

## CORTICOSTEROID-INDUCED HEPATOPATHY IN DOGS

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**Abstract**

Corticosteroid therapy is often used on dogs (*Canis lupus familiaris*) to treat different kinds of diseases. One of the most common complications of corticosteroid use is steroid hepatopathy, a specific pathology only in dogs. The objective of this study was to determine whether and how significant the liver functional changes after one administration of different kinds of corticosteroids in standard dosages are. The study took place in private veterinary clinics in Riga, Latvia, during 2013 - 2014, with the permission of dogs' owners. Twenty animals, which received corticosteroids due to present diagnosis, were divided into four groups. To reach the aim such corticosteroids as dexamethasone sodium phosphate, prednisolone acetate, methylprednisolone acetate and hydrocortisone aceponate were used in standard dosage one time to these dogs, respectively. Then, such blood serum enzymes as alaninaminotransferase (ALAT) and alkaline phosphatase (AP) were determined 24, 48 and 96 hours after the use of corticosteroids. It was discovered that the only one administration of dexamethasone sodium phosphate and methylprednisolone acetate in standard dosage can significantly increase ( $p < 0.05$ ) ALAT and AP mean values in dogs. The corticosteroid prednisolone acetate was used once in standard dosage and hydrocortisone aceponate spray was used once and did not statistically significantly ( $p > 0.05$ ) change the values of alaninaminotransferase (ALAT) and alkaline phosphatase (AP) in dogs' blood serum during this study.

**Key words:** dogs, corticosteroids, liver, blood serum enzymes.

**Introduction**

Corticosteroid or glyocorticoid therapy is often used on dogs (*Canis lupus familiaris*) with allergic, anaphylactic, autoimmune and other diseases (Badylak and van Vleet, 1981; Lucena et al., 1999; Abraham et al., 2006). There are a lot of different types of corticosteroids used in veterinary medicine. Between them are local and systemic medications, short and long-lasting types, spray, oral and injectable forms (Feldman and Nelson, 2004). The choice of use depends on a disease form, character and doctor's preference as well.

Corticosteroids have been used in medicine from 1948. At that moment only one type was discovered and it was cortisone, the synthetic form of the adrenal glands cortex hormone. Some authors of that period divided the history of medicine into two parts – 'before cortisol' and 'after cortisol' (Buttgereit et al., 2005). The doctors started to treat almost every disease with the administration of corticosteroids. Unfortunately, during next two years after 1948, there were described a lot of complications due to the corticosteroids usage. It was common to veterinary medicine as well. One of the most common pathologies in dogs that were treated with corticosteroids is a steroid hepatopathy. First time in scientific studies it was mentioned about 45 years ago (Wimberly et al., 1969). Steroid hepatopathy is corticosteroid induced alterations in liver morphofunctional condition; this is a specific pathology only in dogs (Fittschen and Bellamy, 1984, Feldman and Nelson, 2004). Until now this pathology is not sufficiently described and the main question is: why steroid hepatopathy develops so fast in almost all dogs? Recent findings showed us that there might not be only hepatocyte injury but the specific reaction of

liver stellate Ito cells producing liver fibrosis as well (Sobczak-Filipiak et al., 2014). The investigations in this direction are ongoing.

It is discovered that increased values of such blood serum enzymes as alaninaminotransferase (ALAT), aspartataminotransferase (ASAT), gammaglutamyl-tranferase (GGT), alkaline phosphatase (AP) and corticosteroid-induced thermostable alkaline phosphatase (cAP) are specific for the steroid hepatopathy (Badylak and van Vleet, 1981; Lucena et al., 1999). Increased ALAT and AP values are common to biochemical indicators in the diagnostics of the liver disease (Center et al., 1992).

It is proved that corticosteroids usually cause changes in 2 – 3 days after the beginning of the therapy (Dillon et al., 1980; Center et al., 2005). Unfortunately, it is not mentioned or the information is not available how many administrations of different types of corticosteroids and dosage a dog needs to develop steroid-induced hepatopathy and how significant the injury is.

**The aim of the study** was to determine whether and how significant the liver functional changes after one administration of different kind of corticosteroids in standard dosages are.

