice a year for follow-up of anemia.

Summary

Oral cyanocobalamin replacement may not be adequate for a patient presenting with severe neurologic manifestations that could have devastating consequences if the most rapid-acting therapy is not used immediately. Studies to date have not adequately addressed oral treatment in these patients; therefore, parenteral cobalamin is preferable in neurologically symptomatic patients until resolution of symptoms and hematologic indices. After reviewing the studies, substantial evidence supports the use of oral cobalamin 1000–2000 µg/d as maintenance therapy for all patients with cobalamin-deficient anemia. Safety does not appear to be an issue, as no adverse effects were reported from either the use of oral or intramuscular cyanocobalamin.[14,16,23,24]

Increasing the awareness of oral cobalamin replacement therapy could potentially result in a substantial savings to the rising healthcare costs today. The literature has demonstrated that oral cobalamin replacement is a safe, effective, and less expensive maintenance alternative in patients diagnosed with cobalamin-deficient anemia of any type.

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EXTRACTO

OBJETIVO: Evaluar el uso oral de cianocobalamina como terapia para anemia por deficiencia de cobalamina (vitamina B_{12}).

FUENTES DE INFORMACIÓN: Artículos originales y de revisiones de la literatura primaria se identificaron usando el sistema de búsqueda de información MEDLINE hasta mayo de 2000 y mediante fuentes secundarias.

SÍNTESIS: Anemia por deficiencia de cobalamina es 1 de los diagnósticos más comunes en la población de mayor de edad. La anemia por deficiencia de cobalamina puede ser diagnosticada como si fuera anemia perniciosa causada por problemas en la absorción de proteínas de los alimentos o por deficiencia de factor intrínseco, el cual es necesario para la absorción de cobalamina. Varios estudios proveen evidencia que la cianocobalamina oral diaria, en contraste con la administración parenteral mensual, puede tratar adecuadamente ambos tipos de anemia con deficiencia de cobalamina.

CONCLUSIONES: Pueden usarse dosis orales de 1000–2000 µg para tratar adecuadamente a pacientes con deficiencia de cobalamina si toleran la suplementación oral. Por el contrario, en casos de pacientes que sufren problemas neurológicos severos, los datos actuales no son suficientes para apoyar el uso de cianocobalamina oral como una terapia efectiva.

Jorge R Miranda Massari

RÉSUMÉ

OBJECTIF: Évaluer l'emploi de la cyanocobalamine administrée par voie orale dans le traitement de l'anémie causée par une déficience en cobalamine (vitamine B_{12}).

REVUE DE LITTÉRATURE: La littérature primaire et les articles de revue pertinents ont été identifiés grâce à une recherche dans la banque de données MEDLINE (jusqu'à mai 2000), de même qu'a travers des sources d'information secondaires.

RÉSUMÉ: L'anémie provoquée par une déficience en cobalamine (vitamine B_{12}) fait partie des diagnostics les plus fréquemment posés chez la population âgée. L'anémie causée par une déficience en cobalamine peut provenir de l'absence du facteur intrinsèque nécessaire à l'absorption de la cobalamine (anémie pernicieuse) ou de la malabsorption des protéines, i.e., par une incapacité à déplacer la cobalamine liée aux protéines d'origine alimentaire. Quelques études ont démontré qu'un apport quotidien en cyanocobalamine administrée par voie orale, plutôt qu'une administration mensuelle par voie parentérale, pourrait traiter adéquatement ces 2 types d'anémie causée par une déficience en cobalamine.

CONCLUSIONS: Un supplément oral en cyanocobalamine à des doses de 1000–2000 µg/jour peut être employé pour traiter la plupart des patients atteints de ce type d'anémie causée par une carence en cobalamine, en autant que ceux-ci tolèrent l'administration par voie orale. En ce qui a trait aux patients présentant une atteinte neurologique grave, les données présentement disponibles sont insuffisantes pour supporter l'emploi de cyanocobalamine administrée par voie orale.

Pierre Martineau