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Effects of desmopressin acetate administration in healthy dogs receiving prednisolone

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Abstract

Background: Glucocorticoids are used for a variety of purposes in veterinary medicine but often are associated with clinically important adverse effects. Polyuria and polydipsia are the most frustrating adverse effects noted by owners.

Objective: To determine whether administration of desmopressin ameliorates polyuria and polydipsia associated with prednisolone administration.

Animals: Seven healthy adult Walker Hounds.

Methods: Prospective hypothesis testing study. Daily water intake and urine specific gravity (USG) were measured in dogs under 4 separate sequential conditions: no medications (C), prednisolone only (P), prednisolone and desmopressin (PD), and prednisolone after discontinuation of desmopressin (PAD).

Results: When compared to baseline, 6 of 7 dogs became polydipsic after administration of prednisolone (0.5 mg/kg PO q12h). When desmopressin (5 μg/dog SC q12h) was administered to dogs receiving prednisolone, significant decreases in water intake and serum sodium concentration occurred, and USG increased significantly.

Conclusions and Clinical Importance: Administration of desmopressin to dogs receiving prednisolone significantly decreased water intake and serum sodium concentration, and increased USG. Our results suggest that, in some dogs, desmopressin ameliorates the most important adverse effect of prednisolone noted by owners, but that hyponatremia is an important complication associated with desmopressin use.

KEYWORDS
glucocorticoids, polydipsia, polyuria, urine specific gravity

1 | INTRODUCTION

Glucocorticoids, including prednisolone, are used in the treatment of many diseases in veterinary medicine.[1-3] These include dermatologic diseases in which anti-inflammatory effects are beneficial in providing patient comfort, as well as immune-mediated diseases in which higher doses are used for immunosuppression.[3,4] Glucocorticoids, however, have adverse effects, including polyphagia, muscle wasting, polyuria, and polydipsia.[1,3,5,6] Proposed mechanisms for the polyuria and polydipsia induced by glucocorticoids include primary polydipsia and

Abbreviation: ADH, antidiuretic hormone

antagonism of the antidiuretic hormone (ADH) receptor.[7] Polyuria and polydipsia may become a quality of life issue for both owners and their pets.[8] Because these adverse effects are dose-related,[8] owners may independently decrease doses or discontinue medications to alleviate adverse effects. Doing so may lead to inadequate treatment response or disease relapse.

Desmopressin, a synthetic analogue of ADH, has been used to treat central diabetes insipidus, a disease in which ADH production is deficient.[9] It also has been used successfully in the treatment of nocturia in children,[10] most often by PO administration 60 minutes before bedtime.[11] Efficacy is often evident immediately, and approximately 67% of children will have an intermediate to the full response.[12] To our knowledge, use of desmopressin as an adjunctive treatment to decrease polyuria and polydipsia in dogs being treated with glucocorticoids has not yet been evaluated.

We aimed to determine whether concurrent administration of desmopressin during prednisolone treatment would lead to a decrease in water consumption and increase in urine specific gravity (USG). A secondary aim was to assess the safety of administration of desmopressin, specifically in relation to serum sodium concentration.

2 | MATERIALS AND METHODS

2.1 | Study design

Experiment and animal care protocols were approved by Mississippi State University Institutional Animal Care and Use Committee (IACUC). Mississippi State University is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

Seven adult Walker Hounds, members of a research colony of healthy dogs, underwent screening before drug administration including a complete physical examination as well as a CBC, serum biochemistry profile, and urinalysis; no clinically relevant abnormalities were identified. In 1 dog, USG rather than full urinalysis was performed because of insufficient sample quantity. Each day, water intake and USG were measured for each dog. To determine water intake each day, water remaining in the water bowl was measured using a graduated cylinder. This amount was subtracted from the known amount of water that was placed in the bowl the previous morning. The bowl then was emptied and a measured amount of water was used to fill the bowl for the next day. Water bowls were secured to the sides of the kennels to prevent spillage.