**Materials and Methods**

The study took place in private veterinary clinics in Riga, Latvia during 2013 – 2014, with the permission of dogs' owners. We discussed all advantages and risks of this study and made a signed contract with every dog's owner before the study. Twenty dogs participated in the study. Dogs were of different age, conditions, breeds and genders. All of them had different pathologies, and we prescribed

treatment of corticosteroids. They were divided into four groups, five dogs in each group, depending on corticosteroid usage. All chosen medications were used only once on the first day of study. For the first group we used dexamethasone sodium phosphate in intramuscular route in dosage 2.0 mg kg<sup>-1</sup>, for the second – prednisolone acetate in intramuscular route in dosage 2.0 mg kg<sup>-1</sup>, for the third – methylprednisolone acetate in intramuscular route in dosage 2.0 mg kg<sup>-1</sup> and for the fourth – hydrocortisone aceponate spray locally. It was impossible to find out the dosage of hydrocortisone spray per kilogram because it depends on the size of the lesions.

To find out the influence and the impact of different corticosteroids on hepatic function, such blood serum enzymes as alaninaminotransferase (ALAT) and alkaline phosphatase (AP) were determined on the second day of study, 24 hours after the use of corticosteroids, third, 48 hours after the medication use, and the fifth day, 96 hours after the medication use. We determined the same blood serum enzymes one day before the study to be sure that they are within reference ranges. The blood samples were collected from each animal *v. cephalica*. We centrifuged the blood on 1,300 rounds per minute for 10 minutes to separate the blood serum from the erythrocyte mass (Gulbis, 2011). We analyzed the serum within 15 minutes after the separation. ALAT and AP were determined in serum by biochemical analyzer 'MINDRAY BS-120' at the morphofunctional laboratory of Faculty of Veterinary Medicine, Latvia University of Agriculture

It was proven that the concentration of the hepatic enzymes increased because of the hepatotoxic drug influence (Fittschen and Bellamy, 1984). The steroid hepatopathy usually develops in dogs 2 – 3 days after the use of corticosteroids (Dillon et al., 1980; Center

et al., 2005). We used corticosteroids only once on the first day of study.

The programs MS Excel and 'RStudio' were used for data analysis. P-values less than 0.05 were considered to be statistically significant. T-test was used for the comparison of blood serum enzymes values.

## Results and Discussion

**One day before the study**, i.e., one day before the use of corticosteroid (Day 0), we determined alaninaminotransferase and alkaline phosphatase in each dog. It was found that all the enzyme concentrations are within reference limits (see Table 1).

**On the second day of the study**, 24 hours after the corticosteroid use, such blood serum enzymes as ALAT and AP were determined in all the groups. There was not a significant difference ( $p > 0.05$ ) in alaninaminotransferase (ALAT) concentrations between all the groups and in comparison with the values from the day 0 (a day before the use of corticosteroids). It became apparent that after 24 hours of corticosteroids' usage the change of the concentrations of ALAT is not significant. This fact indirectly reflects that at that moment the hepatic function was not changed or was changed insignificantly regardless of chosen corticosteroid. According to the alkaline phosphatase concentration in the blood serum on the second day of study, it was a significant increase ( $p < 0.05$ ), 2.4 times higher than on the day 0, in the values of the group 1, which was the group where dexamethasone was used. It was mentioned before that AP increase was noticed because of specific thermostable form of alkaline phosphatase, which was produced by hepatocytes due to corticosteroid injury (Badylak et al., 1981). Other

Table 1

### The values of ALAT and AP in dogs during the study

Parameters	Reference limits (Willard and Tvedten, 2012)	Groups**	Day 0	Day 2	Increase from Day 0 (times)	Day 3	Increase from Day 0 (times)	Day 5	Increase from Day 0 (times)
ALAT	10 – 94 U L <sup>-1</sup> *	1.	51.2±26.3	62.2±27.4	1.2	118.9±18.0	2.3	59.8±24.9	1.2
		2.	60.6±16.6	62.0±18.0	No	61.7±10.4	No	64.5±12.8	No
		3.	52.8±7.4	61.1±6.5	1.2	93.9±30.6	1.8	111.6±16.6	2.1
		4.	42.5±21.3	42.5±16.2	No	41.1±15.4	No	39.9±16.8	No
AP	0 – 90 U L <sup>-1</sup>	1.	30.4±17.6	72.3±24.9	2.4	94.3±8.4	3.1	73.3±13.1	2.4
		2.	65.2±26.9	67.1±22.3	No	66.9±24.0	No	69.1±12.3	No
		3.	48.8±16.4	55.9±10.7	1.1	97.8±16.1	2.0	117.4±30.0	2.4
		4.	58.2±19.6	52.0±20.5	No	52.3±10.3	No	59.7±11.6	No

