Journal of Veterinary Internal Medicine
Open Access

J Vet Intern Med 2016;30:101–107

Oral Cobalamin Supplementation in Dogs with Chronic Enteropathies and Hypocobalaminemia

L. Toresson, J.M. Steiner, J.S. Suchodolski, and T. Spillmann

Background: Cobalamin deficiency is commonly associated with chronic enteropathies (CE) in dogs and current treatment protocols recommend parenteral supplementation. In humans, several studies have reported equal efficacy of oral and parenteral cobalamin administration of cobalamin.

Objectives: To retrospectively evaluate whether oral cobalamin supplementation can restore normocobalaminemia in dogs with CE and hypocobalaminemia.

Animals: Fifty-one client-owned dogs with various signs of CE and hypocobalaminemia.

Material and Methods: Retrospective study based on a computerized database search for dogs treated at Evidensia Specialist Animal Hospital, Helsingborg, Sweden during January 2012–March 2014. Inclusion criteria were dogs with signs of CE, an initial serum cobalamin ≤270 ng/L (reference interval: 234–811 ng/L) and oral treatment with cobalamin tablets. Serum cobalamin for follow-up was analyzed 20–202 days after continuous oral cobalamin supplementation started.

Results: All dogs became normocobalaminemic with oral cobalamin supplementation. The mean increase in serum cobalamin concentration after treatment was 794 ± 462 ng/L. Serum cobalamin concentrations were significantly higher after supplementation (mean 1017 ± 460 ng/L; $P < .0001$) than at baseline (mean 223 ± 33 ng/L).

Conclusion and Clinical Importance: Our results suggest that oral cobalamin supplementation is effective in normalizing serum cobalamin concentrations in dogs with CE. Prospective studies comparing cellular cobalamin status in dogs being treated with parenteral versus oral cobalamin supplementation are warranted before oral supplementation can be recommended for routine supplementation.

Key words: Inflammatory Bowel Disease; Oral supplementation; Vitamin B12.

Common causes for cobalamin deficiency in dogs are chronic enteropathies (CE), exocrine pancreatic insufficiency (EPI) and familial cobalamin deficiency (reported in Chinese Shar Peis, Giant Schnauzers, Border Collies and Beagles).[1–6] Anecdotal reports of short-bowel syndrome and cobalamin deficiency in dogs also exist, an association that is well documented in humans.[7,8] Cobalamin deficiency in dogs is commonly associated with canine CE with a reported prevalence of 6–73%.[9–13] Hypocobalaminemia has also been reported to be a negative prognostic factor in dogs with CE or EPI, associated with an increased risk of euthanasia.[9,14]

Abbreviations:

BCS	body condition score
c-PLi	canine pancreatic lipase immunoreactivity
CE	chronic enteropathy
CIBDAI	canine inflammatory bowel disease index
EPI	exocrine pancreatic insufficiency
IF	intrinsic factor
TLI	trypsin-like immunoreactivity

Suggested mechanisms of cobalamin deficiency in canine CE are damage to the ileal mucosal receptors for binding of cobalamin–intrinsic factor (IF) complexes or bacterial competition for nutrients in small intestinal dysbiosis resulting in decreased amounts of cobalamin available for absorption.[15] Cobalamin deficiency induces various clinical and metabolic consequences, including anorexia, weight loss, failure to thrive, central and peripheral neuropathies, immunodeficiency, and intestinal changes including villous atrophy and malabsorption of other vitamins and nutrients.[2,4,16,17]

Gastrointestinal processing and absorption of cobalamin in mammals are mediated by carrier proteins and IF, which in dogs is mainly produced by the pancreas.[3] The cobalamin-IF complex is absorbed by receptors in the ileum.[18] However, studies in humans using radioactively labeled cobalamin have shown that approximately 1% of free cobalamin was absorbed along the entire intestine by passive diffusion, independently of IF.[19] Several studies in humans with hypocobalaminemia suggest that the administration of oral cobalamin might be as effective as parenteral administration in restoring serum cobalamin concentrations in patients suffering from pernicious anemia, various gastrointestinal disorders, or for those on a restricted diet (vegetarians and

From the Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, Helsinki University, Helsinki, Finland (Toresson, Spillmann); Evidensia Specialist Animal Hospital, Helsingborg, Sweden (Toresson); and Gastrointestinal Laboratory, Texas A&M University, College Station, TX (Steiner, Suchodolski).

This study was conducted at Evidensia Specialist Animal Hospital, Helsingborg, Sweden.

A part of the study was presented in abstract form at the 2014 American College of Veterinary Medicine Forum, Nashville, Tennessee.

Corresponding author: L. Toresson, Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, Helsinki University, Helsinki, Finland; e-mail: linda.toresson@evidensia.se

Submitted February 7, 2015; Revised September 12, 2015; Accepted October 22, 2015.

