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A Case Report of the Protein-Losing Enteropathy in a 7-year-old Maltese-Treated Dog with Budesonide in Combination with Cannabidiol Oil

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ABSTRACT

This article discusses the administration of Budesonide (Entocort) in a seven-year-old Maltese presenting constant diarrhea, low serum albumin, and ascites. Initially, the dog exhibited a positive response to the dietary modification and prednisone; nevertheless, a recurrence occurred subsequently. We opted to provide Budesonide (Entocort) for one month in conjunction with Cannabidiol (CBD) oil. This resulted in an enhancement of clinical symptoms and the improvement of serum albumin levels. This study indicates that Budesonide, utilized in human medicine for chronic enteropathy treatment, in conjunction with CBD oil, may also be useful in dogs and is generally well tolerated.

Key words: Chronic Enteropathy, Budesonide, CBD oil, Diarrhea

INTRODUCTION

Canine chronic inflammatory enteropathies (CIE) constitute a group of nonspecific gastrointestinal conditions characterized by persistent gastrointestinal symptoms exceeding three weeks, histopathological evidence of intestinal mucosal inflammation and the exclusion of alternative etiologies (Jergens and Heilmann 2022).

Protein-losing enteropathy (PLE) is a disorder marked by the atypical passage of serum albumin via the intestinal barrier (Procoli 2020). In canines, prevalent disorders linked to PLE encompass chronic enteritis, viral infections and intestinal lymphangiectasia, all of which exhibit analogous clinical manifestations. A histological examination of the gastrointestinal (GI) tract using endoscopic or full-thickness biopsy is often suggested to identify the etiology of protein-losing enteropathy (Rychlik and Kaczmar 2020) and inform treatment strategies; nevertheless, certain instances may necessitate therapeutic trials, such as dietary alterations (Ozen and Lenardo 2023). Specific dog breeds may exhibit increased susceptibility to the illness, and multiple breeds can be impacted. The etiology of protein depletion may differ. A urinalysis, including the protein-to-creatinine ratio, is employed to exclude protein loss via the kidneys. A potential reason of low serum protein may be inadequate production in the liver. To evaluate liver function, preprandial and postprandial serum bile acid levels may be quantified, in conjunction with additional liver function indicators (Wootton et al. 2023). The intensity of clinical manifestations, typically assessed through the canine Inflammatory Bowel Disease (IBD) activity index [CIBDAI] or more specific the canine chronic enteropathy clinical activity index [CCECAI] (Coates 2023). Low serum albumin levels (below 20g/L) and diminished serum cobalamin serve as adverse prognostic factors (Peterson and Willard 2003). In cases of PLE, ultrasound of the abdomen can identify intestinal lesions and related lymphadenopathy, enabling a more precise differentiation between inflammation and neoplasm processes (Washabau et al. 2010; Salavati et al. 2019). Steroids have been shown to effectively diminish or eradicate enteric protein losses in certain patients, possibly by direct effects on the intestinal mucosa. High-dose corticosteroids have been identified as an effective therapy for PLE. Administering prednisone at a rate of 1 to 2 milligrams per kilogram each day for a minimum of 14 to 21 days is crucial for obtaining benefits, and it must be administered parenterally due to inadequate absorption resulting from intestinal edema. The specific mechanism of action is uncertain; nevertheless, it is probable that the reestablishment of cell membrane integrity at the intestinal boundary contributes to the effect (Craven and Washabau 2019). Regrettably, a favorable reaction to steroid therapy is infrequently noted till Cushingoid characteristics and additional negative effects

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manifest. Gradually reducing steroid use can be difficult, frequently resulting in recurrent setbacks (Coates 2023). Budesonide is a halogen-free glucocorticoid developed for the treatment of inflammatory bowel disease in humans, with the objective of minimizing systemic adverse effects. Budesonide exhibits a high ratio of topical to systemic effects in human patients due to substantial first-pass metabolism in the liver. This feature results in reduced side effects relative to systemic corticosteroids (Pietra et al. 2013).

Case details

A 7-year-old, non-spayed, female Maltese weighing 4.5kg was referred to our hospital at University of Veterinary Medicine and Pharmacy in Košice, Department of Internal Medicine with diarrhea lasting 7 months and ascites (Fig. 1) lasting 3 weeks. Dog had a medical history of Metronidazol (Entizol) for 7 days, Famotidin (Quamatel) for 2 weeks and Streptomycin (Streptonamid) for 5 days. The recorded Canine Chronic Inflammatory Enteropathy Activity Index at presentation was 11 (severe). There was evidence of changing diets (hypoallergic, gastrointestinal) for a long time, but no improvements were noticed.

