

STANDARD ARTICLE

Low-dose desoxycorticosterone pivalate treatment of hypoadrenocorticism in dogs: A randomized controlled clinical trial

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Abstract

Background: Desoxycorticosterone pivalate (DOCP) is a commonly used mineralocorticoid replacement for dogs with primary hypoadrenocorticism (HA), but manufacturer-recommended dosing protocols can be cost-prohibitive. Recent reports also have raised concerns that label dose protocols could be excessive.

Objective: To investigate the relative efficacy and adverse effects of 2 DOCP dosages in dogs with primary glucocorticoid and mineralocorticoid deficient HA.

Animals: Thirty-seven dogs, including 19 test population dogs and 18 controls.

Methods: Randomized controlled double-blinded clinical trial. Dogs with newly diagnosed primary HA were assigned to standard (2.2 mg/kg q30d, control population) or low-dose (1.1 mg/kg q30d, test population) DOCP treatment. Clinical and laboratory variables were assessed 10 to 14 days and approximately 30 days after each DOCP treatment for 90 days.

Results: Mean serum sodium to potassium ratios at reevaluations were ≥ 32 in both populations throughout the study. No dog developed electrolyte abnormalities warranting medical treatment, although hypokalemia occurred on at least 1 occasion in 9 controls and 6 test population dogs. Urine specific gravities (median, interquartile range) were lower in control dogs (1.022, 1.016-1.029) as compared to test population dogs (1.033, 1.023-1.039; $P = .006$). Plasma renin activity was overly suppressed on 84 of 104 (80.8%) assessments in control dogs whereas increased renin activity occurred on 23 of 112 (20.5%) assessments in test population dogs.

Conclusions and Clinical Importance: Low-dose DOCP protocols appear to be safe and effective for treatment of HA in most dogs. Standard-dose protocols are more likely to result in biochemical evidence of overtreatment.

KEYWORDS

Addison's disease, aldosterone, DOCP, renin

Abbreviations: DOCP, desoxycorticosterone pivalate; HA, hypoadrenocorticism; IQR, interquartile range; MSU-VMC, Michigan State University Veterinary Medical Center; PRA, plasma renin activity; RI, reference interval.

Alysha M. Vincent and Linda K. Okonkowski contributed equally to this work.

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1 | INTRODUCTION

Primary hypoadrenocorticism (HA), commonly termed Addison's disease, is a severe and potentially fatal disorder that causes a multitude of clinical signs ranging from intermittent vomiting and diarrhea to hypovolemic shock, cardiac arrhythmias, and death.^{1,2} Hypoadrenocorticism typically occurs because of adrenal gland failure, which is likely a consequence of immune-mediated destruction of the adrenal cortices.^{1,3-5} In addition to glucocorticoid deficiency, most affected dogs have concurrent mineralocorticoid deficiency.⁶ Aldosterone deficiency is responsible for many of the classic and severe biochemical abnormalities associated with HA such as hyperkalemia, hyponatremia, and metabolic acidosis.^{1,2} Intensive fluid therapy can partially compensate for aldosterone deficiency in the acute setting, but lifelong maintenance mineralocorticoid treatment is needed for most dogs.^{7,8}

Desoxycorticosterone pivalate (DOCP) is a long-acting synthetic mineralocorticoid administered by SC or IM injection at approximately once monthly intervals.⁹ Treatment with DOCP replaces the mineralocorticoid actions of aldosterone and prevents clinical and biochemical abnormalities associated with aldosterone deficiency.^{7,10} Decreasing arterial pressure and sodium load caused by aldosterone deficiency lead to hypersecretion of renin by the kidneys, and DOCP treatment also suppresses this increased renin activity in dogs with HA.¹⁰ Despite DOCP efficacy, drug costs can be substantial and preclude treatment for an otherwise readily treatable disease. Manufacturer-recommended starting dosages (2.2 mg/kg q25d)^{11,12} and manufacturer-reported average maintenance dosages (1.7-2.2 mg/kg)^{11,12} might be higher than what is required to adequately control HA because lower dosages and longer dosing intervals have been used successfully for HA management.¹³⁻¹⁵ Beyond the benefit of cost savings, the ability to utilize lower DOCP dosages or prolonged dosing intervals raises concerns that label-dose treatment protocols might result in mineralocorticoid excess. The administration of 2.2 mg/kg DOCP to healthy dogs does result in increases in serum sodium concentrations and decreases in serum potassium concentrations and urine specific gravities.¹² Although prolonging dosing intervals would decrease DOCP costs, the near-label DOCP dosages utilized with this strategy fail to address the possibility of mineralocorticoid excess.¹⁴

Treatment strategies using lower starting and maintenance dosages of DOCP would address concerns associated with both cost and over-treatment. Initial DOCP dosages of 1.5 mg/kg were reported to be effective for controlling clinical signs and serum electrolyte abnormalities in dogs with HA.¹⁵ Our experience at the Michigan State University Veterinary Medical Center (MSU-VMC) suggests that even lower starting and maintenance dosages are effective.¹³ It is unknown how these low-dose protocols compare with manufacturer-recommended protocols. Our objectives were to prospectively investigate the efficacy and adverse effect profile of both a standard-dose (2.2 mg/kg) and a low-dose (1.1 mg/kg) DOCP protocol in dogs with primary glucocorticoid- and mineralocorticoid-deficient HA. We hypothesized that both DOCP protocols would prevent biochemical evidence of mineralocorticoid deficiency, but that evidence of mineralocorticoid excess would be more likely to occur in the standard-dose population.

