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The effect of orally administered Budesonide on the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease

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ABSTRACT: The aim of this study was to evaluate the effect of Budesonide on the hypothalamic-pituitary-adrenal (HPA) axis in dogs with inflammatory bowel disease. The effect of orally administered Budesonide (Entocort) on the HPA axis was analysed in 21 dogs with inflammatory bowel disease. Biochemical analyses were carried out to evaluate the activity levels of alanine aminotransferase, asparagine aminotransferase, alkaline phosphatase, cortisol and endogenous adrenocorticotropic hormone. Urine samples were collected from each patient before the study and after 30 days of the experiment to determine the composition and the physical and chemical properties of urine sediments. Considerably lower serum concentrations of cortisol and endogenous adrenocorticotropic hormone were observed after 30 days of treatment. A significant increase in alkaline phosphatase levels was noted on Day 30. In the studied dogs, the drop in HPA axis activity was correlated with side effects associated with the administered glucocorticosteroid (polyuria, polydipsia). In conclusion, we have shown that oral administration of Budesonide to dogs diagnosed with inflammatory bowel disease significantly suppressed the activity of the HPA axis.

Keywords: glucocorticosteroids; IBD treatment; eACTH concentration; side effects; HPA axis

List of abbreviations

ACTH = adrenocorticotropic hormone, **ALKP** = alkaline phosphatase, **ALT** = alanine aminotransferase, **AST** = asparagine aminotransferase, **CD** = Crohn's disease, **CIBDAI** = canine inflammatory bowel disease activity index, **CORT** = cortisol, **eACTH** = endogenous adrenocorticotropic hormone, **GC** = glucocorticosteroids, **HPA** = hypothalamic-pituitary-adrenal axis, **HUC** = histiocytic ulcerative colitis, **IBD** = inflammatory bowel disease, **SG** = urinary specific gravity, **UC** = ulcerative colitis

Canine inflammatory bowel disease (IBD) is a group of chronic enteropathies characterised by persistent or recurring gastric symptoms of unknown aetiology which are related to histopathological changes in the mucosa of the small and large intestines in the form of cellular infiltrations in the mucosal lamina propria (Craven et al. 2004; Day et al. 2008; Simpson and Jergens 2011; Jergens and Simpson 2012). The classification of IBD is determined by the predominant type of inflammatory cells in the lamina propria of the intestinal mucosa (Craven et al. 2004; Garcia-Sancho et al. 2007; Day et al. 2008; Washabau 2008).

Glucocorticosteroids (prednisone, prednisolone) offer the most effective treatment for severe IBD (canine inflammatory bowel disease activity index (CIBDAI) score higher than nine points) in dogs. The mechanism of glucocorticosteroid activity in the treatment of IBD has not been fully elucidated. GCs probably exert anti-inflammatory effects by inhibiting the release of inflammatory mediators and suppressing reactions that involve cytokines (Angelucci et al. 2008). Despite their therapeutic benefits, glucocorticosteroids exert serious side-effects after long-term administration, which include iatrogenic hyperadrenocorticism and lower activity

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of the hypothalamic-pituitary-adrenal (HPA) axis (Tumulty et al. 2004). Other side-effects that limit the use of glucocorticosteroids in dogs include, polyuria, polydipsia, polyphagia, hyperventilation, urinary tract infections, muscular dystrophy and steroid hepatopathy (Tumulty et al. 2004; Malewska et al. 2011).

Recent advances in pharmacology have led to the introduction of non-systemic glucocorticosteroids with low bioavailability which minimise the drug's side-effects while maintaining its therapeutic efficacy (Campieri et al. 1997; Tumulty et al. 2004). These drugs are characterised by high affinity for local glucocorticosteroid receptors and an intensified hepatic first-pass effect, which leads to the production of effective local metabolites in the target organ and a lower incidence of side-effects (Brattsand 1990). The internal activity of Budesonide, measured as its affinity for the glucocorticosteroid receptor, is around 15-times higher in comparison with prednisolone (Brattsand and Miller-Larsson 2003; Edsbacker and Andersson 2004). Glucocorticosteroids of this type are particularly effective in the treatment of local inflammations of the gastrointestinal mucosa. In an inflamed digestive system, the hepatic first-pass effect plays a vital role in reducing systemic effects which ensue when glucocorticosteroids leave the target organ (Zareie et al. 1999).

