AJVR

AVMA

Urine electrolytes do not predict desoxycorticosterone pivalate efficacy in dogs with hypoadrenocorticism

Daniel K. Langlois, DVM, DACVIM*; Casey A. Dropkin, DVM, DACVIM; John M. Kruger, DVM, PhD, DACVIM

Department of Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing, MI

*Corresponding author: Dr. Langlois (langlo21@msu.edu)

Received March 2, 2023
Accepted May 15, 2023

doi.org/10.2460/ajvr.23.02.0042

OBJECTIVE
To determine if urine electrolyte assessments can be used to monitor the adequacy of mineralocorticoid therapy in dogs with hypoadrenocorticism (HA).

ANIMALS
29 dogs with naturally occurring glucocorticoid- and mineralocorticoid-deficient HA.

PROCEDURES
Urine sodium and potassium concentrations, sodium-to-potassium ratios, sodium-to-creatinine ratios, and potassium-to-creatinine (K:Cr) ratios were evaluated in dogs with newly diagnosed HA that were treated with desoxycorticosterone pivalate (DOCP). Dogs underwent measurements of urine and serum sodium, potassium, and creatinine concentrations and plasma renin activities twice monthly for up to 3 months. Regression analyses and calculation of coefficients of determination (R^2) were performed to investigate potential associations between urine and serum variables. Urine variables also were compared between dogs considered to be undertreated or overtreated based on plasma renin activities.

RESULTS
Urine K:Cr ratios were significantly associated with serum potassium concentrations 10 to 14 days (P = .002) and 30 days (P = .027) after the initial DOCP injection, but R^2 values were only 0.35 and 0.17, respectively. Urine K:Cr ratios (median [IQR]) also were higher in dogs that were overtreated with DOCP (1.3 [0.7 to 2.3]) as compared to those dogs that were undertreated with DOCP (0.8 [0.5 to 0.9]) at 10 to 14 days after the initial DOCP injection (P = .039) but not at 30 days after the initial injection. Other urine variables were not significantly different between undertreated and overtreated dogs.

CLINICAL RELEVANCE
Measures of urine electrolytes were not useful for assessing the adequacy of mineralocorticoid therapy in HA dogs that were treated with DOCP.

Naturally occurring hypoadrenocorticism (HA) in dogs is a potentially life-threatening endocrine disorder characterized by a circulating deficiency of adrenocortical hormones.[1–3] Most cases are speculated to be the result of immune-mediated destruction of the adrenal cortex, and the resulting cortisol deficiency causes a multitude of vague and nonspecific clinical signs such as lethargy, weakness, and gastrointestinal disturbances.[4–6] Although the diagnosis of HA is established by documenting a cortisol deficiency, most dogs with HA also are deficient in aldosterone.[7] Aldosterone, the principal mineralocorticoid secreted by the adrenal cortex, acts on receptors in the distal nephron to promote sodium and potassium exchange and sodium and hydrogen exchange.[8–10] As such, it is the aldosterone deficiency that is responsible for many of the classic abnormalities associated with HA such as hyperkalemia, hyponatremia, and metabolic acidosis.[1,2,10]

Prompt recognition and treatment of HA lead to excellent outcomes and several years of survival in most cases, but management can be complicated by considerable lifetime treatment and monitoring costs.[2,11–13] The cortisol deficiency is easily and inexpensively treated with physiologic dosages of prednisone or other glucocorticoids and primarily monitored based on clinical signs.[12,14] The mineralocorticoid deficiency is often treated with monthly injections of the synthetic mineralocorticoid desoxycorticosterone pivalate (DOCP).[1,2,14,15] However, DOCP drug costs can be substantial. Mineralocorticoid replacement therapy also requires

frequent veterinary visits for monitoring of serum electrolyte concentrations, especially during the initial months of treatment.[14,15] The frequent veterinary visits are inconvenient for some owners and contribute to the financial burden. Furthermore, the absence of serum electrolyte abnormalities does not exclude the presence of a mineralocorticoid deficiency.[7]

Recent attempts to lower HA management costs have focused on DOCP dosage reduction or decreased DOCP administration frequency.[16–19] Urine electrolyte concentrations and urine sodium-to-potassium (Na:K) ratios are altered in dogs with HA, which suggests that they might be surrogates for assessing serum electrolyte concentrations and mineralocorticoid adequacy.[20,21] If urine electrolytes were shown to be highly correlated with serum electrolytes in dogs receiving DOCP treatment, HA monitoring might become more convenient and less expensive as owners could simply drop off urine specimens for analysis. The primary objective of this study was to determine if urine electrolyte measurements could be useful for monitoring mineralocorticoid replacement therapy in dogs with glucocorticoid- and mineralocorticoid-deficient HA. We hypothesized that urine electrolyte concentrations, urine electrolyte-to-creatinine ratios, and urine Na:K ratios would correlate with their serum counterparts in HA dogs treated with DOCP. We further hypothesized that the studied urine variables would be different between dogs that were in a state of mineralocorticoid excess or mineralocorticoid deficiency as defined by plasma renin activity (PRA).