Fig. 1: Dog at the initial visit with noticeably enlarged abdominal cavity.

The blood test results (Procyte Dx Hematology Analyzer, IDEXX Laboratories, Inc, Westbrook, ME, USA) from the first examination indicate an elevated white blood cell count (WBC), with neutrophils (NEU) at $18.77x10^9$/L (reference range $2.95\text{-}11.64x10^9$/L). The lymphocytes (LYM), erythrocytes (ERY), basophils (BAS) and eosinophil (EOS) count were all in normal count. Platelet, plateletcrit, and reticulocyte counts were marginally elevated beyond the reference range.

Biochemical parameters were assessed utilizing the Cobas c 111 analyzer (Roche, Switzerland). The outcomes of hematological and biochemical testing are provided in Table 1. A slight elevation in creatinine and urea levels was found. The urine protein-creatinine ratio was below the normal range. Bile acids were within normal limits both preprandially and postprandially.

An ultrasonographic (USG) examination revealed the presence of a wavy duodenum. The wall of the jejunum was thickened (7mm). The colon's thickness measured 2mm (Fig. 2). The liver exhibited normal dimensions and exhibited diffuse hyperechogenicity. Overall, these measures have been successful in inhibiting the onset of colitis and alleviating current inflammation.

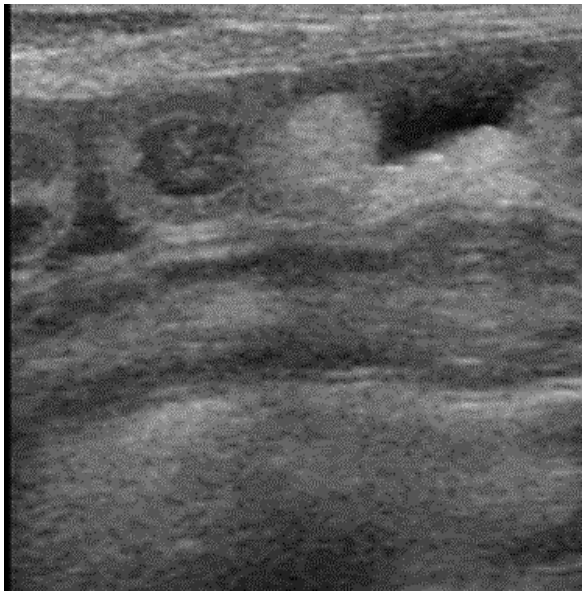

Fig. 2: An ultrasound at first examination. Enlarged hypoechoic wall, with abdominal effusion.

Fecal parasitology, rapid antigen test for Canine Parvovirus, Giardia and Canine Coronavirus were also negative. The stool alpha1-proteinase inhibitor, which is an indicator of protein losses from the intestine, concentrations were nearly three times larger (65.3mg/dL) than the reference value (up to 26.8mg/dL).

Due to too low serum albumin and poor condition of the patient we decided not to perform histopathology examination of small intestine. The diagnosis was established based on the exclusion of all other causes of low albumin such as loss by the kidneys, insufficient production in the liver or due to malnutrition and others together with a high value of stool a1-PI concentrations.

According to these, Furosemide was initiated at a dosage of 2mg/kg twice a day, alongside Prednisolone (0.5mg/kg) and Sulfasalazine (4mg/kg). Additionally, we advised a reduced-fat diet.

Fourteen days after those medicaments administration, there was evidence of minimum fluid in abdomen, but diarrhea did not improve. Also, there were complications of developing cystitis probably as a result of side effects of prednisone. Enrofloxacin (5mg/kg per os q24h) was used for treatment of cystitis for 8 days. After recovery of cystitis, we decided to use Budesonid (Entocort) 1 mg /pro toto with CBD oil in a concentration of 20%, 6 drops 3 times a day. Budesonid was given for 1 month. CBD oil was given for almost 3 months.

Following to this period, we conducted a clinical evaluation. A follow-up abdominal ultrasonography was conducted, demonstrating considerable recovery (Fig. 4). The formerly observed enlarged jejunal wall (7mm) had reduced. Also, there were not any fluid in the abdomen. The wall of the jejunum reduced (3mm).

Based on clinical examination after the treatment the CCECAI score was set to 3 which is very good. The checkup took place after approximately one year. Patient at the check with minimal abdominal distension (Fig. 5). The owner did not experience issues with diarrhea in his dog. Similarly, there was no collection of fluid in the abdominal cavity. The blood test results, and biochemical markers are in the Table 2.

