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Original Article

Comparison of efficacy of oral and parenteral cobalamin supplementation in normalising low cobalamin concentrations in dogs: A randomised controlled study

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ABSTRACT

The aim of this study was to compare the efficacies of parenteral and oral cobalamin supplementation protocols in dogs with chronic enteropathies and low cobalamin concentrations. It was hypothesised that both treatments would increase serum cobalamin concentrations significantly. Fifty-three dogs with chronic enteropathies and serum cobalamin concentrations < 285 ng/L (reference interval 244–959 ng/L) were enrolled. Dogs were randomised to treatment with either daily oral cobalamin tablets (0.25–1.0 mg cyanocobalamin daily according to body weight) or parenteral cobalamin (0.4–1.2 mg hydroxycobalamin according to body weight). Serum cobalamin concentrations were analysed 28 ± 5 days and 90 ± 15 days after initiation of supplementation. After 28 days, all dogs had serum cobalamin concentrations within the reference interval or above. In the parenteral group ($n = 26$), median (range) cobalamin concentrations were 228 (150–285) ng/L at inclusion, 2107 (725–10,009) ng/L after 28 days and 877 (188–1267) ng/L after 90 days. In the oral group ($n = 27$), median (range) serum cobalamin concentrations were 245 (150–285) ng/L at inclusion, 975 (564–2385) ng/L after 28 days and 1244 (738–4999) ng/L after 90 days. In both groups, there were significant differences in serum cobalamin concentrations between baseline and 28 days, and between 28 days and 90 days ($P < 0.001$). In conclusion, both parenteral and oral cobalamin supplementation effectively increase serum cobalamin concentrations in dogs with chronic enteropathies and low cobalamin concentrations.

Introduction

The gastrointestinal transport of cobalamin (vitamin B12) is a complex process, involving several carrier proteins, of which the most important is intrinsic factor (IF) (Banerjee, 2006). Final absorption from the gastrointestinal tract occurs in the ileum, where cobalamin bound to IF is absorbed. In human beings, an alternative route of absorption of cobalamin, independent of IF, has been reported (Berlin et al., 1968); using radioactively labelled cobalamin, ~1% free cobalamin was absorbed along the entire intestine by passive diffusion. However, this route of absorption has not been demonstrated formally in dogs.

Diseases thought to cause cobalamin deficiency in dogs are those that affect ileal receptors, those that cause decreased production of IF, and intestinal dysbiosis. The former can occur in chronic enteropathy (CE), intestinal lymphosarcoma (lymphoma), or familial selective cobalamin malabsorption, in which genetically defective cobalamin-IF receptors are expressed (Batt and Morgan, 1982; Fyfe et al., 1989; Cook et al., 2009; Grützner et al., 2010; Lutz et al., 2013). In canine exocrine pancreatic insufficiency (EPI), decreased production of IF causes hypocobalaminaemia (Batt et al., 1989; Batt et al., 1991). Intestinal dysbiosis may cause bacterial competition for nutrients, resulting in decreased amounts of cobalamin available for absorption in the ileum (Ruaux, 2013).

Hypocobalaminaemia results in a range of clinical and metabolic effects (Arvanitakis, 1978; Ruaux, 2013). Clinical signs in dogs with hypocobalaminaemia include anorexia, lethargy,

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weight loss, failure to thrive, and central and/or peripheral neuropathies (Fyfe et al., 1989; Fordyce et al., 2000; Battersby et al., 2005; Lutz et al., 2013). Immunodeficiency and intestinal changes, such as villous atrophy and malabsorption, have been reported. Cobalamin deficiency has been associated with a negative prognosis in dogs with CE or EPI (Allenspach et al., 2007; Batchelor et al., 2007).

The current supplementation protocol for hypocobalaminaemic dogs calls for repeated parenteral injections (Ruaux, 2013). In human beings with cobalamin deficiency, all studies comparing oral and parenteral cobalamin supplementation have shown equal efficacy of oral supplementation compared to parenteral supplementation (Kuzminski et al., 1998; Bolaman et al., 2003; Castelli et al., 2011; Kim et al., 2011). A Cochrane review suggested that '*high oral doses of B12 could be as effective as intramuscular administration*' (Vidal-Alaball et al., 2005).

We have reported a retrospective study demonstrating successful oral cobalamin supplementation in 51 dogs with CE and hypocobalaminaemia (Toresson et al., 2016). However, there are no published studies comparing oral and parenteral cobalamin supplementation in dogs. The aim of the present study was to compare the efficacy of oral and parenteral cobalamin supplementation in dogs with CE and serum cobalamin concentrations at the lower end of the reference interval, or below. The hypothesis was that both protocols would significantly increase serum cobalamin concentrations.

Materials and methods

Animal inclusion

Inclusion criteria for the study were dogs with signs of CE and serum cobalamin concentrations ≤285 ng/L (reference interval 244–959 ng/L), representing the lower end of the reference interval, or below (referred to as 'low cobalamin' in the remaining text). Exclusion criteria were EPI without histologically verified CE, on-going cobalamin supplementation or intestinal neoplasia. Dogs were enrolled from Evidensia Specialist Animal Hospital, Helsingborg, Sweden, and Halsinge Small Animal Clinic, Sweden, from March 2014 to July 2016. The study was approved by the animal ethics committee of Uppsala University, Uppsala, Sweden (approval number C109/13; date of approval 27 September 2013).