Materials and Methods

Dogs

Dogs with newly diagnosed HA were eligible for study participation. The diagnosis of HA was based on the results of ACTH stimulation testing, which was performed by measuring serum cortisol concentrations immediately before and 1 hour after IV administration of 5 µg/kg (2.3 mg/lb) synthetic ACTH (Cosyntropin; Oakwood Laboratories LLC, for Sandoz Inc). Pre- and post-ACTH–stimulated serum cortisol concentrations ≤ 55 nmol/L (2 µg/dL) were considered diagnostic for HA.[1,2] Dogs were required to have serum electrolyte abnormalities present at baseline evaluation that were indicative of a mineralocorticoid deficiency. These abnormalities included any of the following: Na:K ratio < 28, hyponatremia with concurrent potassium concentration in the upper half of the reference interval, or hyperkalemia with concurrent sodium concentration in the lower half of the reference interval.[22] There were no eligibility requirements based on age, breed, or sex. Dogs that had received exogenous glucocorticoids or azole antifungals in the 4 weeks before evaluation were excluded from participation because these drugs could have influenced the results of ACTH stimulation testing.[23,24] Dogs also were excluded from participation if they were receiving medications known to affect sodium and potassium homeostasis, which included drugs that target the renin-angiotensin-aldosterone system.[25] Although not a requirement for study participation, baseline measurements of urine electrolyte concentrations were performed in those dogs in which samples could be collected either before or within 6 hours of initiation of intravenous crystalloid solutions. This project was approved by the Michigan State University Institutional Animal Care and Use Committee, and informed consent was obtained from the owners of participating dogs.

Experimental protocol

The initial stabilization and treatment of participating dogs were at the discretion of the attending clinician and were independent of study participation. This generally included the administration of IV crystalloid solutions and IV dexamethasone and the provision of symptomatic care such as antinausea medications as needed. All dogs were treated with approximately once-monthly SC injections of DOCP (Zycortal; Dechra Veterinary Products), which were initiated within 48 hours preceding hospital discharge. The DOCP dosage was independent of study participation, but most dogs were participating in a separate clinical trial in which dosages of either 1.1 mg/kg or 2.2 mg/kg were administered for the entire study period unless severe electrolyte disturbances were observed.[19] The cortisol deficiency was treated in all dogs with PO prednisone as prescribed by the attending clinician.

Dogs were evaluated 10 to 14 days after their initial DOCP injection and again at the time of their next scheduled DOCP injection, which was approximately 30 days after the initial DOCP injection. This pattern of monitoring was continued for a total of 3 DOCP treatments resulting in a study duration of 3 months. Dogs underwent up to 6 recheck evaluations during this time. A physical examination was performed at each study visit, and blood and urine samples were collected for assessments of serum and urine electrolyte and creatinine concentrations and PRA. Dogs were not withdrawn from the study if they missed a scheduled recheck evaluation, but dogs were withdrawn from the study if they received IV or SC crystalloids solutions or any nonstudy-prescribed medications known to affect sodium and potassium homeostasis after their initial hospital discharge. Any data collected before withdrawal were retained and used in analyses. No attempts were made to control diet during the study.

Laboratory methods

Laboratory testing was performed at the Michigan State University Veterinary Diagnostic Laboratory, which is an American Association of Veterinary Laboratory Diagnosticians–accredited laboratory. Blood samples were collected at each study visit via routine venipuncture and divided between serum and EDTA plasma collection tubes. Serum was obtained from blood collection tubes after clot formation and centrifugation at 1,700 X g for 10 minutes. The EDTA collection tubes for PRA measurements were immediately placed in wet ice,