Table 1: Hematobiochemical markers at first examination

RBC	HCT	HGB	WBC	NEU	LYM	MONO	EOS	BAS
5.6-8.8 x10^{12}/L	37.3-61.7%	13.1-20.5g/dl	5.0-16.7 x10^9/L	2.9-11.6 x10^9/L	1.05-5.1 x10^9/L	0.16-1.12 x10^9/L	0.06-1.23 x10^9/L	0.0-0.1 x10^9/L
6.20	43.6	15.0	23.48	18.77	2.9	1.12	0.63	0.06
Crea	Urea	3.9- ALT <0.949	ALP <1.24	GLU	ALB	TP	AMYL <7.21	LIP <1.66
46-88 umol/L	8.5 mmol/L	ukat/L	ukat/L	3.6-5.8 mmol/L	26-41 g/L	47-74 g/L	ukat/L	ukat/L
98.9	12.4	0.60	0.71	5.4	18.4	26.2	9.21	3.0

RBC - red blood cells; HCT - haematocrit; HGB - haemoglobin; WBC - white bood cells; NEU - neutrophils; LYM - lymphocytes; MONO - monocytes; EOS - eosinophils; BAS - basophils; CREA - creatinine; ALT - alanine aminotransferase; ALP - alkaline phosphatase; GLU - glucose; ALB - albumin; TP - total protein; AMYL - amylase; LIP - lipase

Table 2: Hematobiochemical markers after the treatment

RBC	HCT	HGB	WBC	NEU	LYM	MONO	EOS	BAS
5.6-8.8 x10^{12}/L	37.3-61.7%	13.1-20.5g/dl	5.0-16.7 x10^9/L	2.9-11.6 x10^9/L	1.05-5.1 x10^9/L	0.16-1.12 x10^9/L	0.06-1.23 x10^9/L	0.0-0.1 x10^9/L
7.3	52.8	18.0	11.16	8.49	1.62	0.52	0.50	0.03
Crea	Urea	3.9- ALT <0.949	ALP <1.24	GLU	ALB	TP	AMYL <7.21	LIP <1.66
46-88 umol/L	8.5 mmol/L	ukat/L	ukat/L	3.6-5.8 mmol/L	26-41 g/L	47-74 g/L	ukat/L	ukat/L
85.5	7.9	1.9	2.0	5.0	26.9	49.1	13.2	3.3

RBC - red blood cells; HCT - haematocrit; HGB - haemoglobin; WBC - white bood cells; NEU - neutrophils; LYM - lymphocytes; MONO - monocytes; EOS - eosinophils; BAS - basophils; CREA - creatinine; ALT - alanine aminotransferase; ALP - alkaline phosphatase; GLU - glucose; ALB - albumin; TP - total protein; AMYL - amylase; LIP – lipase

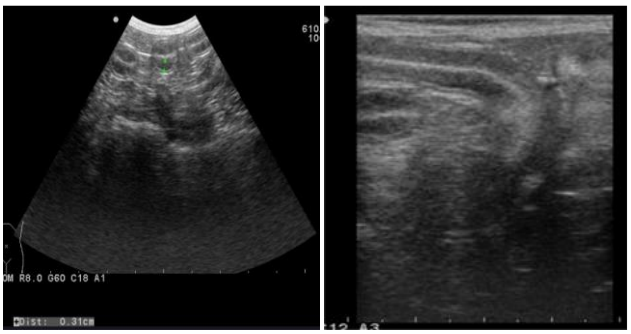

Fig. 4: An USG after treatment without any effusion, thick intestine wall (0,31cm)

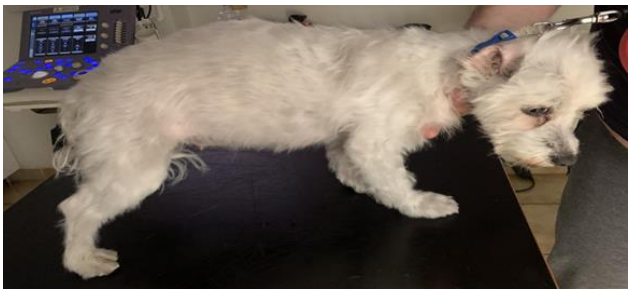

Fig. 5: Patient after treatment. Minimal abdominal distension is present.

DISCUSSION

In humans, 90% of budesonide is metabolized in the liver into inactive forms, minimizing its exposure to corticosteroid effects as little of the active form passes into the bloodstream (Dandrieux et al. 2013). Budesonide's mechanism of action involves binding to an intracellular glucocorticoid receptor with high affinity (Dye et al. 2013).

The dosage of budesonide used in this study was determined empirically. Different dosages for oral budesonide have been documented in veterinary literature, with the most frequently reported dosages being from 1mg for smaller dogs to 3mg for larger dogs (Coates 2023). Given the patient's size, we opted for a dosage of 1mg, suitable for a smaller dog.