Study design, baseline data and laboratory investigation

This was a prospective open, randomised controlled study. Serum cobalamin concentrations were measured at baseline, 28 ± 5 days and 90 ± 15 days after inclusion. The canine inflammatory bowel disease activity index (CIBDAI) was calculated at inclusion and at follow-up visits (Jergens, 2004). The CIBDAIs of the parenteral and oral groups were compared at each time point. Breed, age, medical history, body weight, body condition score (BCS) and findings on physical examination were recorded. Pet food manufacturers of all of the commercial diets that the dogs were fed at inclusion were contacted for information on cobalamin content. However, cobalamin concentrations were not confirmed by chemical analysis. Haematology profiles and selective serum biochemistry profiles were performed, including alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, total protein, albumin, haematocrit, total white blood cell count, folate, trypsin-like immunoreactivity (TLI) and canine pancreatic lipase immunoreactivity (cPL, as measured by Spec-cPL, IDEXX) or SNAP canine pancreatic lipase (SNAP-cPL, IDEXX). Faecal parasitology was performed, comprising three separate samples analysed by the sedimentation-flotation method and the IDEXX SNAP Giardia test or direct immunofluorescence assay. Abdominal ultrasound was performed on 51/53 dogs. Endoscopic biopsies of the stomach, small intestine and large intestine were collected; on average, eight biopsies were collected from each site in each dog. The biopsies were prepared routinely for histopathology at Biovet, Sollentuna, Sweden. Dietary changes and medical treatments during the study were based on clinical judgement (Table 1).

Medication history and diet

Twenty-four dogs were being treated for gastrointestinal disorders at the time of inclusion; corticosteroids ($n = 11$) were the most common medication. At the time of completion of the study, 41/49 dogs were receiving immunomodulatory treatment (Table 1). Three dogs had been supplemented with oral cobalamin previously; supplementation had ended 30–385 days prior to recurrence of low cobalamin levels.

Table 1
Medication and diet in 53 dogs with chronic enteropathy and low cobalamin concentrations; 49 dogs remained in the study after 90 days.

Parameter at inclusion or after 90 days	Variable	Number of dogs (%)
Treatment at inclusion	Corticosteroids[a]	11 (23)
	Cyclosporine[b]	4 (8)
	Antibiotics[c]	6 (11)
	Other[d]	9 (17)
Diet at inclusion	Kibble diet (KD)	41 (77)
	KD: 'Intestinal'	16 (30)
	KD; single protein	11 (21)
	KD; hydrolysed	2 (4)
	Home-cooked	8 (15)
	Raw food (commercial)	4 (8)
Diet change during study		33 (67)
Treatment after 90 days	Corticosteroids[e]	43 (88)
	Cyclosporine	4 (8)
	Chlorambucil[f]	9 (18)
	Antibiotics[g]	2 (49)
	Corticosteroids + miscellaneous[h]	21 (43)
	Miscellaneous[i]	3 (6)
Diet after 90 days	Kibble diet (KD)	45 (85)
	KD 'Intestinal'	14 (26)
	KD single protein	18 (34)
	KD hydrolysed	12 (23)
	Home-cooked	2 (4)
	Raw food (commercial)	2 (4)

[a] Corticosteroids (prednisolone, methylprednisolone or budesonide) ($n = 11$), alone or in combination with olsalazine ($n = 5$).
[b] Three dogs were treated with cyclosporine + corticosteroids.
[c] Metronidazole ($n = 4$), amoxicillin ($n = 1$), unknown antibiotics ($n = 1$).
[d] Omeprazole ($n = 3$), sucralphate ($n = 2$), $n = 1$ each: metoclopramide, chaolin clay, chaolin clay + probiotics, pancreatic enzymes, folate, clomipramine.
[e] Prednisolone/methylprednisolone ($n = 32$), budesonide ($n = 12$).
[f] All dogs were treated with corticosteroids + chlorambucil.
[g] Metronidazole.
[h] Folate ($n = 10$), psyllium ($n = 7$), olsalazine ($n = 7$), pancreatic enzymes ($n = 2$), sucralphate ($n = 2$).
[i] Folate ($n = 1$), psyllium ($n = 1$), metoclopramide ($n = 1$).

At inclusion, 39 dogs received commercial pet food kibble from major pet food companies, two dogs were fed kibble of an unknown brand, four dogs were fed various commercial raw food diets, and eight dogs received primarily a home-cooked meat-based diet (Table 1). Twenty-nine dogs were fed kibble diets labelled 'intestinal', 'single protein', or 'hydrolysed protein'. During the study, 33 dogs were switched to a new diet (Table 1). The cobalamin contents of 38/39 kibble diets were revealed by the manufacturers. On a dry matter (DM) basis, the median cobalamin content was 0.13 mg/kg (0.046–0.35). None of the diets contained less cobalamin than the American Association of Feed Control Officials minimum recommendation of 0.028 mg/kg DM.[1] The raw food manufacturer could not specify the cobalamin content of their diets. Furthermore, the cobalamin content of the home cooked diets was not available.

Cobalamin supplementation

Dogs were supplemented according to a block-randomised schedule designed by an external statistician. Dogs in the 'parenteral group' received one injection per week for 6 weeks, and an additional injection 4 weeks later according to a published protocol (Ruaux, 2013). Depending on body weight, dogs received 0.25–1.2 mg hydroxycobalamin (Behepan, 1 mg/mL, Pfizer) on each occasion. Dogs in the 'oral group' received oral cyanocobalamin (Behepan 1 mg, Pfizer) daily during the study. Dogs with a body weight ≤20 kg received 0.025 mg/kg body weight cyanocobalamin and dogs with a body weight >20 kg received 1 mg cyanocobalamin. Owner instructions included withholding the tablet on the day of the follow-up blood sample and bringing the pill container for tablet counting.

[1] See: http://www.merckvetmanual.com/management-and-nutrition/nutrition-small-animals/nutritional-requirements-and-related-diseases-of-small-animals (accessed 5 December 2017).