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In Dogs With Chronic Enteropathies, Can Oral B12 Tablets Be Used to Treat Hypocobalaminaemia?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In dogs with chronic enteropathy does treatment with oral cobalamin compared to parenteral cobalamin provide serum cobalamin levels greater than 270 ng/L?

Clinical bottom line

The evidence provided by block randomised controlled clinical trials indicates that oral dosing of cobalamin results in normocobalaminaemia, with levels similar to that achieved with parenteral dosing. These studies provide veterinary professionals with dosing schedules, and monitoring serum cobalamin levels is recommended to ensure normocobalaminaemia is achieved. It has been shown that supplementation with both oral and parenteral cobalamin correlates with increased intracellular cobalamin levels. Future studies are needed to investigate the outcome of oral cobalamin dosing in dogs with extra-gastrointestinal disease.

Clinical Scenario

You are treating a dog with chronic enteropathy and have identified hypocobalaminaemia. You recommend commencing a course of parenteral cobalamin but the owner is reluctant. They are concerned about the discomfort of frequent injections, the stress of visits to the hospital, and the cost. The client asks if cobalamin tablets, otherwise known as vitamin B12, can be given instead of a course of injections. You decide to explore the literature to give advice on the subject.

The evidence

There is little published evidence comparing oral and parenteral administration of cobalamin in dogs with chronic enteropathy One case series and two block randomised clinical trials were used to answer the question. Protocols for parenteral doses of cobalamin are based on expert opinion and clinical experience and are not validated protocols (Ruaux, 2013). Serum cobalamin of 252–908 ng/L is considered the normal range for a dog (Vaden et al., 2009). Toresson et al. (2016) produced a retrospective study based on a review of medical records of dogs that had been treated with oral cobalamin; the study concluded that dogs treated with oral cobalamin had normal cobalamin blood serum levels (>270 ng/L). A randomised clinical trial was later performed by Toresson et al. (2018). This experimental trial concluded that both oral and parenteral cobalamin supplementation in dogs provided a significant increase in serum cobalamin concentrations >285 ng/L. This was followed by a study to show that both oral and parenteral supplementation of cobalamin resulted in decreased methylmalonic acid (MMA) levels, with no significant difference between the two groups (Toresson et al., 2019). A cobalamin deficiency leads to accumulation of MMA, and MMA is indicative of the cellular cobalamin level. This indicates that both oral and parenteral cobalamin supplementation provide effective cellular cobalamin levels, and that oral supplementation in dogs is an effective treatment option for hypocobalaminaemia in chronic enteropathies.

Summary of the evidence

Toresson et al. (2016)	
Population:	Client owned dogs with signs of chronic enteropathy and hypocobalaminaemia treated with oral cobalamin tablets. An electronic search of a hospital database for dogs with chronic enteropathy treated with oral cobalamin between Jan 2012–March 2014, Sweden. Cases were excluded if they had extra-gastrointestinal disease, were not compliant with the dose or had concurrent cobalamin parenteral supplementation. Dogs included had initial serum cobalamin levels <270 ng/L, mean 223 +/- 33 ng/L
Sample size:	51 dogs: 34 male, 17 female
Intervention details:	Cyanocobalamin 1 mg tablets were used, once daily dosing for 20–202 days (median 72 days): body weight: 1 kg–10 kg = ¼ of a tablet, 10 kg–20 kg = ½ a tablet and >20 kg = 1 tablet.
Study design:	Retrospective case series
Outcome studied:	Objective assessment of serum cobalamin concentration. Blood samples were taken between 20–202 days (mean 73) after initiation of daily oral tablets.
Main findings: (relevant to PICO question):	• No dogs were hypocobalaminaemic at the time of post treatment blood sampling, mean serum cobalamin: 1,017 ng/L (range 557–1477 ng/L) There was a significant difference between the starting cobalamin concentration and cobalamin after oral tablets (P<0.0001) • Mean increase in serum cobalamin was 794 ng/L (range 332–1256 ng/L)
Limitations:	• Retrospective, uncontrolled study • Incomplete diagnostic work ups and dogs on different treatments for chronic enteropathy and different diets • Empiric dosing and range of doses given • Owners administering tablets may have compliance issues; tablets were not counted at blood sampling to check compliance. Offering dogs' tablets does not ensure they ingest it • Two giant Schnauzers included – this breed has known inherited cobalamin malabsorption (Fyfe et al., 1991) • Follow up serum cobalamin levels were not standardised, repeat blood samples were taken from 20–202 days post treatment. • Blood serum cobalamin concentration assessed – unsure if this correlates with intracellular levels

