

Oral Cobalamin Supplementation in Dogs with Chronic Enteropathy

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Abstract

Cobalamin deficiency is a common sequel to chronic enteropathy and exocrine pancreatic insufficiency in dogs. The current treatment protocol recommends repeated parenteral injections. In humans with cobalamin deficiency, several studies have shown equal efficacy of oral supplementation. Recent studies suggest that oral cobalamin supplementation is effective in increasing serum cobalamin concentrations in dogs with chronic enteropathies and hypocobalaminemia. A very recent study in cats with cobalamin deficiency suggests that the oral route of supplementation is effective in cats too, though comparative studies are warranted.

Introduction

Cobalamin (vitamin B12) deficiency is a common sequel to chronic enteropathies (CE) in dogs, with a reported prevalence of 6 to 73%.¹⁻⁵ Cobalamin deficiency also can occur in exocrine pancreatic insufficiency (EPI), small intestinal (SI) lymphoma, short-bowel syndrome, and congenital selective familial cobalamin deficiency.⁶⁻¹⁰

All cells in the mammalian body require cobalamin. Thus, once the deficiency occurs, numerous clinical and metabolic consequences ensue.¹¹ Reported clinical signs are anorexia, lethargy, weight loss, failure to thrive, and central and/or peripheral neuropathies.^{9,10,12,13} Further, immunodeficiency and intestinal changes such as villous atrophy and malabsorption of other vitamins and nutrients have been reported. It also has been suggested that dogs and cats with cobalamin insufficiency have a poorer response to medical treatment for CE if the insufficiency is not corrected.¹⁴ Lastly, cobalamin deficiency has been associated with a negative prognosis and increased risk of euthanasia in chronic enteropathy and EPI in dogs.^{1,15}

Current supplementation protocols for dogs call for repeated parenteral (PE) injections.^{1,14} The situation is different in humans, where several studies have reported equal efficacy of oral and parenteral cobalamin supplementation,¹⁶⁻¹⁹ though the prescription of oral cobalamin varies immensely between countries. Recently, several reports on successful

Glossary of Abbreviations

CE: Chronic Enteropathy

EPI: Exocrine Pancreatic Insufficiency

IF: Intrinsic Factor

MMA: Methylmalonic Acid

PE: Parenteral

PO: Oral

SI: Small Intestinal

oral cobalamin supplementation in dogs and cats with hypocobalaminemia have been presented.²⁰⁻²⁴

Cobalamin Transport, Absorption, and Mechanisms Behind Cobalamin Deficiency in Dogs

The gastrointestinal transport and absorption of cobalamin is a complex process in

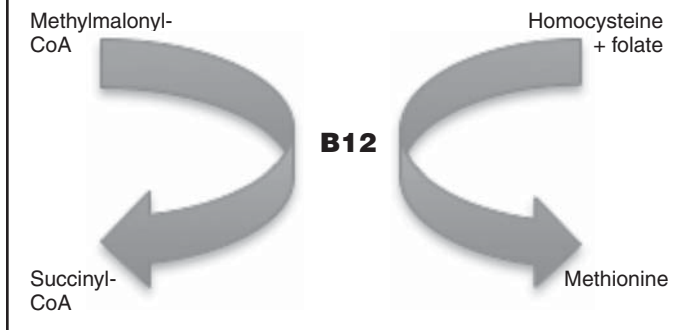
mammals, involving several carrier proteins and an intrinsic factor (IF).²⁵ The final absorption from the gastrointestinal tract occurs in the ileum, where cobalamin bound to IF is absorbed via specific cobalamin-intrinsic factor receptors. IF is mainly produced by the exocrine pancreas in dogs.²⁶ In humans, an alternative absorptive route of cobalamin, independent of IF, has been reported.²⁷ Using radioactively labeled cobalamin, it was demonstrated that approximately 1% of free cobalamin was absorbed along the entire intestine by passive diffusion. Whether this route of absorption exists in dogs has not been demonstrated.