2 | MATERIALS AND METHODS

2.1 | Animals

A randomized, controlled, double-blinded clinical trial was conducted to evaluate 2 DOCP dosing protocols in dogs with primary glucocorticoid- and mineralocorticoid-deficient HA over a 90-day time period. A sample size calculation using prior hospital data and assuming probability (power) of 0.8 and α of .05 suggested studying 16 experimental subjects and 16 control subjects to be able to detect a difference in serum sodium to potassium (Na:K) ratio of 2.5 between groups. Although many variables could have been used in a sample size calculation, we utilized the Na:K ratio because DOCP package inserts recommend using this value to guide treatment decisions.^{11,12}

Dogs evaluated at the MSU-VMC that were suspected to have HA were screened for study participation. Dogs were required to have a serum biochemical profile performed at the time of initial evaluation or within the 72 hours before evaluation. Dogs were excluded from participation if they had received systemic or topical corticosteroids within 45 days of evaluation, had received previous treatment for hyperadrenocorticism, or had previous or active diagnoses of congestive heart failure or chronic kidney disease. Dogs receiving medications known to alter serum sodium or potassium concentrations, which included angiotensin converting enzyme inhibitors, aldosterone antagonists, diuretics, or fludrocortisone, also were excluded.

Dogs were included in the study if ACTH stimulation testing confirmed a diagnosis of HA and if evidence of a concurrent mineralocorticoid deficiency was present. The ACTH stimulation testing was performed by measuring serum cortisol concentrations immediately before and 1 hour after IV administration of 5 μ g/kg synthetic ACTH (Cosyntropin, Oakwood Laboratories LLC, Solon, Ohio, for Sandoz Inc, Princeton, New Jersey). Dogs were diagnosed with HA if both pre- and post-ACTH stimulated cortisol concentrations were ≤ 55 nmol/L (2 μ g/dL).¹ Mineralocorticoid deficiency was considered to be present if the serum or plasma biochemical profile at the time of evaluation had electrolyte abnormalities consistent with aldosterone deficiency. A Na:K ratio ≤ 27 (reference interval [RI], 29-37), hyponatremia with concurrent potassium concentration in the upper-half of the RI, or hyperkalemia with concurrent sodium concentration in the lower-half of the RI were considered to be electrolyte abnormalities indicative of aldosterone deficiency. Plasma aldosterone concentrations also were measured in some dogs at the discretion of the attending clinician, and abnormally decreased post-ACTH stimulated aldosterone concentrations (RI, 197-2103 pmol/L) were considered further support of aldosterone deficiency. Although not required for study participation, blood samples also were collected for baseline plasma renin activity (PRA) measurements when possible.

2.2 | Experimental protocol

Dogs meeting the above criteria were enrolled in the study. Dogs were required to undergo initial in-hospital stabilization that consisted of IV administration of crystalloid solutions and dexamethasone. Additional

symptomatic treatments and diagnostic testing during hospitalization were at the discretion of the attending clinician. Dogs were not discharged from the hospital until they were eating and the attending clinician deemed them to be hemodynamically stable. Dogs were assigned to DOCP treatment group in double-blinded fashion using a computer-generated randomization log. Control population (standard-dose) dogs were treated with 2.2 mg/kg DOCP (Dechra Veterinary Products, Overland Park, Kansas) SC approximately every 30 days for 90 days whereas test population (low-dose) dogs were treated with 1.1 mg/kg DOCP SC approximately every 30 days for 90 days. All DOCP treatments were administered by a technician to maintain blinding, and the DOCP dose was calculated at each visit to account for potential changes in body weight over time. The first DOCP treatment was administered in-hospital and no more than 48 hours before hospital discharge. All dogs were treated with prednisone PO for study duration, but attempts to standardize dosages were not made. Dogs returned for repeat evaluations 10 to 14 days after each DOCP injection and again at approximately 30 days (range, 25-35 days) after each DOCP injection. This resulted in dogs undergoing a total of 3 evaluations that were 10 to 14 days after DOCP treatments and a total of 3 evaluations that were approximately 30 days after DOCP treatments. At each evaluation, a physical examination, hematocrit, total plasma protein concentration, serum biochemical profile, urinalysis, urine protein-to-creatinine ratio, PRA measurement, and blood pressure measurement using Doppler sphygmomanometry were assessed. Any dog developing moderate to severe hyperkalemia (serum potassium concentration > 6.5 mmol/L) or clinical illness requiring hospitalization at any time during the study was withdrawn. Dogs also were removed from the study if they were treated with SC or IV crystalloid fluids after initial hospital discharge. The study was completed after the day 90 evaluation at which time treatment group was unmasked. Continued HA management was at the discretion of the attending or referring clinician, although owners of most control dogs were advised to pursue dose reductions under their veterinarian's guidance.