Budesonide is a synthetic, halogen-free glucocorticosteroid analogue which is metabolised to a form that shows an absence of or minimal steroid activity (Tumulty et al. 2004; Angelucci et al. 2008). After absorption, which can be complete, Budesonide undergoes first-pass metabolism in the liver (80–90%; Spencer and McTavish 1995; Miller-Larsson et al. 2001), which is catalysed by the CYP3A4 isoenzyme of cytochrome p-450, secreted by hepatocytes and intestinal epithelial cells (Jonsson et al. 1995; Thomsen et al. 1998; Tumulty et al. 2004; Angelucci et al. 2008). The above process produces two main metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, which are characterised by negligent glucocorticosteroid activity and are excreted by the kidneys in free or conjugated form. Non-metabolizable Budesonide is undetectable in urine (Angelucci et al. 2008).

The results of clinical and pharmacological trials involving human subjects indicate that controlled release (Entocort) and pH-modified release (Budenofalk) capsules deliver a powerful anti-inflammatory effect. Budesonide is characterised by high solubility in water and moderate lipophilicity, which promotes distribution on the surface of mucosal membranes and penetration of the surrounding tissues. After cellular uptake, Budesonide is transformed to highly lipophilic esters which accumulate in the cell. These esters are gradually hydrolysed to release active Budesonide and prolong its anti-inflammatory effects (Miller-Larsson et al. 2001). The analysed drug is rapidly metabolised and retained in mucous membranes to deliver an intensified local effect with low systemic availability.

There is a general scarcity of research investigating the effect of Budesonide on the HPA axis in the treatment of canine IBD. Budesonide's effectiveness in the treatment of local inflammations of mucosal membranes in the canine gastrointestinal system has not been investigated to date. We undertook this study in an attempt to resolve the contradictory reports regarding the anti-inflammatory activity and side-effects of new generation glucocorticosteroids as well as their effect on the histological structure of the small and large intestinal mucosa. We hypothesised that oral administration of Budesonide in dogs with IBD might supress the activity of the HPA axis. We therefore decided to evaluate both the effect of orally administered Budesonide (brand name – Entocort) on the HPA axis and the side-effects of this treatment.

MATERIAL AND METHODS

The study was performed on 21 dogs of both sexes and various breeds, aged 7–10 years, with body weights of 6–20 kg, admitted to the Veterinary Clinic of the University of Warmia and Mazury in Olsztyn in Poland. The animals showed symptoms of IBD, including chronic small and large intestinal diarrhoea and vomiting of varying intensity and frequency. Systemic diseases, antibiotic response enteropathy, food response enteropathy and parasitic infestations were excluded in all patients according to the recommendations of the WSAVA Gastrointestinal Standardisation Group. The animals qualified for the experiment based on the results of endoscopic and histopathological analyses of mucosa sections from the duodenum, jejunum and the colon. All of the patients were affected by a severe form of IBD with CIBDAI scores ranging from nine to 13 points.

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The animals were divided into three groups: Group I comprised seven dogs with body weights of 6–10 kg (CIBDAI 11.8). The animals were administered Budesonide (Entocort) at a dose of 1 mg/dog/day for 30 days. Group II comprised seven dogs with body weights of 11–15 kg (CIBDAI 12.1). The animals were administered Budesonide (Entocort) at a dose of 1.5 mg/dog/day for 30 days. Group III comprised seven dogs with body weights of 16–20 kg (CIBDAI 12.4). The animals were administered Budesonide (Entocort) at a dose of 2 mg/dog/day for 30 days.