The most important mechanism behind cobalamin deficiency in dogs with CE or SI lymphoma is damage to the ileal mucosal cobalamin-IF receptor.¹⁴ Another suggested mechanism is dysbiosis, which is a common sequel to CE.²⁸ Certain anaerobic bacteria (mainly some *Clostridia* and *Bacteroides*) can adsorb and utilize cobalamin.²⁹ Thus, bacterial competition for nutrients could theoretically lead to less amount of cobalamin available for absorption in the ileum. However, no direct evidence has been published in dogs. The third mechanism behind canine hypocobalaminemia is defect expression of the cobalamin-IF receptors. This occurs in familial congenital cobalamin malabsorption, which has been reported in the Border Collie, Giant Schnauzer, Beagle, and Chinese Shar-Pei.^{8-10,30,31}

Diagnosing Cobalamin Deficiency in Humans: The Role of Intracellular Markers

To diagnose cobalamin deficiency in humans, biomarkers such as homocysteine and methylmalonic acid (MMA) are often analyzed in parallel with serum cobalamin concentration.^{32,33} Serum cobalamin concentration does not directly

Figure 1. A simplified model of the two enzymatic processes requiring cobalamin as a co-factor in mammals. Cobalamin deficiency can result in accumulation of homocysteine and methylmalonic acid.



correlate with intracellular cobalamin levels, as cobalamin is utilized in the cytoplasm and mitochondria.²⁵ Thus, serum cobalamin concentration does not correctly measure the intracellular cobalamin status.

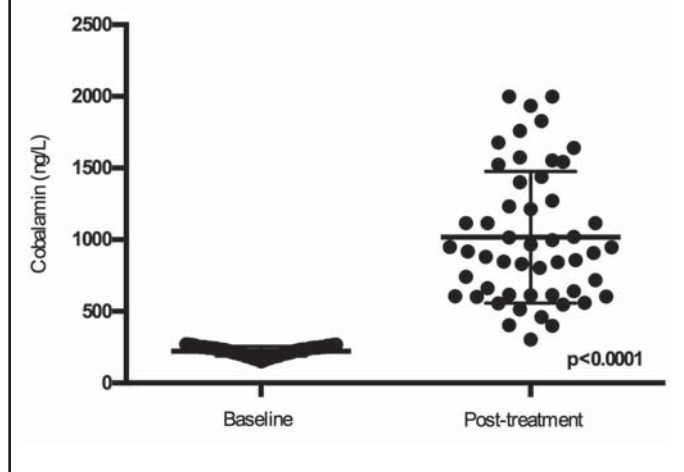
Cobalamin is required for two important enzymatic processes in the mammalian body (Figure 1). When cobalamin is lacking, these processes will not continue in a normal way. As a result, accumulation of substrates or products of alternative metabolic pathways will occur. Two such products are homocysteine and MMA. Elevated homocysteine concentrations have been linked to vascular and thrombotic disease in humans.³⁴ The association between hypocobalaminemia and elevation of homocysteine and/or MMA is strong in humans, though neither is specific for cobalamin deficiency. Other factors, such as a lack of folate, alcohol abuse, renal failure, inborn errors of enzyme function, etc., also can result in increased serum concentrations of homocysteine and/or MMA and must be taken into account. Several authors have proposed that none of the parameters can be used alone to diagnose cobalamin deficiency in humans.²¹⁻²³

In human patients with a normal or a low-normal (within the lowest end of the reference range) serum cobalamin concentration and increased concentrations of homocysteine or MMA, the term “subtle cobalamin deficiency” is used. An unknown number of those patients progress to clinical disease. For that reason, cobalamin supplementation is recommended in subtle cobalamin deficiency in humans.³⁵

Intracellular Markers of Cobalamin Deficiency in Dogs

In dogs, increased serum homocysteine concentration has been reported in Shar-Peis and Border Collies with familial cobalamin deficiency.^{10,36,37} However, in six other breeds with undetectable serum cobalamin concentration, median homocysteine concentration was normal.³⁶ Further, in a recent study³⁸ hyperhomocysteinemia was more common in healthy Greyhounds than in Greyhounds with diarrhea and/or cobalamin deficiency. With the information available at present, homocysteine does not appear to be a useful marker of intracellular cobalamin deficiency in CE in dogs.