In addition to urinating in their kennels and while walked in the morning and evening, the dogs were walked between 11:00 am and 1:00 pm daily, and body weight was recorded and a voided urine sample collected. If urine could not be collected at this time, it was obtained either during an additional walk before 5:00 pm, or from a sample collected from the floor of the dog's run. The USG was measured on these afternoon samples using a standard refractometer (Reichert Vet 360). These procedures were followed for 5 days before administration of any medication to the dogs. This period was considered the control (C) period.

2.2 | Treatment

Starting on day 6, prednisolone (PrednisTab, Lloyd, Inc of Iowa) was administered to each dog at a dosage of 0.5 mg/kg PO q12h, for a total daily dose of 1 mg/kg/d. Medication administration occurred in the morning at approximately 7:00 am and in the evening at approximately 7:00 pm Daily water intake and USG then were measured as described for days 1-5. This time was the prednisolone (P) treatment period, and lasted for 7 days (days 6-12).

After 7 days of PO prednisolone administration, desmopressin acetate (Sun Pharma, Cranbury, New Jersey) administration was started in 6 of 7 dogs, at a dose of 5 μg SC q12h for 5 days (days 13-17). During this time period, daily water intake and USG were measured as previously described.

After finishing the desmopressin treatment, daily prednisolone treatment was continued and daily water intake and daily USG measured as previously prescribed for 5 additional days (days 18-22). This time was the prednisolone after desmopressin treatment period (PAD).

Serum samples were collected by jugular venipuncture for measurement of serum sodium concentration, starting on day 13, after 7 days of prednisolone treatment, and immediately before desmopressin administration that morning. Serum electrolyte concentrations then were measured q72h thereafter (on days 16 and 19) to monitor for hyponatremia.

3 | STATISTICAL METHODS

Descriptive and inferential statistics were performed using commercially available statistical software (SAS for Windows v. 9.4, SAS Institute, Inc, Cary, North Carolina). For each dog, mean USG and mean water intake were calculated for each treatment period, using results from the last 3 days of each treatment. Serum sodium concentration was measured once in each dog during each treatment period. The effect of treatment on mean USG, water intake, and serum sodium concentration was assessed using a generalized linear mixed model within PROC MIXED. For each model, patient identity was considered a random variable. Inspection of conditional residuals was used to assess if model assumptions were met. The model of water intake did not meet the assumptions of homoscedasticity and normality of the residuals, so the data for outcome water intake was $\log_{10}$ transformed. To accommodate the use of patient identity in each linear mixed model as a random effect, least square means were calculated for each level of treatment. An LSMESTIMATE statement was used to make the following sequential comparisons among treatment levels: control (C) vs prednisolone (P), prednisolone (P) vs prednisolone plus desmopressin (PD), prednisolone plus desmopressin (PD) vs prednisolone after desmopressin (PAD), prednisolone (P) vs prednisolone after desmopressin (PAD), and control (C) vs prednisolone plus desmopressin (PD). The simulated adjustment for multiple comparisons was used to adjust *P* values for the differences in the least squares means of treatment levels.

TABLE 1 Treatment means ± standard deviations for urine specific gravity, water intake (back-transformed), and sodium concentration

Treatment	Urine specific gravity	Water intake (mL/kg)	Sodium (mEq/L)
Control (C)	1.034 ± 0.0067	38.90 ± 1.219	143.4 ± 1.55
Prednisolone (P)	1.020 ± 0.0113	85.11 ± 1.585	142.9 ± 1.90
Prednisolone + desmopressin (PD)	1.046 ± 0.0136	47.86 ± 1.343	136.2 ± 3.99
Prednisolone after desmopressin (PAD)	1.014 ± 0.0068	141.25 ± 1.493	145.2 ± 2.97

Treatment means and their standard deviations for each of the outcomes are presented in Table 1. Dog body weight at the beginning of the treatment period, compared to body weight at the end of the treatment period, was evaluated using a paired sample *t* test in PROC TTEST. An alpha level of .05 was used to determine statistical significance.