All patients were subjected to clinical tests, and CIBDAI scores (Jergens et al. 2003) were determined before the study and on Day 30. Biochemical analyses were carried out before the administration of budesonide and on Day 30. The activity of alanine aminotransferase (ALT), asparagine aminotransferase (AST) and alkaline phosphatase (ALKP) was determined in biochemical assays using the IDEXX VetTest8008 dry chemistry analyser. Cortisol (CORT) and endogenous adrenocorticotropic hormone (eACTH) levels in the blood serum were determined in the IDEXX Vet Med Lab. CORT (0.5 ml serum) and eACTH (1 ml frozen plasma with EDTA) concentrations were determined using a chemiluminescent immunoassay (CLIA) in the IDEXX analyser.

Urine samples were collected from each dog before the experiment and on Day 30 to determine the composition and the physical and chemical properties of urine sediments. The above analysis was performed with the use of IDEXX UA strips in the IDEXX VETLab UA analyser, and sediments were examined under the Olympus BX41 light microscope. Urinary specific gravity was measured as a marker for polyuria to provide possible evidence of antidiuretic (ADH) resistance secondary to exogenous GC administration.

Water consumption, micturition frequency and appetite were evaluated in every patient before, during and after the experiment. Water and food consumption were assessed separately with the use of the same scoring system: 0 – refusal to consume water/food; 1 – ¼ of water/food intake before administration of Budesonid; 2 – ½ of water/food intake before administration of Budesonid; 3 – water/food intake not changed, 4 – higher water/food intake before administration of Budesonid. Micturition frequency, defined as the average number of urinations observed per day, was scored as either one to five occurrences or six and greater (Tumulty et al. 2004).

The results of laboratory tests were presented as SI units and were processed statistically. Changes in eACTH, CORT, ALKP, ALT, AST and SG (urinary specific gravity) levels over time were determined using the Wilcoxon matched pair test at $P \leq 0.05$ (significant) and $P \leq 0.01$ (highly significant), and the differences between animal groups were measured using the Kruskal-Wallis rank sum test at $P \leq 0.05$ (significant) and $P \leq 0.01$ (highly significant) in Statistica 9.1 software (StatSoft Inc.).

Statistical analyses to determine changes in water consumption, micturition frequency and food consumption over time were performed with the Friedman nonparametric test at $P \leq 0.05$ (significant) and $P \leq 0.01$ (highly significant), and the differences between groups were analysed using Cochran's Q test at $P \leq 0.05$ (significant) and $P \leq 0.01$ (highly significant) in Statistica 9.1 software (StatSoft Inc.).

The experiment was approved by the Local Ethics Committee for Animal Experimentation in Olsztyn pursuant to resolution No. 47/2009/DTN of June 24, 2009.

RESULTS

The average cortisol levels (± SD) in Group I were determined to be 62.13 nmol/l (± 23.02 nmol/l) before treatment and 23.36 nmol/l (± 23.99 nmol/l) after treatment with Budesonide (reference values: 25–125 nmol/l), pointing to an insignificant drop after 30 days of the experiment ($P = 0.062980$). In Group II, cortisol concentrations were found to be 41.91 nmol/l (± 37.36 nmol/l) before treatment and 17.77 nmol/l (± 11.86 nmol/l) after treatment, indicating an insignificant decrease after 30 days of the experiment ($P = 0.236724$). In Group III, a significant drop ($P = 0.027993$) in cortisol levels was observed, from 53.84 nmol/l (± 22.08 nmol/l) before treatment to 11.69 nmol/l (± 15.58 nmol/l) after treatment. No significant differences ($P = 0.3211$) in average cortisol concentrations were noted between groups at the end of treatment (Day 30; Table 1).

The average concentrations of eACTH in Group I were reported to be 58.57 pg/ml (± 6.6 pg/ml) before treatment and 15.14 pg/ml (± 7.01 pg/ml) after treatment with Budesonide (reference values: 9–67 pg/ml), revealing a significant drop after 30 days of the experiment ($P = 0.017961$). In Group II, a significant decrease in average eACTH levels ($P = 0.017961$) was observed, from 55.71 pg/ml (± 8.48 pg/ml) be-

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Table 1. The mean values and standard deviations of biochemical parameters and specific gravity at Days 0 (before treatment) and 30 (after treatment) for all groups