2.3 | Cortisol, aldosterone, and renin measurements

All samples were evaluated at the Michigan State University Veterinary Diagnostic Laboratory, which is an American Association of Veterinary Laboratory Diagnosticians-accredited laboratory. Serum cortisol concentrations were determined using a commercially available competitive chemiluminescent immunoassay (Immulite 2000 Cortisol, Siemens Healthcare Diagnostics Ltd, Gwynedd, UK) that has been described previously for use with canine serum samples in our laboratory and other laboratories.^{16,17} Plasma aldosterone concentrations were determined using a commercially available radioimmunoassay kit (ACTIVE Aldosterone RIA, Beckman Coulter Inc, Immunotech s.r.o., Prague, Czech Republic). Plasma renin activity was measured using a commercially available radioimmunoassay kit (Angiotensin I RIA, DIASource ImmunoAssays, Louvain-la-Neuve, Belgium). Any PRA results <0.16 ng/mL/h, which was the analytical sensitivity calculated in our laboratory, were treated as 0.08 ng/mL/h for reporting and statistical purposes. The RI for PRA established in our laboratory was 0.41

to 3.73 ng/mL/h, which was similar to the manufacturer reported RI of 0.6 to 4.2 ng/mL/h for upright humans. This was in agreement with other studies in which healthy dogs have been reported to have PRA similar to that of healthy humans.¹⁸ Descriptions of the assays for both aldosterone and PRA are available in Supporting Information (S1 and S2, respectively).

2.4 | Data and statistical analysis

Data sets were assessed for normality by Shapiro-Wilk testing and inspection of normal probability plots. Normally distributed data were reported as means \pm SDs whereas data not approximating normal distributions were reported as medians and interquartile ranges (IQRs). The effect of treatment over time on Na:K ratio was evaluated using a repeated-measures analysis of variance with Tukey's post hoc testing. Body weight and body condition scores at study completion were compared to those at baseline using a Wilcoxon signed rank test. The frequencies of selected biochemical abnormalities were compared between test and control populations using Fisher's exact testing. Spearman's rank correlation coefficients (ρ) were calculated to investigate potential relationships between PRA and serum electrolyte concentrations. For the above analyses, values of $P \leq .05$ were considered significant. Comparisons of variables between treatment groups at each of the 6 reevaluations were made using a Student's t test or a Mann-Whitney U test, and the Holm-Bonferroni adjustment was used to maintain the type I error rate (α) at $\leq .05$.¹⁹ For these intergroup comparisons, the adjusted critical values (α) are reported alongside the calculated P values. Statistical analyses were performed using commercially available software (GraphPad Prism Version 6.0; GraphPad Software Inc, La Jolla, California).

3 | RESULTS

3.1 | Animals

Thirty-nine dogs meeting initial inclusion criteria were enrolled in the clinical trial. One dog was removed after enrollment because it was discharged from the hospital before stabilization, at which time the Na:K ratio was <23. This dog subsequently received fluid therapy on an outpatient basis under the care of its primary veterinarian. Data from this dog were not included in the study. One control dog participated through the first 2 reevaluations, at which time the owner withdrew the dog because of scheduling conflicts. Data from this dog through day 30 were included in the study. The 37 dogs participating in the study included 19 test population dogs (1.1 mg/kg DOCP) and 18 controls (2.2 mg/kg DOCP). The test population consisted of 11 castrated males and 8 spayed females whereas the control population consisted of 9 castrated males, 1 intact male, and 8 spayed females. Only 1 dog in each population was <2 years of age at study commencement. Most dogs were medium or large breed, and only 1 dog in each population was <10 kg. Characteristics of the test and control populations were not different and are summarized in Table 1.

TABLE 1 Characteristics of the 37 dogs participating in a randomized controlled clinical trial in which 2 DOCP dosages were evaluated in dogs with hypoadrenocorticism

Variable	Test (n = 19)	Control (n = 18)	P value
Age (years)	4.3 ± 2.1	4.5 ± 2.5	.78
Sex (male/female)	11/8	10/8	.99
Weight (kg)	25.0 (16.2-33.6)	24.0 (18.5-36.0)	.99
Na:K ratio	18.8 ± 4.7	18.8 ± 4.9	.99
Prednisone (mg/kg)	0.12 (0.10-0.15)	0.11 (0.07-0.2)	.43

Note: Data are shown as mean ± SD, absolute number, or median (interquartile range) in the specified categories. Test population dogs received low-dose DOCP (1.1 mg/kg SC approximately every 30 days) whereas control dogs received label-dose DOCP (2.2 mg/kg SC approximately every 30 days). Values reflect those obtained during initial (baseline) evaluation for the categories of age, weight, and Na:K ratio. The prednisone category depicts the daily maintenance dosage of prednisone that dogs were receiving PO at the time of study conclusion. The P value reflects univariate comparisons of each variable between test and control dogs.

Abbreviation: DOCP, desoxycorticosterone pivalate.

All test and control population dogs had electrolyte abnormalities consistent with mineralocorticoid deficiency. Seventeen test population dogs were hyponatremic, 18 were hyperkalemic, and all 19 test population dogs had Na:K ratios ≤27 (RI, 29-37). Seventeen controls were hyponatremic, 17 were hyperkalemic, and 17 had Na:K ratios ≤27. Three dogs (1 test population and 2 controls), including 2 with mild hyperkalemia and low-normal serum sodium concentrations and 1 with mild hyponatremia and high-normal serum potassium concentrations, had post-ACTH stimulated aldosterone concentrations < 14 pmol/L (RI, 197-2103 pmol/L).