Toresson et al. (2018)	
Population:	Client owned dogs with signs of chronic enteropathy and serum cobalamin <285 ng/L (interval 244–959 ng/L)
Sample size:	53 dogs
Intervention details:	Dogs allocated to treatment group in block randomised schedule design and all dogs had baseline serum blood cobalamin concentration samples. Parenteral group: one subcutaneous injection of 0.25–1.2 mg per dog depending on body weight (weight range 3.1–49 kg). hydroxycobalamin once weekly for 6 weeks and an additional injection 4 weeks later (Ruaux, 2013). Oral group: each dog received 0.025–0.05 mg/kg cyanocobalamin daily for 90 days (+/- 15days). Owners withheld tablets on the day of blood sampling, and tablets were counted to check compliance.
Study design:	Prospective open randomised controlled study on client owned dogs
Outcome studied:	Objective assessment of serum blood cobalamin concentration before treatment, day 28 (+/-5 days) after treatment and day 90 (+/-15 days) after treatment
Main findings: (relevant to PICO question):	• Both the oral group and parenteral group had significantly increased serum cobalamin level at day 28 and day 90 compared to baseline (P<0.001) showing normocobalaminaemia in dogs that completed the study • The parenteral group median showed higher levels at day 28 than the oral group (P< 0.001) • The oral group showed higher levels at day 90 than the parenteral group (P<0.001) • Oral group median at day 28: 955 ng/L (range 564–2385 ng/L) • Parenteral group median at day 28: 1799 ng/L (range 575–9827 ng/L) • Oral group median at day 90: 1244 ng/L (range 768–4999 ng/L) • Parenteral group median at day 90: 600 ng/L (range 38–997 ng/L)
Limitations:	• This study was not blinded, the authors were aware of the treatment allocation to each dog when collecting serum samples • The reference interval provided at the start of the study for normocobalaminaemia is not justified or referenced. • Owner compliance was an issue in terms of administering pills, and three dogs dropped out due to non-compliance with parenteral group, and one dog was lost to euthanasia • All dogs were on different diets and diet changes occurred during the study, diets with a known cobalamin level had a range from 0.046–0.35 mg/kg, however authors did not account for the different cobalamin levels in diets between the groups • The weekly dosing schedule, up to 4 weeks, has been shown

	to normalise MMA concentrations after 4 weekly injections in cats (Ruaux, 2005), beyond this, dosing is empirical and based on expert opinion and clinical experience (Ruaux, 2013). It is commonly followed in practice • Not all dogs had a complete diagnostic work up and dogs were on different treatments • One Border collie was included in the study, this breed has known inherited cobalamin deficiency (Lutz et al., 2013) • Power calculation not performed to indicate significance due to small sample size • Blood serum levels evaluated, this may not reflect cellular cobalamin levels (Berghoff et al., 2012) • Loss to follow-up occurred in the parenteral group

Toresson et al. (2019)	
Population:	Client owned dogs with clinical signs of chronic enteropathy and serum cobalamin concentrations of ≤285 ng/L (interval 244–295 ng/L) (Normocobalaemia 244–959 ng/L)
Sample size:	36 dogs: Oral group n=18. Parenteral group n=18
Intervention details:	Dogs were allocated to groups in block randomised schedule design. All dogs had baseline serum blood cobalamin, methylmalonic acid (MMA) and homocysteine (HCY) concentration samples. Parenteral group: one subcutaneous injection of 0.25–1.2 mg per dog (depending on body weight, weight range 3.1–49 kg) of hydroxycobalamin once weekly for 6 weeks and an additional injection 4 weeks later (Ruaux, 2013). Oral group: each dog received oral daily cyanocobalamin (Behepan® 1 mg, Pfizer). Dogs less than 10 kg body weight received ¼ of a tablet, 10 kg–20 kg body weight ½ a tablet, and if >20 kg received one tablet. Owners were told to withhold tablets on the day of follow-up examination.
Study design:	Prospective open, block randomised controlled study
Outcome studied:	Objective assessment of serum blood cobalamin, MMA and HCY concentration before treatment. Assessment of serum blood MMA and HCY concentration day 28 ± 5 days after treatment and day 90 ± 15 days after treatment.
Main findings: (relevant to PICO question):	• MMA: significant decrease in both oral and parenteral group from day 0 to day 28 (P<0.0001). There was no further decrease in MMA after day 28. There was no significant difference between the oral group and parenteral group at day 28 and day 90. • HCY: there was no significant difference in the HCY concentrations at any time point, and no significant difference between the two groups.