Copyright © 2015 The Authors. Journal of Veterinary Internal Medicine published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1111/jvim.13797

vegans).[20–23] A Cochrane review from 2009 reached the same conclusion.[24]

Oral cobalamin is prescribed to human patients to avoid the discomfort, inconvenience, and cost of monthly injections of vitamin B12. In European countries, oral cobalamin supplementation is widely utilized.[19,25,26] Factors influencing the increase in serum cobalamin concentration after oral administration in humans are dose and time.[19–21,26–29] A daily oral intake of 1,000–2,000 μg cyanocobalamin successfully normalized serum cobalamin in all studies available in human patients.[19–21,23,27] Continuous increases of serum cobalamin concentrations during oral cobalamin treatment have been demonstrated in several studies.[20,21,23,27,28] Current supplementation protocols for cobalamin in dogs call for repeated parenteral injections based on pathophysiologic justification, clinical empiric experience, and specialist opinion.[5,9,15] Currently, studies assessing the effect of oral cobalamin supplementation in dogs with CE are lacking. However, due to reports of successful oral cobalamin substitution in humans with various gastrointestinal disorders, one of the authors (L. T.) has started to use oral supplementation. The purpose of this retrospective study was to evaluate whether oral cobalamin supplementation can restore normocobalaminemia in dogs with CE.

Materials and Methods

Study Design

A retrospective study based on the review of medical records of dogs treated with oral cobalamin at Evidensia Specialist Animal Hospital, Helsingborg, Sweden, that commenced between January 2012 and March 2014.

Study Population

Client-owned dogs with signs of CE and hypocobalaminemia treated with oral cobalamin supplementation at standardized doses were identified by searching the electronic patient database of the hospital. The database fields for treatment and prescription were searched for the brand name of cobalamin used for either tablets or injections.[a,b] All fields were also searched for the brand name as free text. No other brand of cobalamin had been prescribed at the hospital during the last 5 years. All dogs were given oral cobalamin tablets once daily until the day before the collection of the follow-up serum sample for cobalamin determination. If a follow-up sample had been collected on more than one occasion from the same patient, the first sample was chosen. Owners were instructed not to give cobalamin on the day of the blood test and were asked to withhold food from their dogs for at least 8 hours prior to sample collection.

Inclusion Criteria

To be included in the study, a documented physical examination had to be available as well as a dietary and medical history. As far as possible, extra-intestinal diseases were excluded in all dogs by a standardized diagnostic work-up including hematology, serum biochemistry, fecal examination and abdominal ultrasound. Dogs also had to have either signs compatible with CE or previously documented CE verified with intestinal biopsies. All dogs included had an initial serum cobalamin concentration ≤270 ng/L (reference 234–811), and a second serum sample for cobalamin analyses collected after institution of oral cobalamin supplementation. The cut-off of 270 ng/L was chosen as this number represents the lowest 5% of the reference range, and dogs with signs of CE and serum cobalamin concentrations in the lowest reference range might have subtle cobalamin deficiency, as shown in a recent study.[30] Dogs that had previously been treated with cobalamin were included if the last cobalamin treatment was administered at the latest 30 days before a serum cobalamin of ≤270 ng/L was determined. All dogs included had been treated with oral cyanocobalamin tablets[a] (1 mg). Dogs with a body weight of 1–10 kg received ¼ tablet, dogs with a body weight of >10–20 kg received ½ tablet, and dogs with a body weight >20 kg received 1 tablet daily.

Exclusion Criteria

Dogs were excluded if they received any form of cobalamin supplementation at the time of diagnosing hypocobalaminemia or if parenteral cobalamin supplementation had been administered in parallel with oral treatment. Dogs were also excluded when there was documented failure to comply with the prescribed dose of cobalamin, or if medical records were incomplete or contained too little data for retrospective calculation of the canine inflammatory bowel disease activity index (CIBDAI).[31]

Cobalamin Analysis

Serum samples were refrigerated within 2 hours of collection, sent with refrigerated transport and analyzed within 1–4 days. It has been shown previously that cobalamin is stable during these storage conditions.[32] Serum cobalamin concentrations were determined before and after oral cobalamin treatment. Increases in serum cobalamin concentrations after supplementation were further stratified based on initial serum cobalamin concentrations and CIBDAI at inclusion. Increases in serum cobalamin concentrations were also compared between dogs that had a change in diet or medical treatment during supplementation and dogs that had an unaltered diet and treatment. The cobalamin analyses were performed at IDEXX VetMedLabor, Ludwigsburg, Germany using an automated chemiluminescence immunoassay.[c] Serum samples were sent by refrigerated transport.