Glucocorticoid deficits were replaced by IV administration of dexamethasone during hospitalization and by PO administration of prednisone after hospital discharge. Initial prednisone dosages were variable, but were tapered to physiologic ranges over the first 7 to 10 days of treatment. Although prednisone dosing determinations were at the discretion of attending clinicians, the median (IQR) final daily maintenance dosages of 0.12 mg/kg (0.10-0.15 mg/kg) in test population dogs and 0.11 mg/kg (0.07-0.2 mg/kg) in control dogs were not different ($P = .43$).

3.2 | Clinical effects

Dogs did not develop clinical illness during the course of the study that required hospitalization or fluid therapy. Additional treatment of mineralocorticoid deficiency was not required in any dog. The DOCP dosing interval in test population (31.2 ± 2.4 days) and control (31.7 ± 2.9 days) dogs was not different ($P = .3$). Overall, 34 of 37 (91.9%) dogs gained weight during the study. Body weight increased from 25.0 kg (IQR, 16.2-33.6 kg) at the time of initial hospital discharge to 29.1 kg (IQR, 20.6-38.7 kg) at study completion in test population dogs ($P < .001$). Body weight increased from 24.0 kg (IQR, 18.5-36 kg) to 27.8 kg (IQR, 22.2-44.6 kg) in control dogs ($P < .001$). Body weights at initial hospital discharge and study completion were not different between test and control populations ($P = .99$ and $P = .77$, respectively). Analogous to weight, body condition scores (scale, 1-9) were a median of 5 (IQR, 3-6) at baseline and a median of 5 (IQR, 5-6) at study completion in test population dogs and increased from a median of 5 (IQR, 5-6) to a median of 6 (IQR, 5-6.8) in control dogs ($P = .002$ for both comparisons).

Systolic blood pressure measurements were variable and ranged from 144 ± 23 to 156 ± 49 mm Hg at each repeat evaluation in test population dogs and from 146 ± 31 to 162 ± 42 mm Hg in controls. No differences in blood pressure were observed between test population dogs and controls at any time point ($P = .12$, $\alpha \leq .008$). Systolic blood pressures >159 mm Hg occurred on 39 of 110 (35.5%) occasions in test dogs and on 46 of 104 (44.2%) occasions in controls ($P = .21$). The frequency of systolic blood pressures <100 mm Hg in test (8 of 110 [7.3%]) and control (4 of 104 [3.8%]) dogs also was not different ($P = .38$).

Potential adverse clinical effects of DOCP administration were uncommon. One control dog developed a sterile inflammatory reaction at the injection site after the first treatment, which resolved with antibiotics administered PO and warm compresses pending culture results. A similar reaction did not occur after subsequent treatments. One control dog displayed signs of pain during and immediately after each DOCP injection, which included loud vocalization, shivering, and rolling on the ground. A similar pain response was not observed in any other dogs. New onset urinary incontinence was reported in 3 controls and 1 test population dog. The urinary incontinence was self-limiting in 2 of the control dogs. Five dogs, including 3 controls and 2 test population dogs, were reported to have sporadic urinary accidents. Etiologies of the lower urinary tract abnormalities were not investigated in detail, but urinalyses did not identify pyuria or bacteriuria.

Long-term follow-up was not performed as part of the study, but all dogs were reported to be clinically healthy >6 months after study completion. No test population dogs had an increase in DOCP dosage during this time, and 3 test population dogs had further dosage decreases.

3.3 | Biochemical effects

Serum Na:K ratios were not significantly different between test and control populations at any time point (Figure 1; $P = .04$, $\alpha \leq .008$). Serum potassium ($P = .05$, $\alpha \leq .01$) and sodium ($P = .04$, $\alpha \leq .008$) concentrations also were not different (Figure 2). Hypokalemia was documented on 16 of 104 (15.4%) instances in control dogs and 11 of 114 (9.6%) instances in test population dogs ($P = .22$). Hypernatremia was documented on 3 of 104 (2.9%) instances in control dogs and