Figure 2. Serum cobalamin concentrations in 51 dogs with hypocobalaminemia treated with oral cobalamin supplementation at baseline and post-treatment. Long horizontal line represents mean; short horizontal line standard deviation. Reproduced from Toresson, et al. *J Vet Intern Med.* 2016.



Elevated serum MMA concentrations have been reported in 25 to 88% of dogs with subnormal serum cobalamin concentrations.³⁶ Significantly higher serum MMA concentrations were demonstrated in dogs with serum cobalamin concentrations below 251 ng/L (185 pmol/l) compared to dogs with higher serum cobalamin concentrations in another study.³⁹ In that study, some dogs with normal serum cobalamin concentrations had elevated serum MMA concentrations, which may indicate a functional cobalamin deficiency (in parallel with subtle cobalamin deficiency in humans). Increased urinary MMA has also been shown in case series and case reports of dogs with familial cobalamin deficiency.^{9,10,12,13,40,41} Whether serum MMA concentrations should be analyzed routinely in parallel with serum cobalamin concentrations needs further investigation.

Cobalamin Supplementation in Humans

A study from the late '60s in humans with cobalamin deficiency showed that approximately 1% of free cobalamin was absorbed along the entire intestine by passive diffusion, independent of IF.²⁷ This result was achieved using radioactively labeled cobalamin. Since then, four studies comparing parenteral versus oral cobalamin supplementation in humans have been published¹⁶⁻¹⁹ Patients in these studies were suffering from pernicious anemia, various gastrointestinal disorders, or were on a restricted diet (vegetarian, vegan). In the four studies, both treatment options effectively normalized serum cobalamin concentration in all patients. Further, in the studies where MMA and/or homocysteine were analyzed, markers of cobalamin MMA normalized with both PE and PO supplementation,^{16,19} and serum homocysteine concentrations normalized in all patients in the two studies,^{16,18} and to the same extent in both groups in one study.¹⁹ A Cochrane review from 2005 stated that “high doses of oral vitamin B12 daily are as effective as the intramuscular

Figure 3. Serum cobalamin concentrations over time after oral (PO; n=27) versus parenteral (PE, n=25) cobalamin supplementation. Log10 scale, red lines represent reference interval. Long horizontal black lines represent median, shorter black lines depict range. Data shown at the 2016 ACVIM Forum by Toresson, et al.²²