Baseline Data

The following data were obtained from case records: breed, sex, age, body weight and body condition score (BCS) at time of diagnosis. Further, medication history, diet, clinical signs, and physical examination at time of diagnosis and at follow-up were noted. CIBDAI was calculated retrospectively for the time when hypocobalaminemia was diagnosed based on information from the medical records. For dogs that were already receiving immunosuppressive therapies at study inclusion, CIBDAI was also retrospectively calculated for the time-point before these dogs had undergone endoscopy and before immunosuppressive treatment being commenced. Other laboratory parameters available for some of the patients included folate, serum trypsin-like immunoreactivity (TLI), canine pancreatic lipase immunoreactivity (c-PLi, as measured by Spec-cPL) or SNAP canine pancreatic lipase (SNAP-cPL), and histopathologic reports from gastrointestinal biopsies. All biopsies were analyzed by board certified pathologists at the veterinary pathology laboratory Biovet in Sollentuna, Sweden.

Statistical Analyses

The D'Agostino & Pearson omnibus normality test was used for normality testing. Serum cobalamin concentrations before and after cobalamin supplementation were analyzed with a paired *t*-test. CIBDAI in dogs receiving immunosuppressive treatment was compared to that in dogs not receiving immunosuppressive treatment using a Mann–Whitney test. CIBDAI was also compared at the time of initiation of immunosuppressive treatment to that at the time of study inclusion using a Wilcoxon matched-paired signed rank test. Increases in serum cobalamin concentrations stratified after initial serum cobalamin concentrations were analyzed with an unpaired *t*-test. Comparison of increases in serum cobalamin concentration based on CIBDAI at inclusion were analyzed with ordinary one-way ANOVA. An unpaired *t*-test was used for the statistical analysis of increases in serum cobalamin concentrations in patients with an unaltered treatment plan compared to patients that underwent changes in diet or medical treatment during supplementation. All statistical analyses were performed using a commercially available software package.[d]

Results

Baseline Characteristics

Fifty-one dogs met the inclusion criteria, of which 34 were males (67%; 26 intact and 8 neutered males) and 17 were females (33%; 15 intact and 2 spayed females). Thirty different breeds were represented, including mixed breed dogs (7/51; 14%), followed by German Shepherd (3), Labrador Retriever (3), Soft Coated Wheaten Terrier (3), Cavalier King Charles Spaniel (3), and Miniature poodle (3). Of the remaining 29 dogs, there were 2 Giant Schnauzers present, a breed for which familial cobalamin deficiency has been reported.[2] No other breeds for which familial cobalamin deficiency has been reported were noted.

All dogs were older than 1 year of age, ranging from 1.3 to 12.8 years (median 4.9). Body weights ranged from 2.6 to 52.0 kg (median 14.0) at the time of diagnosis and BCSs ranged from 2–7/9 (median 5/9).

Medication History and Diet

Twenty-two of the 51 dogs were receiving immunosuppressive treatment at the time of study inclusion when hypocobalaminaemia was documented (Table 1). Median duration of immunosuppressive treatment was 566 days (range 9–2,811 days) before study inclusion. Miscellaneous treatments in this group consisted of olsalazin (6), metoclopramide (3), folate (2), or metronidazole (1).

The remaining 29 dogs were not treated with immunosuppressive drugs when hypocobalaminemia was diagnosed. However, 4 dogs had received miscellaneous treatments for gastrointestinal disease, such as folate (2), sucralfate (1), and pancreatic enzymes (1). Of those 29 dogs, 8 were started on immunosuppressive drugs during oral cobalamin supplementation. Six of those 8 dogs had endoscopically collected biopsies confirming chronic gastrointestinal inflammation. CE was also suspected in the remaining 2 dogs that were concurrently diagnosed with chronic pancreatitis, but the owners declined further work-up. Immunosuppressive treatment was hence started without endoscopy in those dogs and led to clinical improvement.

Table 1. Selected data and treatment of 51 dogs with hypocobalaminemia.

Variable at Inclusion[a] or During Cobalamin Supplementation[b]	Range (Median) or Amount
Age (years)[a]	1.3–12.8 (4.9)
CIBDAI[a]	1–13 (5)
IS tx[a]	22/51
IS tx started before inclusion (days)	9–2,811 (566)
Previous cbl tx[a]	12/51
Previous cbl tx ended before inclusion (days)	37–1,788 (146)
Concurrent GI diseases[a]	Pancreatitis 4[c]/51, EPI 1/51
IS tx started/changed[b]	14/51
Diet change[b]	19/51
Unaltered diet/tx[b]	26/51

CIBDAI, canine inflammatory bowel disease index. IS, immunosuppressive; cbl, cobalamin; tx, treatment.