4 | RESULTS

4.1 | Baseline characteristics of study subjects

Seven dogs initially were enrolled. All received prednisolone as described. Six of 7 dogs received desmopressin injections as described. Desmopressin was withheld from 1 dog because it did not become polydipsic or polyuric during the prednisolone treatment period. This dog's 3-day mean water intake was 56 mL/kg/d, and its urine remained concentrated with a 3-day mean USG of 1.033. Therefore, concern for development of free water overload and hyponatremia after desmopressin precluded safe administration. Data from this dog was excluded from analysis of serum sodium concentrations.

4.2 | Effect of treatment on USG and water intake

Administration of desmopressin significantly decreased water intake and increased USG. Treatment means and their standard deviations for each of the outcomes are presented in Table 1. Treatment least squares means and their standard errors for each of the outcomes from the linear mixed model are presented in Figures 1-3. During prednisolone administration, $\log_{10}$ water intake was significantly increased ($P < .001$) and USG was significantly decreased ($P = 0.01$) compared to the control period. When desmopressin treatment was started, $\log_{10}$ water intake decreased significantly ($P = 0.007$) and USG increased significantly ($P < 0.001$). However, once desmopressin treatment was withdrawn, $\log_{10}$ water intake increased significantly ($P < 0.001$) and USG decreased significantly ($P < 0.001$) compared to the previous treatment period, PD.

A large amount of individual variation was observed in both the polydipsia induced by prednisolone and the improvement (decreased water consumption) in response to desmopressin. Of the 6 dogs treated with desmopressin, the mean decrease in water consumption was 53.4 mL/kg/d (Table S1).

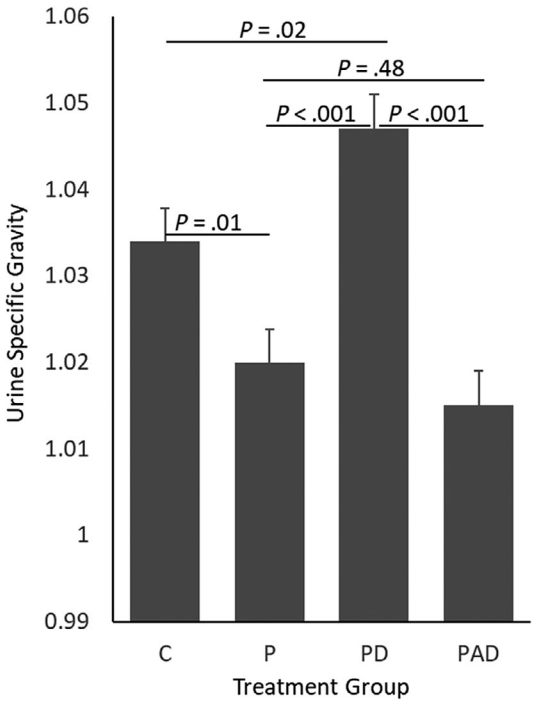

FIGURE 1 Bar chart showing comparisons of linear mixed model least squares means with SE bars of urine specific gravity between treatment groups (C = control, P = prednisolone, PD = prednisolone and desmopressin, PAD = prednisolone after desmopressin). Horizontal lines with *P* values illustrate the comparisons between treatment groups at each end of the line

4.3 | Effect of treatment on serum sodium concentration

No significant difference was detected when serum sodium concentration treatment was compared to those after administration of prednisolone. A significant decrease in serum sodium concentration occurred after administration of desmopressin and a significant increase occurred 36 hours after desmopressin was discontinued while the dogs still were receiving prednisolone (Figure 3). In the model of serum sodium concentration, treatment level comparisons of least square means were as follows: C vs P ($P = .98$), P vs. PD ($P = .001$), PD vs PAD ($P < .001$), P vs PAD ($P = .40$), and C vs PD ($P = .001$).