	Group I				Group II				Group III			
	Day 0		Day 30		Day 0		Day 30		Day 0		Day 30	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
CORT (nmol/l)	62.13	23.02	23.36	23.99	41.91	37.36	17.77	11.86	53.84	22.08	11.69*	15.58
ACTH (pg/ml)	58.57	6.6	15.14*	7.01	55.71	8.48	18.43*	5.62	60.57	8.81	19.57*	5.03
ALKP (U/l)	60	22.13	155.43*	120.17	71.71	32.36	137.29*	110.76	108.29	93.13	177.29	215.74
ALT (U/l)	27	11.31	57.71	58.43	37.71	9.05	47.29	33.23	38.43	10.18	50.71	42.15
AST (U/l)	25.57	17.39	37.86	21.71	31	5.45	26.86	8.69	33.14	9.37	37.29	15.66
Urine specific gravity	1.026	0.01	1.028	0.01	1.025	0.01	1.026	0.01	1.029	0.01	1.030	0.01

ACTH = adrenocorticotropic hormone, ALKP = alkaline phosphatase, ALT = alanine aminotransferase, AST = asparagine aminotransferase, CORT = cortisol

*$P < 0.05$, **$P < 0.01$

fore treatment to 18.43 pg/ml (± 5.62 pg/ml) after treatment. In Group III, a significant drop in eACTH levels ($P = 0.017961$) was observed, from 60.57 pg/ml (± 8.81 pg/ml) before treatment to 19.57 pg/ml (± 5.03 pg/ml) after treatment. No significant differences in average eACTH concentrations ($P = 0.2930$) were determined between groups at the end of the experiment (Day 30; Table 1).

Significant differences in average ALKP levels (reference range: 23–212 U/l) were found in Group I before (60 U/l [± 22.13 U/l]) and after (155.43 U/l [± 120.17 U/l]) treatment ($P = 0.027993$) and in Group II before (71.71 U/l [± 32.36 U/l]) and after (137.29 U/l [± 110.76 U/l]) Budesonide treatment ($P = 0.042523$), see Table 1.

No significant differences between average ALT and AST values before and after treatment were observed in Group I (Table 1).

The average urinary specific gravity values (reference range: 1.016–1.045) were not characterised by any significant differences between values measured before and after treatment in any groups with Budesonide (Table 1).

No significant differences ($P = 0.09293$) between average water consumption in Group I before (3 [± 0]) and after (3.29 [± 0.49]) the 30-day period of Budesonide administration were determined. The average water intake in Group II was significantly ($P = 0.00001$) altered (before, 3 [± 0]) in response to treatment (after, 3.43 [± 0.53]). Significant differences in average water consumption were also noted in Group III ($P = 0.00001$) (before, 3 [± 0]) at the end of the experiment (3.57 [± 0.53]). No significant changes in average feed consumption were observed in Group I in response to treatment; before: 3 [± 0], after: 3 [± 0.58] ($P = 0.99999$), in Group II; before: 3 [± 0], after: 2.86 [± 0.9] ($P = 0.82921$), or in Group III; before: 3 [± 0], after: 3 [± 1] ($P = 0.99997$). The average micturition frequency in Group I varied from 3 [± 0.58] before the treatment to 3.29 [± 0.49] after Budesonide treatment (no significant change, $P = 0.67231$), in Group II – from 3 [± 0.58] before treatment to 4.43 [± 0.53] after treatment (significant change, $P = 0.00001$), and in Group III – from 3.43 [± 0.53] before treatment to 4.43 [± 0.53] after treatment (significant change, $P = 0.00001$; Table 2).

