CASE REPORT

Successful Sublingual Cobalamin Treatment in a Child with Short-Bowel Syndrome

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Vitamin B12 (B12) is essential for deoxyribonucleic acid synthesis, to maintain normal hematologic and neurologic functions. Studies suggest that cobalamin deficiency in children is more common than previously recognized. Main causes are decreased intake, abnormal absorption, and inborn errors of metabolism. The classic treatment for cobalamin deficiency is intramuscular administration of B12. There are no data concerning the use of alternative routes of cobalamin administration in children. This report shares the experience of sublingual administration of B12 to a patient with short-bowel syndrome and B12 malabsorption. We report the case of successful treatment of cobalamin deficiency by sublingual administration in a 9-year-old patient who had undergone intestinal resection and jejunum-colon, with anastomosis of 32 cm of residual small intestine and absence of distal jejunum and ileocecal junction. We determined a B12 deficiency because low serum cobalamin levels (<200 pg/mL) were shown in 2 consecutive tests (130 pg/mL and 170 pg/mL). The patient presented with neither clinical nor hematological manifestations. He received sublingual cobalamin preparation, 1000-mcg sublingual nuggets per day for 1 month. Normalization of serum cobalamin was obtained (790 pg/mL) after 1 month of treatment. The sublingual route of administration not only improved the quality of life of this patient by avoiding monthly painful injections but also reduced the cost of treatment and the number of hospital visits.

INDEX TERMS: cobalamin, pediatric, short-bowel syndrome, sublingual administration, vitamin B12 deficiency

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INTRODUCTION

Vitamin B12 deficiency is common, with an estimated prevalence among the general population ranging from 1.5% to 15%.^{1–3} Main causes in adults are pernicious anemia and malabsorption of cobalamin from food. Although it was previously thought to be rare in children, studies suggest that B12 deficiency is more common than previously recognized.⁴

Causes of B12 deficiency in children fall into three categories: 1) decreased intake; 2) abnormal absorption; and 3) inborn errors of B12 transport and metabolism. Clinical manifestations include mainly hematologic abnormalities (megaloblastic anemia) and neurological changes; however, B12 deficiency in children often presents with non-specific manifestations such as developmental delay, irritability, weakness, and failure to thrive.⁵

Cobalamin deficiency is treated generally with intramuscular (IM) injection of B12 in the form of cyanocobalamin and, more rarely, hydroxycobalamin. Although an evidence-based analysis by the B12 Cochrane Group also supports the efficacy of oral cobalamin therapy in adults,⁶ no data are available to support use of oral vitamin replacement in children. Furthermore, it is difficult to ensure successful treatment with oral B12 for patients with conditions that cause malabsorption. Alternative routes of cobalamin administration have not been described in children. This report shares our experience with sublingual administration of B12 to a patient presenting with short-bowel syndrome and B12 malabsorption.

CASE REPORT

A 9-year-old Caucasian male was born with

small intestine atresia. On day 2 of life, the patient underwent surgery for an intestinal resection and jejunum-colon anastomosis of 32 cm of residual small intestine and the absence of distal jejunum and ileocecal junction. He received parenteral nutrition at home through a tunneled, centrally placed catheter and enteral nutrition through nasogastric tube. He stayed on parenteral nutrition from the age of 2 days until he was 7 months old. Continuous

enteral feeding was administered from the age of 1 month until he was 5 months old, using an amino acid formulation. Oral alimentation was started at 3 months. At 5 months, textured foods were introduced. Evolution was excellent, with good tolerance of oral alimentation and normal growth and development (weight: 1 SD; height: 0 SD for age). Although a patient with short-bowel syndrome can live a normal life, independent of parenteral nutrition or enteral formula feeding, our patient presented with zinc, B12, and vitamin D deficiency due to a loss of terminal ileal function. He received IM injections of vitamin D every 3 months from the age of 2 years until he was 5 years old. He was then switched to oral administration as preventive therapy. He also received oral zinc supplementation. He developed B12 deficiency for the first time at 3 years old. He underwent B12 IM injections for several years. Normalization of B12 was not easy to obtain as the IM administration of B12 caused pain that led to patient non-compliance. During the last months, the pain associated with the IM injections made this route clinically unacceptable.

We decided to choose an alternative method of administration of B12. Although studies have shown the efficacy of oral B12 supplementation in adults with malabsorption of cobalamin from food, pernicious anemia, or insufficient nutritional B12 intake, no data are available in patients suffering from short-bowel syndrome, especially in those in whom the ileocecal junction is absent. In addition, there is no study of the oral intake of B12 in the pediatric population. Based on a few reports, we decided to administer sublingual supplementation of B12 to this 9-year-old boy.

Figure. Cobalamin levels since 2005. Cobalamin deficiency (<200 pg/ml) since the age of 3 years and low levels of cobalamin persisting after supplementation by intramuscular injections. Suboptimal treatment due to non-compliance of the patient. Sublingual supplementation started on October 2012. Correction of cobalamin levels 1 month later. Normal cobalamin levels (496 pg/mL) at 6-month follow-up.

We defined B12 deficiency as a serum cobalamin concentration below 200 pg/mL on 2 consecutive tests.⁷ Such was the case with our patient who had concentrations of 130 pg/mL and 170 pg/mL. Despite these low concentrations, the patient did not have clinical or hematological manifestations of B12 deficiency.

He received sublingual cobalamin (sublingual nuggets of 1000 mcg cobalamin; Solgar Laboratories, Leonia, NJ) at a dose of 1000 mcg per day for 1 month. We insisted on the correct sublingual administration (not swallowing the nugget) before a meal, in the absence of dry mouth. After 1 month of treatment, the patient's serum cobalamin concentration had normalized (i.e., reached 790 pg/mL). Subsequent serum cobalamin concentrations were maintained in the target range by using 1000 mcg per day for 10 days each month. The patient's compliance remains excellent (Figure).