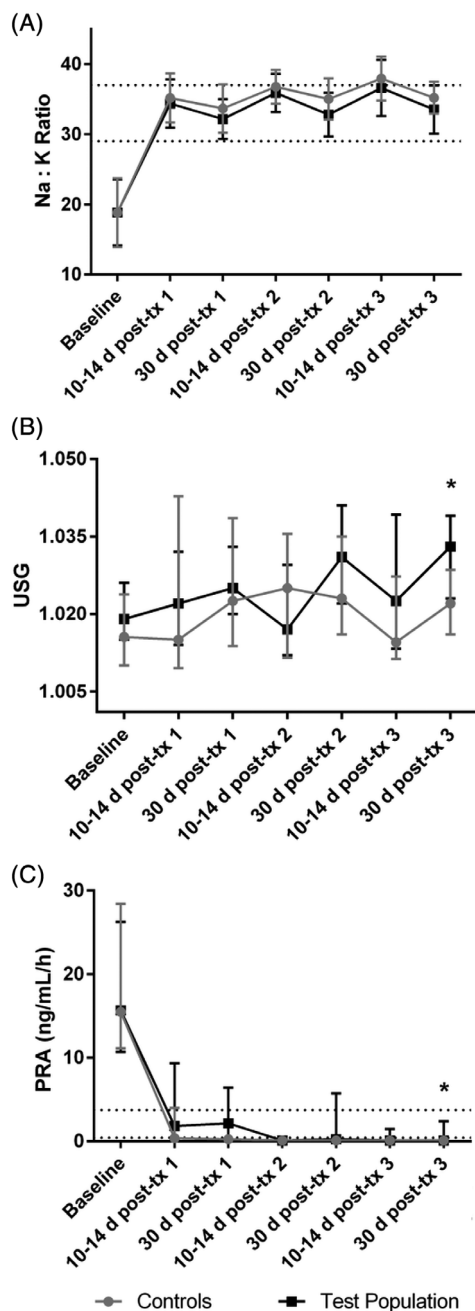


FIGURE 1 Line graphs depicting (A) the mean \pm SD serum sodium to potassium (Na:K) ratio, (B) the median (IQR) urine specific gravity (USG), and (C) the median (IQR) plasma renin activity (PRA) in the 18 controls (2.2 mg/kg DOCP q30d) and 19 test population dogs (1.1 mg/kg DOCP q30d). Each time point is listed as the number of days post DOCP treatment (post-tx). The reference interval is depicted by dashed lines in each panel. There were no differences in Na:K ratios between populations at any of the evaluations ($P = .04$, $\alpha \leq .008$). However, at the time of study conclusion, urine specific gravity in controls (median, 1.022; IQR, 1.016-1.029) was significantly less than in test population dogs (median, 1.033; IQR, 1.023-1.039). Similarly, PRA in controls (median, 0.08 ng/mL/h; IQR, 0.08-0.08 ng/mL/h) was significantly less than in test population dogs (median, 0.08 ng/mL/h; IQR, 0.08-2.38 ng/mL/h) at study conclusion. Note, PRA data from 4 controls and 4 test population dogs are not included in the baseline time point because these 8 dogs had received IV fluid therapy for >24 hours before sample collection. * $P = .006$, $\alpha \leq .008$. DOCP, desoxycorticosterone pivalate; IQR, interquartile range

2 of 114 (1.8%) instances in test population dogs ($P = .67$). At the time of study conclusion, urine specific gravity was significantly decreased in controls as compared to test population dogs (Figure 1; $P = .006$, $\alpha \leq .008$). Other hematologic and biochemical variables, including hematocrit ($P = .21$, $\alpha \leq .008$), serum albumin concentration ($P = .11$, $\alpha \leq .008$), serum creatinine concentration ($P = .18$, $\alpha \leq .008$), total CO_2 concentration ($P = .02$, $\alpha \leq .008$), and urine protein-to-creatinine ratio ($P = .66$, $\alpha \leq .008$), were not different between populations (Table 2).

Several time-related effects were observed in the combined study population (test dogs + control dogs). Serum Na:K ratios 10 to 14 days after the first (34.8 ± 3.5), second (36.6 ± 2.6), and third (37.2 ± 3.6) DOCP treatments were higher than the Na:K ratios 30 days after the first (32.9 ± 3.2), second (33.8 ± 3.2), and third (34.3 ± 3.0) treatments ($P = .02$, $P < .001$, and $P < .001$, respectively). Serum Na:K ratios 10 to 14 days after the second and third DOCP treatments were not different from each other ($P = .65$), but were both higher than the Na:K ratios 10 to 14 days after the first DOCP treatment ($P = .03$ and $P = .002$, respectively). The Na:K ratios 30 days after the second and third DOCP treatments were not different ($P = .85$), but the Na:K ratios 30 days after the third DOCP treatment were higher than those 30 days after the first DOCP treatment ($P = .05$).

3.4 | Plasma renin activity

Plasma renin activity was significantly lower in control dogs as compared to test population dogs at study completion (Figure 1; $P = .006$, $\alpha \leq .008$). Decreased PRA (RI, 0.41-3.73 ng/mL/h) was documented on 84 of 104 (80.8%) assessments in control dogs as compared to 59 of 112 (52.7%) assessments in test population dogs (Table 3; $P < .001$). Conversely, increased PRA was documented on 8 of 104 (7.7%) assessments in control dogs as compared to 23 of 112 (20.5%) assessments in test population dogs ($P = .01$).

Plasma renin activity was moderately and positively correlated with serum potassium concentration and moderately and negatively correlated with serum sodium concentration and serum Na:K ratio (Figure 3; $P < .001$ for all correlations). A weak and negative correlation was found between PRA and blood pressure ($\rho = -0.21$; $P = .002$). Plasma renin activity was decreased in 20 of 25 (80%) instances in which hypokalemia was documented. Plasma renin activity was increased in 3 of 4 instances in which hyperkalemia was documented. The Na:K ratio was normal (RI, 29-37) in 25 of the 31 (80.6%) instances in which increased PRA was observed and in 108 of 142 (76.1%) instances in which decreased PRA was observed.

3.5 | Individual dogs with hyperkalemia or hyponatremia

Hyperkalemia occurred on 2 occasions in 1 control dog (6.1 and 5.9 mmol/L) and on 2 occasions in 1 test population dog (5.7