Dogs under immunosuppressive treatment at inclusion were treated with the following drugs as single treatment or in combination: Methylprednisolone (10), Prednisolone (10), Azathioprine (3), Cyclosporine (2) and/or Budosenide (1).

[a]At inclusion.

[b]During cobalamimin supplementation.

[c]1 dog had borderline PLI.

Previous parenteral cobalamin supplementation had been administered to 12/51 dogs (24%, Table 1). The supplementation ended 37–1,788 days before study inclusion. Eight dogs had received parenteral supplementation alone (1 injection/week during 4–6 weeks), while 4 dogs had received both parenteral and enteral supplementation concurrently (1–4 injections parallel with oral treatment during 100–200 days). In all dogs, recurrence/persistence of hypocobalaminaemia following withdrawal of cobalamin supplementation had been documented before study inclusion.

Forty of 51 dogs were fed commercial pet food kibbles from a major pet food company, 5 dogs were fed various commercial raw food diets, 4 dogs received kibbles mixed with a home-cooked diet, and 2 dogs were exclusively fed a home-cooked diet. When the second serum cobalamin sample was collected, 19/51 dogs were fed a new diet (Table 1). In total, 26/51 dogs had no change in medical treatment or diet compared to baseline at follow-up aside from the addition of oral cyanocobalamin (20/26) or cyanocobalamin and folate (6/26).

Historical Findings and CIBDAI

Presenting complaints at time of diagnosis included anorexia (21), diarrhea (17), lethargy (16), weight loss (14), vomiting (13), increased frequency of defecation (9), signs of abdominal pain (6), pica (3), borborygmus (3), excessive licking of the mouth, paws, or the floor (3), halitosis (2), retching (2), melena (2), bad hair coat

(1), syncope (1), seizures (1), and polyuria and polydipsia (1).

The median CIBDAI for all dogs at study inclusion was 5 (range 1–13; Table 1). The CIBDAI scores at inclusion were significantly lower ($P = .0005$) for dogs receiving immunosuppressive therapies (n = 22; CIBDAI = 3, range 1–13) compared to the remaining dogs (n = 29; CIBDAI = 6, range 2–14).

For the 22 dogs already receiving immunosuppressive treatment at study inclusion, the CIBDAI had progressively improved following initiation of immunosuppressive treatments, and was significantly lower ($P = .0059$) by the time of study inclusion (CIBDAI = 3, range 1–13) compared with that calculated retrospectively and before medical intervention (CIBDAI = 6, range 2–10).

Cobalamin

Mean serum cobalamin concentrations at inclusion was 223 ± 33 ng/L (reference interval: 234–811). At follow-up 20–202 days (median 72) after initiation of continuous oral cobalamin supplementation, the mean serum cobalamin concentration was 1,017 ± 460 (Fig 1). The difference between serum cobalamin concentrations before and after treatment was statistically significant ($P < .0001$). The mean increase in serum cobalamin concentration was 794 ± 462 ng/L. The smallest increase was 73 ng/L. The dog with the smallest response, a German Shepherd dog sampled 54 days after start of supplementation, had previously been treated with parenteral cobalamin supplementation achieving an equally poor response. This dog was unfortunately lost to further follow-up. The dogs with the second and third smallest response had follow-up blood samples collected at 64 and 76 days, respectively. Both dogs were continued on oral cobalamin supplementation. At the next follow-up, serum cobalamin concentrations had continued to increase by 122 and 128% as compared to serum cobalamin concentration during the first follow-up, respectively. Increases in serum cobalamin concentrations were stratified based on serum cobalamin concentrations at time of inclusion (Fig 2) or CIBDAI at time of inclusion (Fig 3). There were no statistically significant differences between the groups ($P = .98$ and .83, respectively). Furthermore, there was no statistically significant difference between the increase in serum cobalamin concentrations between the dogs that had an unaltered diet or medical treatment during supplementation compared with the dogs that had a change in diet or medical treatment ($P = .27$; Fig 4).

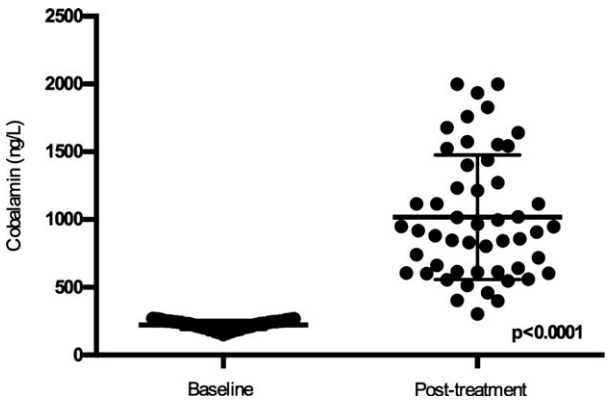

Fig 1. Serum cobalamin concentrations in 51 dogs with hypocobalaminemia treated with oral cobalamin supplementation at baseline and post treatment. Long horizontal line represents mean; short horizontal line standard deviation.