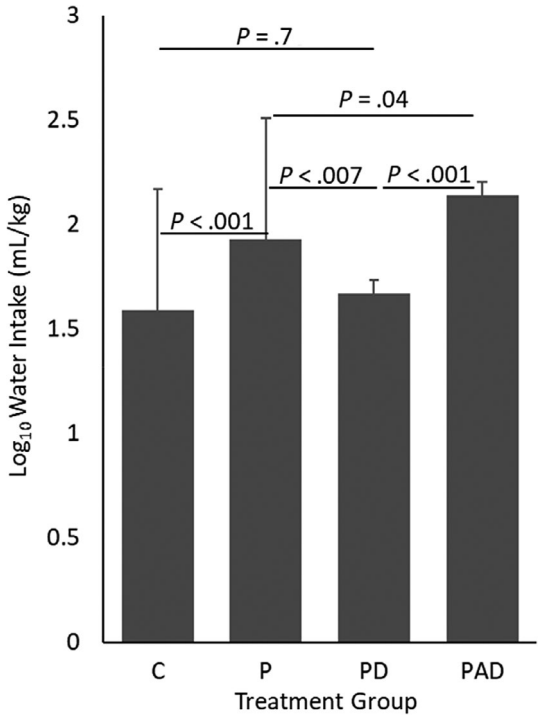

FIGURE 2 Bar chart showing comparisons of linear mixed model least squares means with SE bars of log_{10} water intake between treatment groups (C = control, P = prednisolone, PD = prednisolone and desmopressin, PAD = prednisolone after desmopressin). Horizontal lines with *P* values illustrate the comparisons between treatment groups at each end of the line

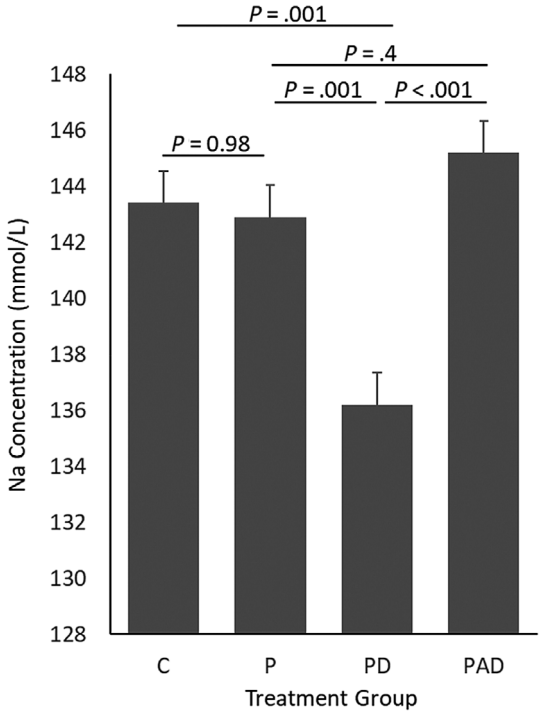

FIGURE 3 Bar chart showing comparisons of linear mixed model least squares means with SE bars of sodium concentration between treatment groups (C = control, P = prednisolone, PD = prednisolone and desmopressin, PAD = prednisolone after desmopressin). Horizontal lines with *P* values illustrate the comparisons between treatment groups at each end of the line

4.4 | Effect of treatment on weight

Dog weight at the start of the treatment period (mean 27.96 ± 5.85 kg) was higher than dog weight (26.39 ± 5.79 kg) at the end of the treatment period ($P < .001$).

5 | DISCUSSION

Our results indicate that administration of desmopressin significantly decreased the polyuria and polydipsia exhibited by dogs during prednisolone administration. These results support previous research that suggests prednisolone causes polyuria and polydipsia by either inhibiting release of ADH[7,13] or antagonizing the action of ADH in the renal tubule.