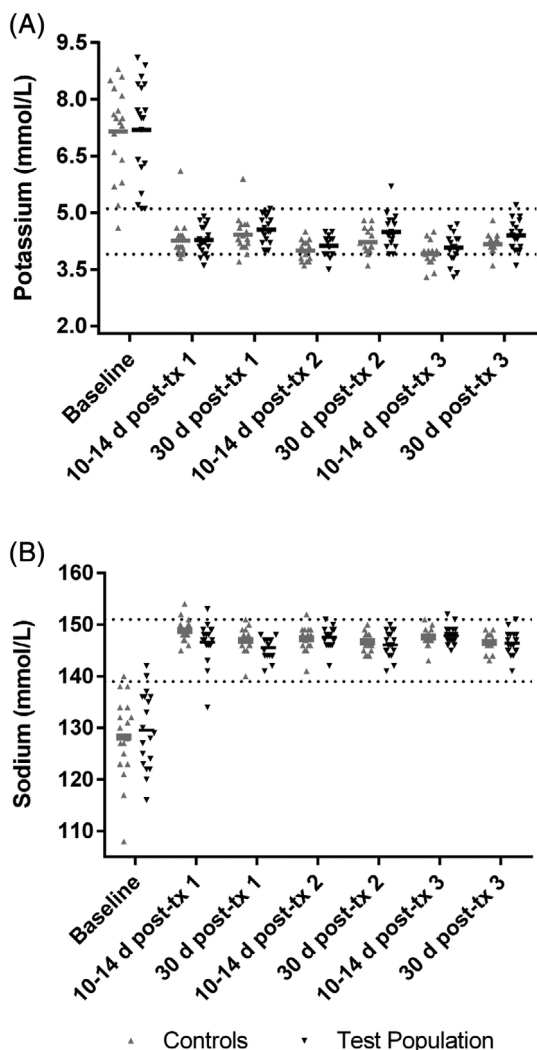


FIGURE 2 Scatterplots depicting serum (A) potassium and (B) sodium concentrations in the 18 controls (2.2 mg/kg DOCP q30d) and 19 test population dogs (1.1 mg/kg DOCP q30d). The central line within each scatter represents the mean, and the reference intervals are depicted by dashed lines. A total of 9 controls and 6 test population dogs developed at least one instance of hypokalemia. There were no differences in potassium ($P = .05, \alpha \leq .01$) or sodium ($P = .04, \alpha \leq .008$) concentrations between populations at any of the evaluations. DOCP, desoxycorticosterone pivalate

and 5.2 mmol/L). These were the 2 smallest dogs in the study at 7.5 kg and 6.5 kg, respectively, and the control dog was 3 months old. The corresponding serum sodium concentrations were normal in the control (148 and 141 mmol/L) and test population dog (141 mmol/L at both times). Plasma renin activity was increased at 1 of these occasions in the control dog (14.36 ng/mL/h) and at both occasions in the test population dog (30.0 and 12.76 ng/mL/h). The only instance of hyponatremia (134 mmol/L) occurred in a 24.6 kg control population dog. Serum potassium concentration (4.1 mmol/L) and PRA (1.8 ng/mL/h) were both normal. No other dogs developed hyponatremia or hyperkalemia at any time point.

TABLE 2 Selected hematologic and biochemical parameters from the control population (standard-dose DOCP) and test population dogs (low-dose DOCP) with hypoadrenocorticism that participated in the clinical trial

	Days after DOCP treatment					
	10-14 days post-tx 1	30 days post-tx 1	10-14 days post-tx 2	30 days post-tx 2	10-14 days post-tx 3	30 days post-tx 3
HCT (43%-59%)	Control 37.0 ± 3.7	44.2 ± 3.7	46.1 ± 4.5	49.8 ± 4.7	49.5 ± 4.4	51.9 ± 4.6
	Test 37.5 ± 5.8	44.5 ± 5.3	45.7 ± 5.1	49.0 ± 4.5	47.6 ± 4.5	50.2 ± 4.3
TCO ₂ (16-27 mmol/L)	Control 23.8 ± 2.5	23.9 ± 2.3	25.1 ± 2.6	23.4 ± 2.6	24.0 ± 2.2	23.5 ± 2.5
	Test 23.2 ± 2.5	21.8 ± 2.9	24.2 ± 2.8	22.7 ± 2.9	24.1 ± 2.2	23.4 ± 2.5
Albumin (2.8-3.6 g/dL)	Control 3.0 ± 0.3	3.3 ± 0.2	3.3 ± 0.2	3.4 ± 0.2	3.3 ± 0.2	3.4 ± 0.3
	Test 3.2 ± 0.4	3.4 ± 0.4	3.4 ± 0.4	3.5 ± 0.4	3.4 ± 0.3	3.5 ± 0.4
Creatinine (0.6-1.5 mg/dL)	Control 0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
	Test 0.9 ± 0.3	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	1.1 ± 0.3
UPC (<0.4)	Control 0.1 (0.1-0.2)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.1 (0.1-0.3)	0.2 (0.1-0.4)
	Test 0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.2 (0.1-0.2)	0.1 (0.1-0.4)	0.1 (0.1-0.6)	0.1 (0.1-0.3)

Note: Data are shown as mean ± SD or median (interquartile range) for the hematologic and biochemical variables. Reference intervals are listed below each variable. Each column represents 10 to 14 days or approximately 30 days after each of the 3 total DOCP treatments. There were no significant differences between populations at any time point for the above parameters. Abbreviations: DOCP, desoxycorticosterone pivalate; HCT, hematocrit; TCO₂, total carbon dioxide; tx, treatment; UPC, urine protein to creatinine ratio.