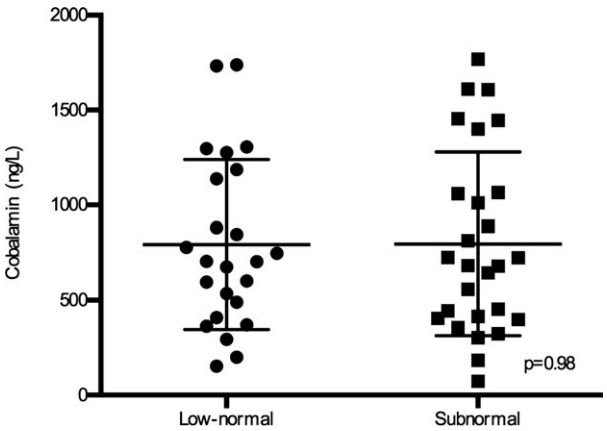

Fig 2. Increase in serum cobalamin concentrations post supplementation in dogs stratified after serum cobalamin concentrations at inclusion (low-normal = 234–270 ng/L; n = 24, subnormal = <234 ng/L; n = 27) Long horizontal line represents mean; short horizontal line standard deviation.

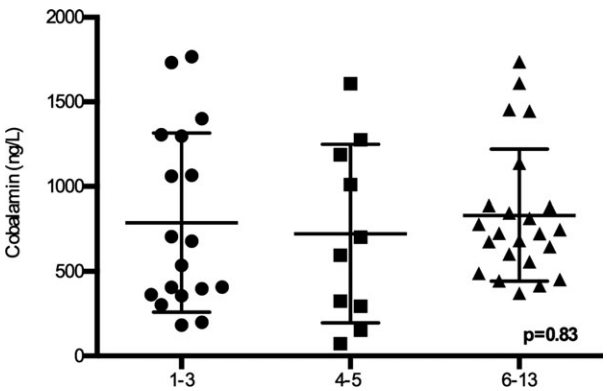

Fig 3. Increase in serum cobalamin concentrations post supplementation in dogs based on canine inflammatory bowel disease index (CIBDAI) at inclusion (CIBDAI 1–3; n = 18, CIBDAI 4–5; n = 10, CIBDAI > 6; n = 23). Long horizontal line represents mean; short horizontal line standard deviation.

Folate and Pancreatic Function Tests

Serum folate concentrations at time of inclusion were available for 49 of 51 dogs. Two of these 49 dogs were treated with oral folate because of previously diagnosed folate deficiency. Of the remaining 47 dogs, subnormal serum folate concentrations were noted in 20 of 47 dogs (43%), while 7 dogs (15%) had

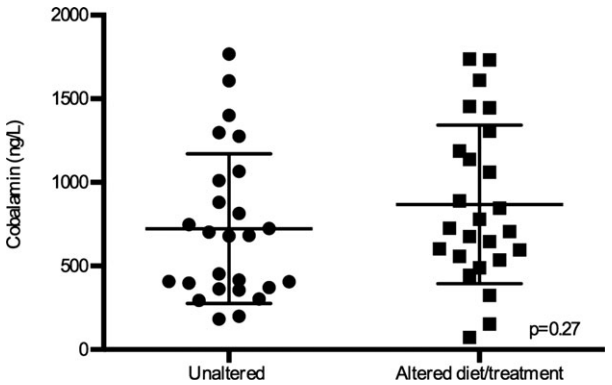

Fig 4. Increase in serum cobalamin concentrations post supplementation in dogs with unaltered diet and medical treatment during supplementation (n = 26) compared with dogs that had a change in diet or treatment (n = 25). Long horizontal line represents mean; short horizontal line standard deviation.

increased levels of serum folate concentrations (reference interval 9.3–24 ng/mL).

Serum TLI concentrations were available for 31/51 dogs. One dog, a mixed-breed, had a TLI of 1.6 μg/L consistent with EPI (reference interval 8.5–35 μg/L, IDEXX VetMed Labor). Of the remaining dogs, 28/30 had serum TLI concentrations within the reference interval while 2/30 had a serum TLI above 50 μg/L. The 2 dogs with increased serum TLI concentrations were further tested for pancreatitis by measurement of serum Spec-cPL concentration or by running a SNAP-cPL test, which were normal or negative, respectively.

Results for canine pancreatic lipase testing were available for 22 dogs and a canine SNAP-cPL was available for 13 dogs. Eighteen of 22 dogs had a cPLI concentration within the reference interval of 0–200 μg/L, one mixed-breed dog had a cPLI of 251 μg/L, and 3 dogs (a Miniature Poodle and 2 Cavalier King Charles Spaniels) had cPLI concentrations above 400 μg/L.