Limitations:	• This study was not blinded, owners and authors were aware of which treatment group the dog was in., • This study had a small sample size, with thirty-six dogs at the start of the study and thirty one on completion, one dog was lost to euthanasia, one sample lost in shipment, and three did not comply with the protocol. No confidence intervals or effect sizes were calculated. • Samples were shipped twice within Sweden and once to USA. This is acknowledged by the authors. Human studies show MMA and HCY are stable for up to 8 days at room temperature (Hustard et al., 2012), but no studies are available for canine MMA and HCY. Samples included in this study were refrigerated within two hours of collection, and frozen within 1–3 days. They were transported to USA within 12–18 months. The authors do not state how long it took for samples to be tested. 13 samples were accidentally left at room temperature for 13 days and excluded from the study. • Owners were instructed not to give tablets on the day of sampling, while the parenteral group were sampled 5–7 days after cobalamin supplementation. The fluctuations of MMA concentrations after tablet administration and subcutaneous injection of cobalamin are unknown. • Three of the authors work for the laboratory used in this study, however this is declared, and reports no personal or financial relationship. • The weekly dosing schedule, up to 4 weeks, has been shown to normalise MMA concentrations after 4 weekly injections in cats (Ruaux, 2005), beyond this, dosing is empirical and based on expert opinion and clinical experience (Ruaux, 2013). However despite the small sample size, this study demonstrates significant decreases in MMA.

Appraisal, application and reflection

Dogs with chronic enteropathy (CE) display signs of 'vomiting, diarrhea, borborygmus, hyporexia, abdominal pain, nausea and/or weight loss' (Dandrieux, 2016). Hypocobalaminaemia has been shown to be a negative prognostic indicator in dogs with CE (Craven et al., 2004) and serum cobalamin <200ng/L has an increased risk of poor outcome (Allenspach et al., 2007. Normocobalaminaemia has been described as serum levels between 252–908 ng/L, (Vaden et al., 2009). However, in the studies described cobalamin is supplemented once levels are below 285 ng/L as this level represents the lowest 5% of the reference range (Toresson et al., 2018). Cobalamin is necessary for the methylmalonyl CoA mutase (MCM) system (Solomon, 2007) and deficiencies can result in the production of methylmalonic acid (Stabler et al., 1986). Berghoff et al. (2013) showed that the prevalence of hypocobalaminaemia in dogs with CE was 36%, while a quarter of these dogs had increased levels of methylmalonic acid. It has been recommended that all dogs showing signs of chronic gastrointestinal disease should have cobalamin levels assessed (Dossin, 2011).

The current protocol used most commonly in practice has been suggested by Ruaux (2013) and the Gastrointestinal Laboratory at Texas A&M University. This protocol involves an injection of cobalamin once weekly for 6 weeks, and a follow-up injection 4 weeks later of hydroxycobalamin, 0.25–1.25 mg/dog depending on boady weight (Ruaux, 2013) (subcutaneously). These doses have not been validated, and are based on clinical experience and expert opinion (Ruaux, 2013). Some dogs with gastrointestinal disease need long-term

management, and Ruaux (2013) reports using up to weekly injections in these cases. This requires frequent visits to veterinary clinics, can be distressing for both owners and dogs, and costly. Toresson et al., (2018) found that one dog was hypocobalaminaemic (38 ng/L) at day 90 after following this parenteral protocol. This suggests that the parenteral protocol was not adequate at supplementing cobalamin in this case. Intrinsic factor mediates the absorption of cobalamin in the intestines and human studies have shown that one percent of cobalamin was absorbed separately from intrinsic factor by passive diffusion (Berlin et al., 1968). This led to doctors treating patients with oral cobalamin and a Cochrane review indicates that 'high oral doses of B12 could be as effective as intramuscular administration' (Vidal-Alaball et al., 2005). In our veterinary patients, tablets are more cost effective, convenient and cause the dog less discomfort.