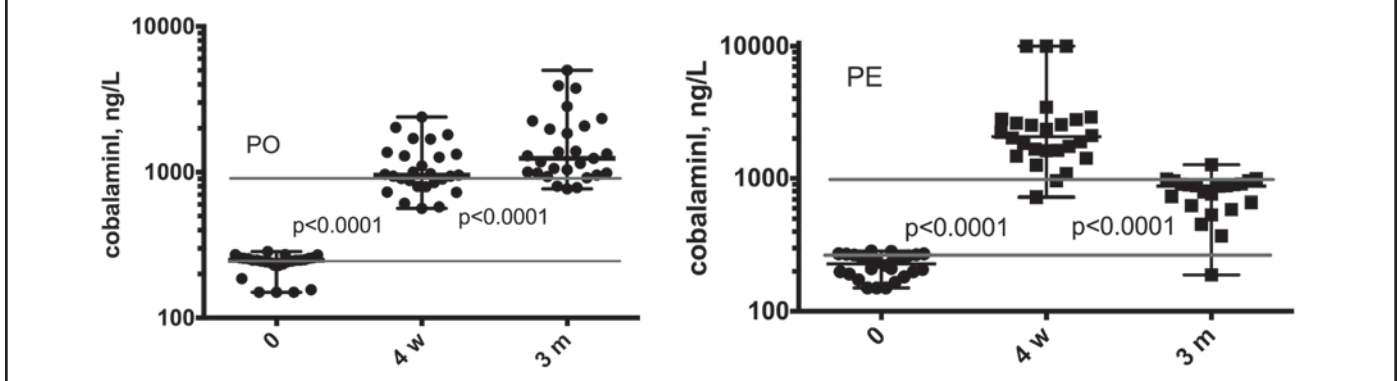
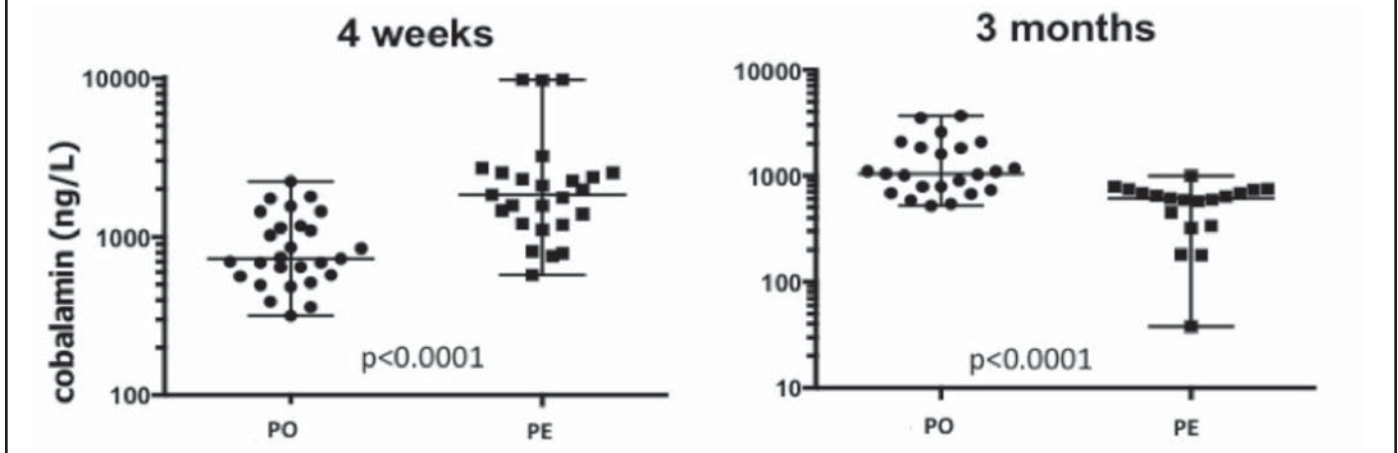


Figure 4. Difference (Δ) in serum cbl concentrations compared to baseline over time after oral (PO, n=27) versus parenteral (PE, n=25) cobalamin supplementation. Log10 scale, short black lines represent range and long black lines show median. Data shown at the 2016 ACVIM Forum by Toresson, et al.²²



administration,”⁴² though only two comparative studies were available at the time. Several other noncomparative studies have been published, in which oral cobalamin supplementation was effective in restoring serum cobalamin concentrations in patients suffering from various conditions or successfully switched from parenteral to oral supplementation.^{27,43-47} Studies from Canada and Great Britain have shown that switching from PE to PO (oral) supplementation would have been associated with substantial savings to the National Health Care system.^{48,49} Despite compelling evidence, Sweden is the only country where prescription of oral cobalamin is more common than prescription of parenteral cobalamin.⁵⁰

Cobalamin Supplementation in Dogs

Current supplementation protocols call for repeated PE injections in dogs. This recommendation is based on pathophysiologic justification, clinical empiric experience, and specialist opinion.^{1,10,14} In some countries such as Sweden and Finland, dog owners are not allowed to give injections at home (apart from insulin and allergen-specific immunotherapy).²⁰ Parenteral cobalamin injections, thus, have to be

given by a veterinary health care provider, increasing inconvenience, time, and costs. Even in countries where pet owners are allowed to give injections, not all owners are comfortable handling hypodermic needles and syringes or injecting their dog.