DISCUSSION

Normally, B12 is derived from cobalamin in food (mainly animal sources). Cobalamin is released by the acidity of the stomach, where it combines with R proteins and intrinsic factor (IF). The complex transverse the duodenum, where pancreatic proteases break down the R proteins. This enables absorption via specific IF-cobalamin receptors in the distal ileum. Of particular interest is the observation that approximately 1% to 5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion. This absorption explains the mechanism underlying the oral cobalamin treatment of

Table 1. Definitions of Cobalamin (B12) Deficiency¹⁰⁻¹¹

1	Serum cobalamin concentration <200 pg/mL (<150 pmol/L) and clinical features and/or hematological anomalies related to cobalamin deficiency
2	Serum cobalamin concentration <200 pg/mL (<150 pmol/L) on 2 separate occasions
3	Serum cobalamin concentration <200 pg/mL (<150 pmol/L) and total serum homocysteine concentration >13 µmol/L or methylmalonic acid level >0.4 µmol/L (in the absence of renal failure and folate and vitamin B6 deficiencies)
4	Low serum holotranscobalamin concentration <35 pmol/L

cobalamin deficiencies.⁸⁻⁹ IF-cobalamin complex dissociates in the enterocyte, and the free vitamin enters the portal circulation while being bound to transcobalamin II, which transports B12 into tissues. B12 is a cofactor for 2 important metabolic reactions: methylation of homocysteine to methionine and conversion of methylmalonyl coenzyme A to succinyl coenzyme A. When B12 is deficient these precursors accumulate.

Plasma also contains 2 other B12 binding proteins: transcobalamin I and III. These two subsequent forms of transcobalamin have no specific transport role but are known to reflect B12 tissue stores. In fact, almost all B12 in plasma is bound to transcobalamin I and III; consequently, the measure of serum B12 concentration reflects the storage of this vitamin. In contrast to folate stores, older children and adults have sufficient B12 stores to last for 3 to 5 years. However in young infants born to mothers with low B12 stores, clinical signs of cobalamin deficiency can become apparent in the first 6 to 18 months of life. Cobalamin deficiency is defined in terms of the value of serum cobalamin (<200 pg/mL or <150 pmol/L) and of homocysteine (>13 µmol/L) and methylmalonic acid (>0.4 µmol/L) (Tables 1 and 2).

The usual treatment for B12 deficiency is parenteral administration of cyanocobalamin or hydroxycobalamin. Intravenous injection is not considered because of rapid elimination of cobalamin when injected intravenously. In children, the schema proposed^{5,14} is low initial cobalamin doses of 0.2 mcg/kg for 2 days (to avoid the risk of hypokalemia observed in cases of severe anemia), followed by 1000 mcg/day given subcutaneously or by IM injection for 7 days and subsequent weekly doses of 100 mcg for 1 month. Long-term treatment is often necessary, and monthly maintenance doses of 100 mcg have been recommended. Intramuscular injections can be painful, are difficult in patients who have a tendency to bleed or who are very thin, and are costly when administered by health care

professionals. Alternative routes of cobalamin administration have included oral, nasal, and sublingual.¹⁵ Although evidence-based analysis supports the efficacy of oral cobalamin therapy in adults,^{6,7} there is a lack of evidence in the pediatric population. In addition, it is not clear whether patients with concurrent malabsorptive conditions may be successfully treated with oral B12 because trials included no or few patients with conditions that interfere with absorption in the terminal ileum, such as Crohn's disease, celiac disease, ulcerative colitis, or ileal resection.⁶ The adult therapeutic scheme for use of oral cyanocobalamin would be 1000 mcg/day for 1 month, followed by 125 to 500 mcg/day in case of intake deficiency and food cobalamin malabsorption, and 1000 mcg/day in case of pernicious anemia.¹⁶

Sublingual administration is another treatment modality for cobalamin deficiency applicable in patients who refuse parenteral treatment, who present with either diarrhea or vomiting, or who are unable to take oral medication.^{17,18} In a study by Delpre et al.,¹⁷ normalization of serum cobalamin concentration was obtained in 18 adults with B12 deficiency who received 2000 mcg of sublingual cobalamin for 7 to 12 days.¹⁷ A second prospective study of 30 adults compared the sublingual and oral routes and concluded that sublingual and oral administration of 500 mcg per day for 1 month was equally effective in correcting cobalamin concentrations.¹⁸

We report the case of a 9-year-old child with short-bowel syndrome and cobalamin deficiency who was successfully treated with sublingual B12. The sublingual route of administration not only improved this patient's quality of life by avoiding monthly painful injections but also reduced the cost of treatment and number of hospital visits. An extremely important aspect in the successful use of this modality is the patient's willingness to adhere to and their understanding of sublingual administration, which limits this route to children of a certain age. Additionally, there are a lack of

Table 2. Causes of B12 Deficiency in Children^{5,12,13}

Decreased intake

Breast-fed infants of mothers who have undiagnosed B12 deficiency

Children and adolescents on atypical diets

Abnormal absorption

Absent or abnormal intrinsic factor

Decreased B12 release from food protein

Failure of R protein degradation

Competition for B12 absorption at the ileum

Loss of the ileal absorptive surface

Abnormal ileal receptor

Inborn errors of vitamin B12 transport and metabolism.

data to support sublingual administration, particularly in the pediatric population. Follow-up is needed to evaluate the long-term efficacy of this administration method in the treatment of B12 deficiency in pediatric patients.

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Abbreviations B12, vitamin B12; IF, intrinsic factor

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