Histopathology

Histopathology reports from gastrointestinal biopsies were available for 33/51 dogs (65%). Biopsies were collected endoscopically in 32 dogs and surgically via laparotomy in 1 dog. Endoscopic biopsies were retrieved from the gastric mucosa, duodenum, and colon in 28/32 dogs and only from the gastric mucosa and duodenum in 4/32 dogs. Ileal biopsies were available only from the dog undergoing laparotomy. Lymphocytic-plasmacytic inflammation was seen in 28 dogs while 5 dogs had a predominantly eosinophilic inflammation of the gastrointestinal tract. The inflammation of the small intestine and colon was characterized as mild to moderate in all dogs. Evidence for gastrointestinal neoplasia was not found in any of the biopsies.

Discussion

In this study, serum cobalamin concentrations increased significantly and normocobalaminemia was restored in all dogs with CE and hypocobalaminemia after daily oral cobalamin supplementation for 20–202 days. These results suggest that oral cobalamin supplementation might be an alternative to parenteral administration in dogs with CE and cobalamin deficiency. Daily oral cobalamin supplementation is usually a cheaper, simpler, and pain-free alternative to weekly cobalamin injections. Parenteral cobalamin supplementation has been the only recommended route of cobalamin administration in dogs with cobalamin deficiency.[5,9,15] Studies validating parenteral supplementation protocols in dogs are however lacking. Similarly, to our knowledge, no studies evaluating the efficacy of oral cobalamin supplementation in dogs with CE and hypocobalaminemia have been published. This is in contrast to human medicine where oral supplementation has already been widely studied in various conditions associated with cobalamin deficiency.[19–22,28,29] In humans, parenteral cobalamin is administered intramuscularly or subcutaneously, which has been associated with adverse effects such as pain and, rarely, adverse reactions including localized scleroderma or tissue necrosis.[26,33,34] Parenteral cobalamin administration might have other disadvantages compared to oral supplementation. In some countries, such as Sweden or Finland, pet owners are not legally allowed to give injections to their pets aside from insulin and hyposensitization treatment. 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 performing this task. Dogs might show pain and some people are very reluctant to handle hypodermic needles and syringes. In this study, the injectable form of cobalamin was more than double the price of the oral supplement for a 3-month treatment period, without the costs for veterinary consultation and injections.

One possible explanation why oral cobalamin might be effective in restoring normocobalaminemia in dogs with CE is the possibility of an alternative absorptive pathway of cobalamin beyond receptor-mediated transport in the ileum, which has been reported in humans.[19] This might explain why oral cobalamin supplementation has been effective in normalizing serum cobalamin concentrations as well as serum MMA and homocysteine concentrations in humans lacking IF or an intact ileum.[19–23,28]

Factors known to influence serum cobalamin concentrations in humans treated with oral cobalamin supplementation are dose and time. When oral cobalamin was given to human patients at 500 μg/day, it produced satisfactory responses in the majority of patients but caused borderline circulating concentrations in a few patients.[19,26,27] A daily oral starting dose of 1,000–2,000 μg/day is currently recommended for humans.[19–21,24–26] Using this dose, there has been no statistical difference between oral and parenteral supplementation in serum cobalamin concentrations during and post treatment.[20,21,23] The dose used for dogs in this study was extrapolated from human stud-

ies. However, it is possible that some dogs require higher doses, or that not all dogs in the study received their daily dose as prescribed. Regarding increase in serum cobalamin concentration over time, 5 separate studies demonstrate that serum cobalamin concentrations increase with continuous oral cobalamin supplementation in humans.[20,21,23,27,28] Serum cobalamin concentrations were only measured at one time-point post treatment during our study. Thus, we cannot evaluate if a continuous oral cobalamin supplementation in dogs would be associated with a continuous increase in serum cobalamin concentration. Further studies are needed to answer this question.

Another factor potentially influencing response to cobalamin supplementation in dogs is breed. Two Giant Schnauzers were included in our study, a breed in which familial cobalamin deficiency has been reported. These dogs were 6 and 8.7 years old, respectively, at the time of inclusion. Both were diagnosed with chronic eosinophilic enteritis. Histopathology reports and age of onset in these dogs made familial cobalamin deficiency less likely than cobalamin deficiency as a result of CE. No other breeds known for familial cobalamin deficiency were represented in this study.

As the main source of IF in dogs is the exocrine pancreas, exocrine pancreatic function is also likely to influence the effect of cobalamin absorption.[3] However, exocrine pancreatic function was not assessed in all dogs. Only 1 dog in our study had confirmed EPI and CE. This dog responded well to oral cobalamin substitution. Whether all dogs with EPI and cobalamin deficiency would respond to oral cobalamin supplementation remains to be determined.