In a recent retrospective study in 51 dogs with hypcobalaminemia and clinical signs of CE, oral cobalamin supplementation significantly increased serum cobalamin concentration compared to baseline (Figure 2).²⁰ The mean increase in serum cobalamin concentration after treatment was 794 ± 462 ng/L after 20 to 202 days (median 72) of supplementation. There was no statistical difference in the increase in serum cobalamin concentrations at follow-up if the dogs had changed diet and/or other medication in addition to cobalamin supplementation or just had been treated with cobalamin supplementation +/- folate. Further, there was no statistical difference regarding an increase in serum cobalamin concentrations in dogs with a high clinical disease activity index (canine inflammatory bowel disease index; CIBDAI)⁵¹ at inclusion compared to dogs with a lower disease activity index. In that study, the injectable form of cobalamin was more than double the price of the oral

Figure 5. Serum MMA-concentration over time in dogs treated with oral (PO; n=19) or parenteral (PE, n=17) cobalamin supplementation. Short black lines represent range, longer lines depict median, and the grey lines represent reference interval. MMA decreased significantly in both groups from 0 to 4 weeks, with no further reduction between 4 weeks and 3 months in either group. Data shown at the 2016 Congress by Toresson, et al.²⁴

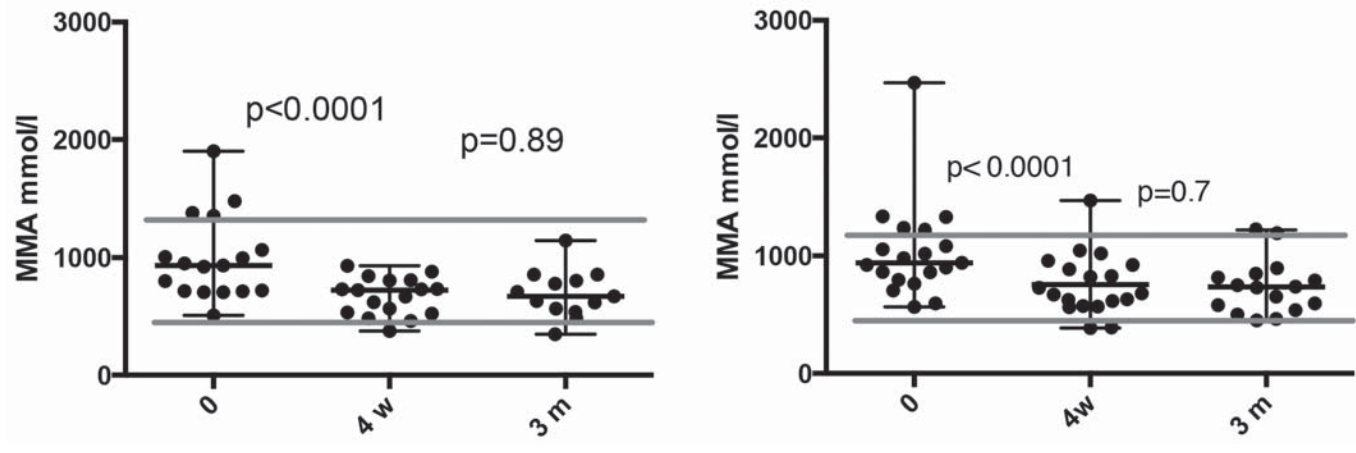
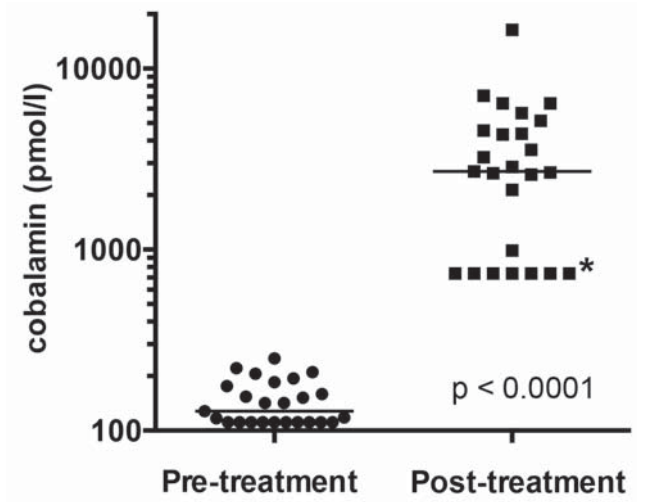