Table 2. Mean values and standard deviations of water intake, food intake and micturition frequency at Days 0 (before treatment) and 30 (after treatment) for all groups

	Group I				Group II				Group III			
	Day 0		Day 30		Day 0		Day 30		Day 0		Day 30	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Water intake	3	0	3.29	0.49	3	0	3.43**	0.53	3	0	3.57**	0.53
Food intake	3	0	3	0.58	3	0	2.86	0.9	3	0	3	1
Micturition frequency	3	0.58	3.29	0.49	3	0.58	4.43**	0.53	3.43	0.53	4.43**	0.53

*$P < 0.05$, **$P < 0.01$

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DISCUSSION

In our experiment, oral administration of Budesonide to dogs with inflammatory bowel disease significantly reduced the activity of the HPA axis. In the experimental group of dogs receiving Budesonide at a daily dose of 2 mg/animal, a significant decrease in cortisol levels was observed after 30 days of treatment. In a study by Tumulty et al. (2004), a significant drop in the activity levels of the HPA axis was observed in a group of six dogs with IBD receiving a pure powder formulation of Budesonide at a dose of 3 mg/m^2, which is roughly equivalent to 1 mg/10.7 kg (Tumulty et al. 2004). The cited authors demonstrated a significant drop in average serum cortisol levels and ACTH-stimulated average serum cortisol levels after 30 days of treatment. Since base cortisol levels in the blood serum are not an accurate indicator of HPA axis activity (Schlaghecke et al. 1992), serum concentrations of ACTH-stimulated cortisol were also evaluated by Tumulty et al. (2004). The ACTH test is regarded as the most precise tool for determining changes in the activity of the HPA axis (Tumulty et al. 2004). Its results showed that monthly administration of Budesonide impaired adrenocortical function in a significant number of dogs, and the above was manifested by a drop in the serum levels of ACTH-stimulated cortisol. In our experiment, the serum levels of ACTH-stimulated cortisol were not measured after 30 days of oral administration of Budesonide. Some owners of the laboratory animals did not agree to repeated examinations of serum cortisol levels after ACTH stimulation; therefore, the results of those tests could not be included in statistical analyses. The examinations performed in dogs whose owners consented to the procedure confirmed the results reported by other authors, including Tumulty et al. (2004).

In our experiment, the dogs subjected to Budesonide treatment were characterised by significantly lower serum levels of eACTH after 30 days of therapy. A significant decrease in eACTH concentrations was also reported by other authors (Tumulty et al. 2004; Stroup et al. 2006). In the work of Stroup et al. (2006), serum eACTH levels were significantly lowered after 14 days of treatment, whereas a drop in cortisol concentrations was noted already on Day 7. In most cases, serum eACTH levels decrease before adrenocortical activity is suppressed. ACTH is secreted irregularly, and eACTH concentrations in blood could be relatively high when sampled on Day 7.

In our experiment, a significant increase in ALKP levels was noted in the group of dogs administered Budesonide at a daily dose of 1 mg/animal and 1.5 mg/animal after 30 days of treatment. In the group of animals receiving a higher daily dose of 2 mg/animal, average ALKP concentrations did not change significantly at the end of therapy, but a trend towards higher ALKP values was noted after monthly administration of the studied glucocorticosteroid. In other studies, ALKP levels did not change significantly throughout the experiment (Tumulty et al. 2004; Stroup et al. 2006). Exogenous glucocorticosteroids are known for their ability to intensify ALKP activity in canine serum (Dillon et al. 1980; Badylak and Van Vleet 1981; Meyer 1982; DeNovo and Prasse 1983; Dillon et al. 1983; Meyer et al. 1990; Rutgers et al. 1995), although the noted clinical effects are determined by the dose and duration of therapy. The results of our experiment support the conclusion that Budesonide's effects on ALKP activity in the serum are correlated with the degree of inhibition of HPA axis activity. No significant increase in the serum concentrations of ALT or AST was observed after 30 days of Budesonide treatment. Similar findings were reported by other authors (Stroup et al. 2006).

In our study, no significant changes in urinary specific gravity were noted in response to Budesonide therapy. Similar results were obtained in other experiments (Tumulty et al. 2004; Stroup et al. 2006). In the work of Stroup et al. (2006), urinary specific gravity exceeded 1.025 in every test in all but one of the analysed dogs.