The paper by Toresson et al. (2016) is a retrospective review of cases that suggests oral cobalamin provides serum cobalamin concentrations above the reference range (mean serum level increase of 794 ng/L +/- 462). This was followed by a block randomised controlled clinical trial (Toresson et al., 2018). Dogs were split into two groups by random allocation and either treated with cobalamin orally or parenterally, Block randomization is used to reduce bias by assigning equal numbers to each treatment group. While dogs were given a range of doses and sample sizes were small; this study showed promising results that the oral group had similar results to the parenteral group. This study was not blinded as both owners and authors were aware of the treatments provided to each group; however the authors were collecting objective data so this may not have influenced results greatly. One limitation of the study was owner compliance, and in some instances owners did not fully comply with the protocol; however these cases were included in the results and still had normocobalaminaemia. In the randomised controlled clinical trial (Toresson et al, 2018) the parenteral cobalamin protocol was taken from Ruaux (2013). As mentioned already this is not a validated protocol and while cobalamin levels were higher at day 28 than the oral groups, levels dropped at day 90. This suggests that monthly injections of cobalamin may not be sufficient at maintaining cobalamin levels in some dogs. It has been mentioned above that Ruaux (2013) has used weekly injections to maintain cobalamin levels in some cases. Further studies may be needed to determine frequency of injections after the initial course. Serum cobalamin levels from the oral group were increased at day 90; suggesting daily oral supplementation may be preferable long-term than the current parenteral protocols.

Serum cobalamin levels in these studies post treatment surpass' the reference range provided, for example in Toresson et al., (2018), the median serum cobalamin level of the oral group at day 90 is 1244 ng/L (768–4999 ng/L). Toresson et al., (2018) address this as 'signalling a satisfactory response to oral supplementation in most dogs'. The origin of the reference range for 'normocobalaminaemia' in all the studies is not referenced. The interval provided at the start in all the studies for normocobalaminaemia is not justified or referenced. The normal range is >251ng/L (Berghoff et al., 2012) and hypocobalaminaemia in the studies described is considered once serum cobalamin levels are <270-285ng/L, as it represents the lowest 5% of the reference range.

Finally, the paper by Torresson et al. (2019) demonstrates a reduction in MMA levels, indicating that oral and parenteral supplementation are effective at a cellular level. This supports the use of oral cobalamin supplementation in dogs with chronic enteropathy, however, there was no significant change in HCY levels, suggesting the need for further studies in breeds with congenital or familial cobalamin malabsorption. Recent reports have shown that both cobalamin and MMA concentrations have normalised in dogs with congenital hypocobalaminaemia treated with oral supplementation (McCallum & Watson, 2018 and Kook & Hersberger, 2019). Holotranscobalamin is used as a marker for hypocobalaminaemia in humans (Herrmann & Obeid, 2012 and Devalia et al., 2014), further studies are needed to determine the use of this marker in our canine patients.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB abstracts (1989–2019), accessed via the OVID platform and Pubmed (1910–2019), accessed on the NCBI website
Search terms:	CAB abstracts: 1. (dog or dogs or canine or canines or bitch) 2. (cobalamin or B12) 3. (enteropath* or IBD or inflammatory bowel disease) 4. (oral or parenteral) PubMed: ((((dog or dogs or canine or canines or bitch)) AND (cobalamin or B12)) AND (enteropath* or IBD or inflammatory bowel disease)) AND (oral or parenteral)
Dates searches performed:	12/05/2019

Exclusion / Inclusion Criteria	
Exclusion:	Papers not written in English, did not answer the PICO question, book chapter
Inclusion:	Original research papers investigating oral treatment or comparing oral to parenteral treatment

Please add rows as necessary

Search Outcome					
Database	**Number of results**	**Excluded – Not written in English**	**Excluded – Book chapter**	**Excluded – did not answer PICO question**	**Total relevant papers**
CAB Abstracts	5	0	0	2	3
Pubmed	5	1	0	1	3
Total relevant papers when duplicates removed					**3**

CONFLICT OF INTEREST

The author declares no conflict of interest.

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