Figure 6. Pre- and post-treatment serum cobalamin concentrations in 25 cats with hypocobalaminemia supplemented with oral cobalamin. Log10 scale long horizontal line represents median. *Results were reported as >738 pmol/l for seven cats, which has been truncated to 738. Remaining samples were diluted to exact numbers. Reproduced from *J Feline Med Surg*, Toresson, et al.²³



supplement for a three-month treatment period, without the costs for veterinary consultation and injections.

Comparison of Oral and Parenteral Supplementation in Dogs

The first results from an ongoing prospective randomized study comparing oral and parenteral cobalamin supplementation in 52 dogs with hypocobalaminemia and signs of CE have recently been presented in abstract form.^{22,24} The PO group received daily oral cobalamin supplementation throughout the study (cyanocobalamin 1 mg/tablet; dogs <20 kg ¼ tablet/10 kg dog, dogs ≥ 20 kg 1 tablet/day). The PE group received one cobalamin injection/week during six weeks and a final injection four weeks later according

to a recent protocol.¹⁴ Concurrent medical treatment and diet was given based on clinical judgment. Serum concentrations of cobalamin and MMA were analyzed at baseline, 28±5 days and 90±15 days after the start of supplementation.

Serum cobalamin concentrations increased significantly in all dogs after supplementation (Figure 3). The increase in serum cobalamin concentration compared to baseline was significantly higher in the PE group after 28 days, but significantly higher in the PO group after 90 days (Figure 4).

Serum MMA concentrations decreased significantly in both groups after 28 days of treatment but did not decrease further at 90 days (Figure 5).²⁴ There was no difference in the reduction in MMA between the groups. This suggests that on a cellular level both treatments were equally effective in normalizing intracellular cobalamin status.

Oral Cobalamin Supplementation in Cats

Successful oral cobalamin supplementation in 14 geriatric research cats with fat malabsorption was reported in abstract form in 2014.²¹ In a very recent retrospective study, 25 client-owned cats with hypocobalaminemia and signs of CE were successfully treated with oral cobalamin supplementation (Figure 6).²³ Median (range) serum cobalamin concentration was 128 pmol/l (111–250 pmol/l) prior to treatment and 2701 pmol/l (738–16,359 pmol/l) after supplementation (reference interval: 214–738 pmol/l). One of the cats was diagnosed with small intestinal lymphoma and two cats were suffering from EPI. Several cats had other comorbidities, but supplementation appeared effective regardless of the initiating cause of cobalamin deficiency. Results from MMA analysis were only available from two cats due to the retrospective nature of the study. In those two cats, serum MMA concentrations prior to supplementation were 23,945 nmol/l and 852 nmol/l (reference interval 139–898 nmol/l), respectively, which decreased after supplementation to 865 nmol/l and 233 nmol/l, respectively. These results suggest that oral cobalamin

supplementation is effective in hypcobalaminemic cats, though prospective comparative studies are recommended before routine oral supplementation can be recommended.

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