4 | DISCUSSION

Ours was the first prospective study to compare 2 DOCP dosing protocols in dogs with HA. Dosages of both 1.1 and 2.2 mg/kg q30d resulted in mean Na:K ratios remaining ≥ 32 throughout the study. No dog in either population required treatment, or developed clinical illness, because of electrolyte disturbances. Mild hyperkalemia was documented on only 2 occasions in 1 control dog and on 2 occasions in 1 test population dog. Hypokalemia was more common, occurring on 15.4% and 9.6% of assessments in control and test dogs, respectively. These results further support previous findings that lower starting and maintenance DOCP dosages can be used to treat most dogs with HA.^{13,15} The manufacturer-recommended starting dosage for DOCP is 2.2 mg/kg q25d.^{11,12} The recommended approach for adjusting the DOCP protocol is to alter the dosage by 0.1 to 0.2 mg/kg based on Na:K ratio, or alternatively, to alter the dosing interval by several days based on Na:K ratio. According to product inserts, most dogs are maintained on 1.7 to 2.2 mg/kg q21d to q30d or 1.9 ± 0.27 mg/kg q20d to q46d.^{11,12} Reasons why maintenance dosages remained similar to starting dosages in these field trials are unknown, but continued dosage reductions likely were not pursued once the Na:K ratio was within the target range. Even if DOCP dosages were decreased by 0.1 to 0.2 mg/kg at each treatment, 6 to 12 months would elapse before reaching the 1.1 mg/kg dosage used in test population dogs. Numerous veterinary visits and biochemical evaluations also would be necessary. Considering this, lower starting and maintenance DOCP dosages result in potentially substantial short-term and long-term cost savings. These results should be applicable to both commercial DOCP formulations because they have been shown to exhibit similar clinical effects.²⁰

Treatment protocols utilizing DOCP dosages of approximately 2.2 mg/kg administered approximately once monthly have been used for decades to treat HA in dogs, and long-term survival is common.^{9,11,12} Most dogs receiving 2.2 mg/kg DOCP in our study were likely overtreated. The mean Na:K ratios were either in the upper end of the RI or increased throughout the study, and mean serum potassium concentrations were consistently in the lower end of the RI. The less concentrated urine in control dogs at study completion also was speculated to be a result of mineralocorticoid excess.²¹⁻²³ Plasma renin activity commonly was suppressed below the RI in control dogs in our study, which would be consistent with overtreatment in humans with adrenal insufficiency.²⁴ In fact, 16 of 17 controls had PRA below the quantification limit of the assay at study completion. The adverse consequences of hyperaldosteronism are well documented in cats, and to a lesser extent dogs, with aldosterone-secreting adrenocortical tumors.²¹⁻²³ The mineralocorticoid excess associated with DOCP treatment in control population dogs is presumably mild compared to these reports. Blood pressure measurements, albeit highly variable, were not different between test and control dogs, and all controls were reported to be healthy during the study. However, the dramatic improvement in clinical status of HA dogs after initiating glucocorticoid and mineralocorticoid treatment might have precluded owners from noticing subtle clinical signs of overtreatment. In humans, mild imbalances in aldosterone are thought to be clinically relevant.²⁵⁻²⁷ Excess mineralocorticoid replacement might even be a contributing factor

to the increased risk of cardiovascular mortality observed in humans with primary adrenal insufficiency.²⁸ Whether or not mild mineralocorticoid excess associated with DOCP treatment results in clinically relevant pathology over the lifetime of dogs with HA is unknown.

A DOCP dosage of 1.1 mg/kg appeared to be safe and effective in our test population during the study period and follow-up, but this dosage might not be appropriate for all patients. Only 2 dogs in our study were <2 years of age, 1 of which was a 3-month-old dog. Young and growing dogs might require higher DOCP dosages, but this association has not been studied in detail.¹³⁻¹⁵ In addition, the majority of dogs in our study were medium and large breed dogs. The 2 dogs that developed hyperkalemia were the only 2 dogs that were <10 kg, 1 of which was the juvenile dog. We also excluded dogs with comorbidities such as kidney disease and heart disease, conditions that could alter serum electrolyte concentrations and perhaps DOCP responsiveness.^{29,30} The effects of age, size, and various other factors on DOCP dose requirements are important considerations that warrant future investigation.

Instances of increased PRA were more common in test population dogs than in controls. Four test population dogs had increased PRA at the time of study conclusion, all of which had multiple instances of increased PRA during the study. One of these dogs was the small-breed dog that developed mild hyperkalemia on 2 occasions. The other 3 dogs did not develop any electrolyte abnormalities or alterations in Na:K ratios suggestive of mineralocorticoid deficiency. This finding emphasizes that undertreatment can occur in the absence of serum biochemical abnormalities, but an ideal range for PRA in DOCP-treated dogs has not been determined. A high-normal to mildly increased PRA is targeted in humans with primary adrenal insufficiency.^{31,32} Also, mineralocorticoid dosage adjustments are not based solely on PRA in humans, but also on assessments of serum electrolyte concentrations and blood pressure.³³ It is unknown if 1.1 mg/kg DOCP dosages were appropriate for the dogs with increased PRA and normal serum electrolyte concentrations in our study, but all dogs were reported to be well >6 months after study completion.

When evaluating the entire study population, we observed that Na:K ratios were higher after the second and third DOCP treatments as compared to the first. A similar pattern seemed to be present in a previous study of HA in dogs, but statistical comparisons were lacking.¹⁰ These findings suggest that an acclimation period occurs after the initial DOCP treatment, and Na:K ratios appear to stabilize after the second treatment. The clinical relevance of this observation warrants further study, but it raises questions about the traditional practice of adjusting DOCP dosages based on biochemical assessments performed after the first treatment. Dosages required to maintain normal serum electrolyte concentrations are probably higher for the first treatment of a newly diagnosed HA dog as compared to subsequent treatments. An ideal protocol might entail avoiding dosage increases based on the initial biochemical assessments unless electrolyte disturbances are severe. Alternatively, perhaps starting at a higher dosage and empirically decreasing to the target dosage at the next injection would achieve a similar outcome.