In all but 1 dog, USG was higher in dogs treated with desmopressin when the C group was compared to the PD group, and the comparison of least square means showed a significant difference in C vs PD ($P = .02$). A significant decrease in serum sodium concentration occurred in the dogs receiving prednisolone when desmopressin was added as a treatment (P vs PD, $P = .001$), and the least square means comparison of serum sodium concentration between C and PD showed a significant decrease in the PD group ($P = .001$). Additionally, the least square means of $logH_2O$ mL/kg was not different between C and PD ($P = .7$). This finding suggests that, when compared to C, desmopressin administration normalized the increased water intake caused by prednisolone, and caused the urine to be concentrated compared to C, causing free water retention and a decrease in serum sodium concentration. This result is likely a consequence of renal free water reabsorption caused by the desmopressin and unrestricted water intake in the dogs. This finding supports that the polyuria and polydipsia caused by prednisolone are a result of inhibition of pituitary secretion or renal tubular action of ADH. A lower dose of desmopressin may have prevented or lessened the decrease in serum sodium concentration.

The magnitude of decrease in serum sodium concentrations in some of the dogs in the PD group was clinically relevant. Although the least square means serum sodium concentration in the PD group was 136 mEq/L, 1 dog decreased from 142 mEq/L to 131 mEq/L. This decrease took place over a 3-day period. Acute decreases in serum sodium concentration can be detrimental, resulting in seizures and cerebral edema.[14] No clinical signs associated with the decreased serum sodium concentration were noted in any of the dogs in our study. Concurrent desmopressin and prednisolone treatment was only continued for 5 days and it is difficult to know if serum sodium concentrations would have continued to decrease more over a longer period of time. Additionally, 1 dose of desmopressin (5 μg) was used for all dogs. A lower dose may have resulted in less clinically relevant

hyponatremia. Although water restriction also would lessen the severity of hyponatremia, it was not attempted, and water restriction is not recommended in clinical patients because of potential complications associated with excessive restriction. In people with diabetes insipidus and hyponatremia associated with desmopressin use, it is recommended to skip 1 dose of desmopressin per week to allow for aquaresis.[15]

In our study, prednisolone was chosen as the glucocorticoid administered at a dosage of 1 mg/kg/d, representing what many practitioners use as the high end of the anti-inflammatory dosage. Administration of different prednisolone dosages would be expected to result in similar adverse effects but of potentially different magnitudes. Desmopressin was administered SC rather than PO or conjunctivally to ensure consistent absorption. Oral or conjunctival administration may have produced different results.

One dog in our study (dog 2) did not become polydipsic after administration of prednisolone, and desmopressin was withheld because of concern that desmopressin would cause hyponatremia. Thus, it is important to note that not all dogs given 1 mg/kg/d of prednisolone will become polydipsic. Furthermore, desmopressin should not be administered to dogs given prednisolone without first establishing the presence of polyuria and polydipsia because the magnitude resultant of hyponatremia is unknown and may not be safe. Interestingly, the dogs lost weight over the course of the study which is suspected to be a consequence of muscle catabolism.

Our study had several limitations. Only 1 breed of dog, the Walker Hound, was utilized; other breeds may respond differently to prednisolone. However, substantial variation was noted, even within this breed. Although urine collection was attempted at noon each day (approximately 6 hours after morning medications were given), it was not successful in each individual dog and urine samples obtained within a 6-hour window were used in the statistical analysis. Cystocentesis would have allowed more consistency regarding timing of urine collection, but was not pursued because of concerns posed by the IACUC regarding daily cystocenteses. Additionally, water intake was measured based on how much water was remaining in the bowl. It is possible that some water was spilled throughout the day, but we attempted to minimize spillage by securing the bowls to the sides of the kennels.

Another limitation is that water intake was not measured after prednisolone was discontinued. Given that the water intake increased (nonsignificantly) after discontinuation of desmopressin while the dogs were still on prednisolone, it would have been interesting to determine if water intake decreased back to baseline after discontinuation of prednisolone.

Our study provides evidence that desmopressin may be useful in controlling polyuria and polydipsia in some dogs receiving prednisolone. Insufficient data however is available regarding appropriate dosage, and longer-term safety considerations still need to be determined. Future studies should include different routes of administration (conjunctival, PO) of desmopressin and adjustment of desmopressin dose based on serum sodium concentration.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC of Mississippi State University, protocol #20-159.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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