The side effects (polyphagia, polydipsia and polyuria) elicited by conventional glucocorticosteroids were also evaluated in our experiment. Long-term administration of glucocorticosteroids can lead to the inhibition of antidiuretic hormone (ADH) activity at the level of renal tubules, a higher glomerular filtration rate which initiates diuresis, decreased water permeability of nephrons and cortisol-induced impairment of ADH release from neurosecretory cells (Raff 1987). In our study, no significant differences in feed consumption were observed when rates before and after Budesonide treatment were compared. After 30 days of Budesonide administration, a significant increase in water consumption and micturition frequency was reported

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in dogs with IBD. In the cited studies, oral administration of Budesonide was not correlated with side effects, such as increased appetite, thirst or urination frequency (Tumulty et al. 2004; Stroup et al. 2006). Our findings undermine the theory that Budesonide is subject to first-pass metabolism in dogs with IBD, leading to the production of metabolites characterised by high effectiveness in the target organ and a decreased incidence of side-effects.

In humans, Budesonide absorption is not determined by the severity of inflammatory bowel disease. No differences in the drug's availability were noted in a pharmacokinetic analysis of children with mild and acute Crohn's disease (Lundin et al. 2003). The systemic availability of Budesonide was determined at 9–12% in patients with Crohn's disease (Lundin et al. 2003) and in healthy subjects (Edsbacker and Andersson 2004). The drug's availability in dogs affected by IBD of different levels of severity has not been investigated. In a study by Stroup et al. (2006), inhibited HPA axis activity was observed in dogs with normal gastrointestinal mucosa, which suggests that Budesonide is also absorbed by healthy subjects (Stroup et al. 2006).

One limitation of our experiment was the limited duration of treatment. The activity of the HPA axis was suppressed already at the early stages of therapy, but an objective evaluation of the side-effects produced by glucocorticosteroids should be performed after at least six weeks of oral administration of Budesonide. A longer period of IBD treatment in dogs would probably lead to significant changes in other biochemical parameters or adverse side-effects. Prolonged inhibition of HPA axis activity could produce clinical symptoms of adrenocortical insufficiency after the discontinuation of treatment.

The Budesonide doses that we selected represent another limiting factor in our experiment. According to our best knowledge, pharmacokinetic studies of dogs with IBD have not been carried out to date. For this reason, the Budesonide dose was selected as follows: dose for small breeds – 1 mg/animal/day (body weight 6–10 kg), dose for medium-sized breeds – 2 mg/animal/day (body weight 16–20 kg) and dose for large breeds – 3 mg/animal/day (body weight 26–30 kg). Similar doses were used by Tumulty and colleagues (3 mg/m^2, which is equivalent to 1 mg/10.7 kg) and Stroup and co-workers (2 mg per dog with body weight less than 18 kg and 3 mg per dog with body weight greater than or equal to 18 kg; Tumulty et al. 2004; Stroup et al. 2006). In humans, the pharmacokinetics and systemic availability of Budesonide are similar in children with body weight below 20 kg and in adults who are administered the drug at a daily dose of 9 mg (Lundin et al. 2003). This dose is believed to be the lowest effective one for the maintenance of remission in patients with Crohn's disease (Greenberg et al. 1994). The Budesonide dose seems to be less dependent on body weight in humans than in dogs which are characterised by much greater differences in body weight across breeds. In humans receiving a Budesonide dose of 3 mg, significant differences in the maintenance of remission of Crohn's disease were not reported in comparison with the control group which was subjected to placebo treatment (Greenberg et al. 1994). If the pharmacokinetic parameters of Budesonide are similar in dogs and humans, then the maximum dose of 3 mg for dogs weighing up to 30 kg could be too low. If effective treatment of IBD requires higher doses, then the side-effects of Budesonide therapy, apart from suppressed activity of the HPA axis, could be observed at earlier stages of treatment.

In human medicine, Budesonide is administered because it causes fewer side-effects. The results of our experiment indicate that oral administration of Budesonide to dogs with inflammatory bowel disease significantly suppresses the activity of the HPA axis. Inhibited HPA axis activity in dogs was correlated with the side-effects (polyuria, polydipsia) of glucocorticosteroid therapy. Taking into account the results of the present study it should be assumed that the administration of Budesonide in dogs with IBD may have limited application. Further studies analysing the systemic availability and pharmacokinetic properties of Budesonide in dogs are needed to evaluate the drug's clinical effectiveness.

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