Most dogs responded very well to oral cobalamin supplementation, but some responded less well than others. When specifically looking for similarities in the 3 dogs with the smallest response to oral cobalamin substitution regarding history, dose in mg/kg, diet and type and degree of intestinal inflammation, none could be identified. Why some dogs do not respond as satisfactorily to oral treatment is unknown and requires further investigation, as does the optimal dosing regimen (higher or lower) to restore normocobalaminaemia.

The inclusion criterion for this study was a serum cobalamin concentration of ≤270 ng/L (reference interval: 234–811 ng/L). The majority of the patients had a serum cobalamin concentration below the reference interval, but it might be argued that dogs with a serum cobalamin concentration between 234 and 270 ng/L were not truly deficient. However, hypocobalaminemia can result in severe metabolic consequences and is associated with a negative outcome.[9,16,17] Thus, rapid identification and early intervention is recommended.[35] Therefore, some centers recommend starting cobalamin supplementation when serum cobalamin concentration is in the low reference range (see www.vetmed.tamu.edu/gilab). A recent study assessing MMA in dogs with different levels of serum cobalamin concentrations demonstrated that 19% of all dogs with serum cobalamin concentrations in the lower reference range had an increased MMA.[30] This suggests that some of these dogs were cobalamin deficient on a cellular level, and supports the recommendation to start treatment in the low reference range. It also parallels recommendations in human medicine, where supplementation often is started at the lowest end of normal reference interval, if serum homocysteine and/or MMA concentrations are concurrently increased.[36]

This study has several limitations. The time-point for the follow-up blood sample varied substantially from 20 to 202 days, which might influence the results as serum cobalamin levels have been shown to increase over time with continuous treatment in humans.[20,21,23,27,28] The owners were further instructed not to give cobalamin tablets on the day of the follow-up blood test, but some might have forgotten, potentially causing falsely elevated serum levels. Furthermore, EPI could not be excluded in 20/51 dogs since serum TLI concentrations were not available. Consequently, more than 1 dog in the study might have had both CE and EPI. This might influence the response to oral cobalamin substitution. Homocysteine and MMA were not measured in this study, which is a prerequisite in many countries to diagnose and treat cobalamin deficiency in humans.[37,38] Whether such an approach would also be favorable for canine patients still needs to be studied. Despite several study limitations, our results suggest that oral cobalamin appears effective in restoring normocobalaminemia in dogs with CE, although 3 dogs had only a modest increase in their serum cobalamin concentration in response to oral cobalamin treatment. To further evaluate the efficacy of oral cobalamin supplementation, a randomized prospective study comparing serum cobalamin and cellular cobalamin status in dogs treated with oral or parenteral cobalamin supplementation is warranted.

Off-Label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

Footnotes

[a] Behepan (1 mg), Pfizer, Sollentuna, Sweden
[b] Behepan (1 mg/mL), Pfizer
[c] ADVIA Centaur, Siemens Healthcare Diagnostics, Erlangen, Germany
[d] GraphPad Prism 6.0, GraphPad Software, Inc., La Jolla, CA

Acknowledgments

The authors gratefully acknowledge the Swedish Veterinary Care Foundation for financial support.

Conflict of Interest Declaration: At time of submission, February 7, 2015, Dr Toresson had stock or stock options, travel and accommodations covered or reimbursed from the Evidensia Specialist Animal Hospital, Helsingborg, Sweden or from the Swedish Veterinary Care Foundation.