The analysis of the study by Pietra et al. (2013) indicated substantial clinical improvement following the initiation of treatment, evidenced by a considerable decrease in CCECAI values. In our case, there was a notable enhancement of CCECAI values following treatment. Initially, the CCECAI index was 11 (severe), and following treatment, it decreased to 3, indicating a positive result. Budesonide proved to be more effective than a placebo due to Kuenzig et al. (2018) in treating Crohn's disease in humans, but it did not show superior therapeutic efficacy compared to other orally administered glucocorticosteroides.

The optimal treatment due to Rychlik et al. (2016) for IBD must substantially decrease patients' CIBDAI scores and enhance the macroscopic and histopathological state of intestinal mucosa. Medications that positively impact all three aspects play a vital role in treatment effectiveness and in extending remission periods, a crucial factor in managing IBD. The study of (Rychlik et al. 2016) found that budesonide was ineffective in severe IBD in dogs as it did not improve clinical symptoms, reduce CIBDAI scores, or enhance the macroscopic appearance of intestinal mucosa. The most pronounced efficacy of budesonide treatment was seen in mild condition of especially in the histopathological evaluation of the mucosa in the duodenum, jejunum and large bowel.

In the coming years, substantial alterations in the management of human IBD are anticipated, since continuing investigations into novel biologic medicines may facilitate their earlier application in disease development, especially in Crohn’s disease. Innovative delivery strategies, such as multi-matrix formulations for conventional medications like budesonide and 5-ASA, may present new first-line therapeutics for ulcerative colitis (Berera and Lichtenstein 2022). The growing accessibility of alternate formulations for noncorticosteroid drugs and biologic therapies may prompt a reduction in corticosteroid usage due to apprehensions regarding their harmful effects.

Progress in genetics and epigenetics may facilitate personalized medical treatments tailored to specific host characteristics (Silverman and Otley 2011).

Cannabidiol, a non-psychotropic phytocannabinoid derived from Cannabis sativa L, is under investigation as a potential alternative therapy for health conditions in canines and felines. Research indicates that CBD helps alleviate symptoms associated with osteoarthritis, itching, epilepsy, and gastrointestinal diseases in canines, with evidence pointing to its anti-inflammatory properties resulting from CB2 activation. The CB2 receptor, a G protein-coupled peripheral receptor for cannabinoids, possesses immunosuppressive and anti-inflammatory characteristics, with the capacity to reduce the production of specific proteins, and is found in leukocytes and microglia (Corsato et al. 2023).

Cannabinoid receptors in the gastrointestinal tract regulate processes including motility, secretion, sensation, emesis, satiety and inflammation (DiPatrizio 2016; Lee et al. 2016). Numerous studies suggest that cannabinoid receptors may have a positive impact on inflammatory bowel disease in humans, highlighting the potential therapeutic advantages of employing pharmacological drugs to target these pathways (Fabisiak and Fichna 2017).

The activation of cannabinoid receptors reduces vomiting, intestinal motility, and secretion, while inhibiting gastric acid secretion and relaxation of the lower esophageal sphincter. Conversely, in circumstances such as inflammatory bowel disease or endotoxic inflammation, the activation of these receptors diminishes intestinal motility, presenting a potential novel approach to reestablish normal gut function after an inflammatory episode (Vinci et al. 2022).

Martínez et al. (2020) identifies the primary aims for managing IBD as diminishing inflammation, easing symptoms such as abdominal discomfort and diarrhea, improving quality of life, and preventing consequences. Current medications demonstrate efficacy in disease management and remission maintenance; nevertheless, they may not be universally beneficial, and some patients may have a decline in responsiveness over time. Patients with IBD frequently pursue complementary drugs, such as cannabis, to alleviate symptoms that endure despite treatment or remission.

Research (Abalo et al. 2012; Alhouayek and Muccioli 2012; Zoppi et al. 2012) utilizing various experimental rodent models of intestinal inflammation has demonstrated that cannabis have immunomodulatory and anti-inflammatory effects. These properties encompass the suppression of inflammatory cell recruitment, induction of T cell apoptosis, reduction of pro-inflammatory cytokine production, promotion of wound healing and restoration of intestinal barrier function, inhibition of gastrointestinal motility and secretion to mitigate diarrhea, and diminution of visceral hypersensitivity and abdominal pain. These measures have successfully inhibited the onset of colitis and diminished existing inflammation.

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical considerations: The study was approved by Ethics Committee for the approval of research involving animals in accordance with the legislative requirements applicable at the UVMP in Košice, permit No. EKVP/22-17.

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