\* U L<sup>-1</sup> – units per liter;

\*\* For the first group (1.) – dexamethasone sodium phosphate was used; the second (2.) – prednisolone acetate; the third (3.) – methylprednisolone acetate and the fourth (4.) – hydrocortisone aceponate spray locally.

groups did not show a significant increase ( $p>0.05$ ) on the second day of the study in comparison to the day 0.

**On the third day of the study**, 48 hours after the corticosteroid use, the same blood serum enzymes were determined. The mean value of ALAT in dogs from the group one and three, which were the groups where dexamethasone and methylprednisolone acetate, respectively, were used, on the third day increased to  $118.9\pm 18.0\text{ U L}^{-1}$  and  $93.9\pm 30.6\text{ U L}^{-1}$ , which was 2.3 and 1.8 times higher than ALAT value on the day 0; both values were significantly higher ( $p<0.05$ ) than the concentration of ALAT on the day 0 (see Table 1). The mean value of the alkaline phosphatase (AP) in dogs from the group one and three increased to  $94.3\pm 8.4\text{ U L}^{-1}$  and  $97.8\pm 16.1\text{ U L}^{-1}$ , respectively, both values were significantly higher ( $p<0.05$ ) than the concentration of AP on the day 0 (see Table 1). The mean values of ALAT and AP in dogs from the groups two and four, where prednisolone and hydrocortisone spray were used, did not significantly change ( $p>0.05$ ) in comparison to the day 0 (see Table 1).

**On the fifth day of the study**, 96 hours after the corticosteroid injection, the last time ALAT and AP were determined. The significant difference ( $p<0.05$ ) from the day 0 in ALAT mean value was discovered only in the group three, where long-lasting methylprednisolone acetate was used once. It was important to mention that the increase was even higher than in the same group on the day 3, 1.8 times and 2.1 times, respectively. The mean value of AP in dogs from the group one and three increased to  $73.3\pm 13.1\text{ U L}^{-1}$  and  $117.4\pm 30.0\text{ U L}^{-1}$ , respectively, both values were significantly higher ( $p<0.05$ ) than the concentration of AP on the day 0 (see Table 1). The mean values of ALAT and AP in dogs from the groups two and four did not significantly change ( $p>0.05$ ) in comparison to the day 0 even on the fifth day (see Table 1).

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It should be noted that ALAT and AP mean values in the group one, where dexamethasone injection was used, had a tendency to decrease on the day 5, but the same values in the group three, where methylprednisolone acetate was used, had a tendency to increase.

The results of this study prove the fact of the negative effect induced by some corticosteroids, such as dexamethasone and methylprednisolone acetate, to the liver functional condition (Badylak and van Vleet, 1981; Lucena et al., 1999; Center et al., 2005; Abraham et al., 2006). These negative effects have been reflected by enzymes ALAT and AP significant increase in blood serum. It should be noted that despite some scientific information about the use of corticosteroids, one injection of prednisolone in standard dosage and hydrocortisone spray did not significantly ( $p>0.05$ ) change liver functional condition during this study.

## Conclusions

1. The corticosteroid dexamethasone sodium phosphate and long-lasting methylprednisolone acetate used once in standard dosage statistically significantly increase the values of alkaline phosphatase (AP) after 24 hours from the injection time and the values of both alaninaminotransferase (ALAT) and alkaline phosphatase (AP) in dogs' blood serum after 48 hours from the injection time.
2. The mean values of alaninaminotransferase (ALAT) and alkaline phosphatase (AP) have the tendency to increase after 48 and 96 hours from the injection of methylprednisolone acetate.
3. The corticosteroid prednisolone acetate used once in standard dosage and hydrocortisone aceponate spray used once did not statistically significantly change the values of alaninaminotransferase (ALAT) and alkaline phosphatase (AP) in dogs' blood serum during this study.

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