Off-Label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Batt RM, Morgan JO. Role of serum folate and vitamin B12 concentrations in the differentiation of small intestinal abnormalities in the dog. Res Vet Sci 1982;32:17–22.
2. Fyfe JC, Giger U, Hall CA, et al. Inherited selective intestinal cobalamin malabsorption and cobalamin deficiency in dogs. Pediatr Res 1991;29:24.
3. Batt RM, Horadagoda NU, McLean L, et al. Identification and characterization of a pancreatic intrinsic factor in the dog. Am J Physiol 1989;256:G517.
4. Fordyce HH. Persistent cobalamin deficiency causing failure to thrive in a juvenile beagle. J Small Anim Pract 2000;41:407.
5. Lutz S, Sewell AC, Reusch CE, Kook PH. Clinical and laboratory findings in border collies with presumed hereditary juvenile cobalamin deficiency. J Am Anim Hosp Assoc 2013;49:197.
6. Grützner N, Bishop MA, Suchodolski JS, et al. Association study of cobalamin deficiency in the Chinese Shar Pei. J Hered 2010;101:211.
7. Nightingale JM. Management of patients with a short bowel. World J Gastroenterol 2001;7:741.
8. Allenspach K, Gaschen FP. Small intestinal disease; short bowel syndrome. In: Steiner JM, ed. Small Animal Gastroenterology. 1st ed. Schlütersche Verlagsgesellschaft; Hannover 2008:199.
9. Allenspach K, Wieland B, Gröne A, Gaschen F. Chronic enteropathies in dogs: Evaluation of risk factors for negative outcome. J Vet Intern Med 2007;21:700.
10. Craven M, Simpson JW, Ridyard AE, Chandler ML. Canine inflammatory bowel disease: Retrospective analysis of diagnosis and outcome in 80 cases (1995–2002). J Small Anim Pract 2004;45:336.
11. German AJ, Day MJ, Ruaux CG, et al. Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic-responsive diarrhea in dogs. J Vet Intern Med 2003;17:33.
12. Berghoff N, Parnell NK, Hill SL, et al. Serum cobalamin and methylmalonic acid concentrations in dogs with chronic gastrointestinal disease. Am J Vet Res 2013;74:84.
13. Kathrani A, Steiner JM, Suchodolski J, et al. Elevated canine pancreatic lipase immunoreactivity concentration in dogs with inflammatory bowel disease is associated with a negative outcome. J Small Anim Pract 2009;50:126.
14. Batchelor DJ, Noble PM, Taylor RH, et al. Prognostic factors in canine exocrine pancreatic insufficiency: Prolonged survival is likely if clinical remission is achieved. J Vet Intern Med 2007;21:54.
15. Ruaux CG. Cobalamin in companion animals: Diagnostic marker, deficiency states and therapeutic implications. Vet J 2013;196:145.
16. Arvanitakis C. Functional and morphological abnormalities of the small intestinal mucosa in pernicious anemia – a prospective study. Acta Hepatogastroenterol (Stuttg) 1978;25:313.
17. Battersby IA, Giger U, Hall EJ. Hyperammonaemic encephalopathy secondary to selective cobalamin deficiency in a juvenile border collie. J Small Anim Pract 2005;46:339.
18. Banerjee R. B12 trafficking in mammals: A for coenzyme escort service. ACS Chem Biol 2006;1:149.
19. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Med Scand 1968;184:247.
20. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. Blood 1998;92:1191.
21. Castelli MC, Friedman K, Sherry J, et al. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: A randomized, open-label, parallel-group study. Clin Ther 2011;33:358.
22. Bolaman Z, Kadikoylu G, Yukselen V, et al. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: A single-center, prospective, randomized, open-label study. Clin Ther 2003;25:3124.
23. Kim H, Hyung WJ, Song KJ, et al. Oral vitamin B12 replacement: An effective treatment for vitamin B12 deficiency after total gastrectomy in gastric cancer patients. Ann Surg Oncol 2011;18:3711.
24. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev 2005;3:1–24. CD004655.
25. Andrès E, Mecili M. Oral vitamin B12 therapy. Ann Surg Oncol 2011;18(Suppl 3):S196.
26. Elia M. Oral or parenteral therapy for B12 deficiency. Lancet 1998;352:1721.
27. Eussen SJ, de Groot LC, Clarke R, et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: A dose-finding trial. Arch Intern Med 2005;165:1167.
28. Vanderbrink BA. Is oral vitamin B(12) therapy effective for vitamin B(12) deficiency in patients with prior ileocystoplasty? J Urol 2010;184:1781.
29. Andrès E, Kurtz JE, Perrin AE, et al. Oral cobalamin therapy for the treatment of patients with food-cobalamin malabsorption. Am J Med 2001;111:126.
30. Berghoff N, Suchodolski JS, Steiner JM. Association between serum cobalamin and methylmalonic acid concentrations in dogs. Vet J 2012;191:306.
31. Jergens AE. Clinical assessment of disease activity for canine inflammatory bowel disease. J Am Anim Hosp Assoc 2004;40:437.
32. Drammeh BS, Schleicher RL, Pfeiffer CM, et al. Effects of delayed sample processing and freezing on serum concentrations of selected nutritional indicators. Clin Chem 2008;54:1883.
33. Hovding G. Anaphylactic reaction after injection of vitamin B12. Br Med J 1968;3:102.
34. Ho J, Rothchild YH, Sengelmann R. Vitamin B12-associated localized scleroderma and its treatment. Dermatol Surg 2004;30:1252.
35. Dossin O. Laboratory tests for diagnosis of gastrointestinal and pancreatic diseases. Top Companion Anim Med 2011;26:86.
36. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014;166:496.
37. Herrmann W, Obeid R. Cobalamin deficiency. Subcell Biochem 2012;56:301.
38. Allen LH. Vitamin B-12. Adv Nutr 2012;3:54.