Our study had some limitations. A larger sample size would have been required to detect more subtle biochemical differences that

TABLE 3 Plasma renin activity in controls (standard-dose DOCP) and test population dogs (low-dose DOCP) with hypoadrenocorticism

	PRA (ng/mL/h)	10-14 days post-tx 1	30 days post-tx 1	10-14 days post-tx 2	30 days post-tx 2	10-14 days post-tx 3	30 days post-tx 3
Controls	>3.73	5/18	2/18	0/17	1/17	0/17	0/17
	0.41-3.73	3/18	5/18	1/17	2/17	0/17	1/17
	<0.41	10/18	11/18	16/17	14/17	17/17	16/17
	<0.16	2/18	8/18	11/17	10/17	17/17	16/17
Test	>3.73	6/19	6/19	1/19	5/19	1/18	4/18
	0.41-3.73	6/19	8/19	5/19	3/19	4/18	4/18
	<0.41	7/19	5/19	13/19	11/19	13/18	10/18
	<0.16	5/19	4/19	10/19	6/19	11/18	10/18

Note: Data are shown as the number of dogs in each population with plasma renin activity (PRA) above, within, or below the reference interval of 0.41 to 3.73 ng/mL/h. In addition, the number of dogs with PRA < 0.16 ng/mL/h, which was the analytical sensitivity of the assay, are also provided. Each column represents the specified number of days after each of the 3 DOCP treatments (tx). Note, 1 control dog withdrew from the study after day 30. Samples for PRA were unavailable for 1 test population dog 10 to 14 days after the third DOCP treatment and 30 days after the third DOCP treatment. Abbreviations: DOCP, desoxycorticosterone pivalate; PRA, plasma renin activity.

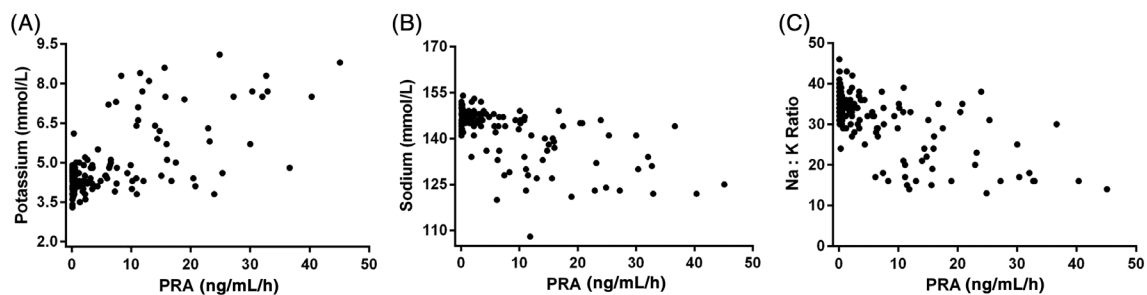


FIGURE 3 Scatterplots depicting the correlation between plasma renin activity (PRA) and serum (A) potassium concentrations, (B) sodium concentrations, and (C) Na:K ratio in the 38 study dogs. Plasma renin activity was positively correlated with serum potassium concentration ($\rho = 0.48$; $P < .001$) and negatively correlated with serum sodium concentration ($\rho = -0.47$; $P < .001$) and serum Na:K ratio ($\rho = -0.50$; $P < .001$)

might have existed between populations. The Na:K ratio was numerically higher in control population dogs throughout the study, but the associated P values were not significant when α was adjusted to account for multiple comparisons. In order to detect a 1.5 to 2 difference in Na:K ratios between populations in a similarly designed study, approximately 35 dogs would have been required in each treatment arm. Another possible limitation is that DOCP duration of action was not addressed. Although intriguing, incorporation of this variable would have resulted in additional complexity that was beyond the scope of our predefined study objectives. A median DOCP dosing interval of 2 months has been described in dogs receiving approximately 2.2 mg/kg DOCP.¹⁴ It is plausible that higher dosages result in prolonged dosing intervals. The cost savings with either approach would be comparable. However, administration of 2.2 mg/kg DOCP every 2 months seems likely to result in transient periods of both mineralocorticoid excess and deficiency when considering our study results and the pharmacologic profile of DOCP.^{9,11,12}

In conclusion, 1.1 mg/kg starting and maintenance dosages of DOCP for treatment of HA appeared to be safe and effective in our study population. Based on serum electrolyte concentrations and PRA, dosages of 2.2 mg/kg were unlikely to have been necessary for most dogs in the standard-dose population. Additional studies are

needed to further refine DOCP treatment protocols and determine the long-term outcomes of these different approaches for HA management.

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CONFLICT OF INTEREST DECLARATION

Dr Langlois has presented continuing education lectures that were sponsored by Dechra Veterinary Products, LLC, which manufactures the desoxycorticosterone pivalate product used in this study. The other authors declare no potential conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE APPROVAL

This study was approved by the Michigan State University IACUC (AUF 11-17-204-00), and informed consent was obtained from all owners.

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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