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Topical Review

A Pilot Study Exploring the Plasma Potassium Variation in Dogs Undergoing Steroid Therapy and Its Clinical Importance

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In most situations in veterinary medicine, glucocorticoids are the drugs of choice used, that is, to reduce the inflammatory response or limit an inappropriate immune response. Their use in long-term therapy may cause side effects that may weaken the patient. The aim of the study was to evaluate possible variations in the plasma potassium concentrations and their clinical relevance in dogs undergoing steroid therapy with methylprednisolone in anti-inflammatory doses. The study used a sample of 21 dogs ($n = 21$) presented for consultation, with a clinical condition requiring a corticosteroid therapeutic protocol with an anti-inflammatory dose of methylprednisolone. All the individuals were submitted to a corticosteroid therapeutic protocol administered orally during 18 days. During this period, 3 time points were considered: T0 (the day the prescription was first given), T1 (3 days later), and T2 (8 days later). Blood samples were collected from a peripheral vein to measure plasma potassium concentrations in T0, T1, and T2. Corticosteroid therapy on an outpatient basis statistically significantly decreased plasma potassium levels, especially between T1 and T2 ($P = .03$). The plasma potassium levels decreased in 12.5% of the males, compared with a decrease of 23.1% in the females. No statistically significant relationships were observe between the decreased plasma potassium levels and age, clinical condition, and patient's body weight. However, we found a statistically significant association between decreased plasma potassium levels and sex. The study results may justify the need for the systematic prescription of potassium supplements in patients undergoing steroid therapy, similar to what already occurs in human medicine.

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Introduction

In most situations in veterinary medicine, glucocorticoids are used to reduce the inflammatory response or limit an inappropriate immune response. Their effects vary with the type of glucocorticoid, its potency, the type of dosage form, the dose administered, the route of administration, the duration of treatment, and individual factors.[1] Depending on the biological half-life period, glucocorticoids can be divided into the following 3 groups: short-acting glucocorticoids with a half-life lower than 12 hours (hydrocortisone and cortisone); intermediate-acting glucocorticoids with a half-life between 12 and 36 hours (prednisone, prednisolone, triamcinolone, and methylprednisolone); or long-acting glucocorticoids with a half-life greater than 48 hours (betamethasone and dexamethasone).[1-3] The anti-inflammatory potency of methylprednisolone is approximately 5 times higher than that of cortisol, and its mineralocorticoid activity is negligible.[4] Although glucocorticoids are the drugs of choice, their use in long-term therapy may cause side effects that may weaken the animal or not be tolerated by owners. The most common side effects are polyuria, polydipsia, muscle weakness, skin changes, predisposition to infections, gastrointestinal ulcers, and muscle atrophy. They can also cause insulin resistance, hyperglycemia, and hepatic disease. Tolerance to side effects varies from patient to patient. Large dogs are particularly sensitive, and cats are more resistant to these effects than dogs.[2] At the kidney level, glucocorticoids may increase the glomerular filtration rate, excretion of water, sodium and chlorine retention, and the excretion of potassium and calcium.[1,3] This can lead to hypokalemia and hypocalcemia, which are described as rare.[4] The poor preservation of potassium may be due to a decreased resorption at the ascending portion of Henle's loop level or an increase in secretions at the distal nephron level.[5] These effects may result from glucocorticoids' interference with the actions of vasopressin, the renin-angiotensin system,[3,6,7] the epithelial sodium channel,[7] aquaporin-2 channels, prostaglandins, or Na+/K+ pumps either directly or through brokers.[7-10] Human patients receiving corticosteroid therapy rarely develop clinical hypokalemia. However, when this occurs, it may have serious effects on skeletal muscles and the myocardium. The increased risk of atrial fibrillation observed in patients undergoing corticosteroid treatment may be in part due to hypokalemia. To the authors' knowledge, no studies have been conducted to date with dogs to examine this issue. In prevention, this may justify the systematic prescription of potassium supplements to veterinary patients undergoing treatment with glucocorticoids, which is already practiced in human patients.[11] The present study aimed to evaluate possible variations in the plasma potassium concentrations and their clinical relevance in dogs undergoing steroid therapy with methylprednisolone in anti-inflammatory doses.

Materials and Methods

The study used a sample of 21 individuals ($n = 21$) of the species *Canis familiaris* presented for consultation. The individuals had a clinical condition requiring a corticosteroid therapeutic protocol with an anti-inflammatory dose (0.5 mg/kg) of methylprednisolone administered orally in an outpatient setting for a period of 18 days. The prescribed drug protocol included the

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methylprednisolone administration each 12 hours in the first 3 days, each 24 hours in the next 5 days, and every 48 hours during the last 10 days of treatment. The inclusion criteria for all patients in the study included the ability to follow-up with all patients during an 18-day period and access to peripheral blood to measure plasma potassium concentrations at 3 time points—T0 (the day the prescription was first given), T1 (3 days later), and T2 (8 days later). The design of the study was approved by the Clinical Board, and the study began only after obtaining informed consent from the patients' owners. The samples were collected in an aseptic manner by directly puncturing the cephalic or saphenous veins. The blood samples were then placed in lithium heparin tubes and immediately used to measure the potassium values. A control group was also formed with 21 individuals not submitted for corticosteroid therapy and without any diagnosed clinical disease. These animals were surgical patients subject to elective spay surgery, and their plasma potassium levels were measured during their routine presurgical examinations. At no time were these animals regarded as experimental animals. To measure the plasma potassium levels, we used the Reflotron device that allowed us to measure plasma potassium concentrations between 2.0 and 12.0 mmol/L. The analysis was performed according to the recommendations from the device manufacturer. The plasma potassium levels were defined as follows: normokalemia if the values were within the reference range established by the manufacturer; mild hypokalemia if the values were within the range of 3-3.5 mmol/L; and moderate hypokalemia if the values were within the range of 2.5-3 mmol/L. Statistical analysis was performed in the sample throughout the considered therapeutic period and in each time point (from T0-T2) to evaluate the average, median, minimum, maximum, and standard deviation of the plasma potassium levels. For statistical analysis, we used the Statistics 12 software. The Shapiro-Wilk test was used to test the normality of the sample, followed by a paired *t*-test for correlated samples. We also performed an analysis of variance with the repeated measures analysis of variance (ANOVA) test for correlated samples to verify the existence of statistically significant changes in plasma potassium levels in groups of individuals of different sexes, clinical conditions, ages, and weights. Values of $P < .05$ were considered statistically significant.

Results

Table 1 characterizes the used sample, consisting of a total of 42 individuals divided in the following 2 groups: control group and study group, each with 21 specimens of both sexes. Study sample presented a group with 13 females (62%) and 8 males (38%), with an average age of 8.4 years, and a body weight mean of 12.35 kg. Clinical situations with indication for corticosteroid therapy protocol were disc hernia in 14 cases (67%), atopy in 3 cases (14%), and the remaining 4 cases (19%) with dermatitis, furunculosis, and cauda equina syndrome. Table 1 presents the Shapiro-Wilk test results where it is possible to verify that all data presented a normal distribution, and also we can observe that the mean, maximum, and minimum values of study group potassium assays gradually decreased during the treatment period. However, the average and the median are within the reference range. The average is always a value close to the median and standard deviation values are low, which suggest that the sample values have a normal distribution. Furthermore, the standard deviation of the last assay was inferior to others, which not only indicates that the distance of each measurement to the average decreased, but also shows that the variability decreased. This can also be confirmed by the following box diagram (Fig 1). Control group presented a plasma potassium mean of 3.96 ± 0.29 mmol/L, with a minimum of 3.50 mmol/L and a maximum of 4.40 mmol/L, within the reference range for the species considered between 3.5 and 4.6 mmol/L. In the study group, before steroid therapy initiation (T0), it was found that 4 of 21 cases (19.1%) showed mild hyperkalemia (within the range: 4.6-5.1 mmol/L), 15 patients (71.4%) had normokalemia, and 2 cases (9.5%) had mild

Table 1
Sample Characterization For Age, Body Weight, Sex, Breed, and Serum Potassium Levels in the 3 Time Points Considered: T0, T1, and T2

Type of Group	Parameter		*N*	$\bar{x}$	SD	Min	Max	SW Test *P* Value
Control	Age, y		21	8.66	2.39	5.4	11.4	.76
Study			21	8.4	2.81	5.0	12.0	.68
Control	Body weight, kg		21	9.97	3.69	6.95	16.0	.80
Study			21	12.3	4.14	7.5	17.9	.76
Control	Sex	Female	10	–	–	–	–	–
		Male	11	–	–	–	–	–
Study		Female	13	–	–	–	–	–
		Male	8	–	–	–	–	–
Control	Breed	Crossbreed	14	–	–	–	–	–
		Poodle	6	–	–	–	–	–
		Pug-Carlin	1	–	–	–	–	–
Study		Crossbreed	12	–	–	–	–	–
		Poodle	6	–	–	–	–	–
		Pequinois	2	–	–	–	–	–
		French Bulldog	1	–	–	–	–	
Control	Clinical disease	–	21	–	–	–	–	–
Study		Disc hernia	14	–	–	–	–	–
		Atopy	3	–	–	–	–	–
		Dermatitis	1	–	–	–	–	–
		Furunculosis	2	–	–	–	–	–
		Cauda equina syndrome	1	–	–	–	–	
Control	Serum potassium level	T0	21	3.96	0.29	3.50	4.40	.72
Study		T0	21	4.07	0.55	3.07	5.10	.65
		T1	21	4.01	0.56	2.90	4.98	.46
		T2	21	3.86	0.46	2.82	4.60	.07

To test sample normality at the considered time points, the Shaphiro-Wilk test was used.
Max, maximum; $\bar{x}$, mean; min, minimum; *N*, sample; SD, standard deviation; SW test, Shaphiro-Wilk test.

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