centrifuged, and plasma harvested and stored at less than −20 °C until later batch analysis. Urine samples were collected via cystocentesis or during natural voiding and placed in an additive-free specimen collection tube. Urine was centrifuged at 1,700 X *g* for 10 minutes, and the urine supernatant was used for analyses. Serum and urine concentrations of sodium, potassium, and creatinine were measured using a clinical chemistry analyzer (AU680; Beckman Coulter, Inc), which is routinely used for clinical testing and research purposes. Serum cortisol concentrations were measured using a commercially available competitive chemiluminescent immunoassay (Immulite 2000 Cortisol; Siemens Healthcare Diagnostics Ltd). Plasma renin activities were mere measured using a commercially available human radioimmunoassay kit (Angiotensin I RIA; DIASource ImmunoAssays), which quantitatively determines PRA via the in vitro generation of angiotensin I. Detailed descriptions of the assays used for cortisol and PRA measurements in our laboratory can be found elsewhere.[19,22]

Data and statistical analysis

Data were assessed for normality with Shapiro-Wilk testing and box-plot analysis and reported as median and interquartile (25th to 75th percentile) range (IQR). Urine electrolyte data were assessed in multiple ways including absolute electrolyte concentrations and Na:K ratios, as well as sodium-to-creatinine (Na:Cr) or potassium-to-creatinine (K:Cr) ratios to account for potential differences in urine concentration. Statistical testing was performed to determine (1) if there were differences in urine variables based on DOCP dosage, (2) if there were associations between serum and urine variables, and (3) if there were differences in urine variables based on the adequacy of DOCP therapy.

Potential differences in urine variables between low-dose (1.1 mg/kg) and label-dose DOCP (2.2 mg/kg) protocols were assessed at each of the study time points by Mann-Whitney *U* testing. Potential associations between urine and serum variables were evaluated at the first (10 to 14 days after the initial DOCP treatment) and second (30 days after the initial DOCP treatment) evaluation time points by simple linear regression analyses and calculation of the coefficients of determination or *R*-squared (R^2). These initial time points were selected for regression analyses because there was greater variability in serum electrolyte concentrations. Potential associations between the urine and serum variables also were investigated by calculating Spearman's rank correlation coefficients (rho [ρ]), which are available as supplementary information **(Supplementary Table S1)**. Data were further analyzed by comparing the urine electrolyte variables between dogs that were in a state of mineralocorticoid excess and mineralocorticoid deficiency with Mann-Whitney *U* testing. Mineralocorticoid adequacy was determined by PRA assessments (reference interval, 0.41 to 3.73 ng/mL/h), with PRA values greater than the upper end of the reference interval considered to be an instance of mineralocorticoid deficiency and PRA values less than the lower end of the reference interval considered to be an instance of mineralocorticoid excess. Assessments of PRA are considered the standard for monitoring mineralocorticoid adequacy in humans with primary adrenal insufficiency, and the same appears to be true for dogs with HA.[26–28]

Finally, potential associations of urine and serum variables over the duration of the study were explored in several individual dogs to ensure that potential effects were not overlooked in the population analyses. The only dogs included in these regressions were those that had data available from 7 time points (baseline evaluation and 6 recheck evaluations) and had at least 2 recheck evaluations where serum sodium or potassium concentrations were abnormal. Fewer data points or minimal variability in serum electrolyte concentrations would have precluded the detection of possible relationships between serum and urine variables. Statistical testing was performed using commercially available software (GraphPad Prism Version 6.0; GraphPad Software Inc), and values of $P \leq .05$ were considered significant for all analyses.

Results

Dogs

A total of 29 dogs with newly diagnosed HA met the inclusion criteria and participated in the clinical trial. All dogs underwent an initial period of hospitalization that included treatment with IV fluids and IV dexamethasone under the direction of the attending clinician. The median age and weight were 3.2 years (IQR, 2.0 to 5.5 years) and 25.1 kg (IQR, 19.8 to 32.6 kg), respectively. The study population consisted of 13 castrated males, 2 sexually intact males, and 14 spayed females. There were 9 mixed-breed dogs, 4 Standard Poodles or Poodle-crosses, 2 Labrador Retrievers, 2 German Shorthaired Pointers, 2 Mastiffs, and 2 Cane Corso dogs; no other breed was represented by more than 1 dog. At the time of initial evaluation, 27 of 29 dogs had a serum Na:K ratio < 28. Twenty-five of 29 dogs were both hyponatremic (serum sodium concertation < 139 mmol/L) and hyperkalemic (serum potassium concentration > 5.1 mmol/L). The 4 dogs that were not both hyperkalemic and hyponatremic included 3 dogs that were hyponatremic with a concurrent serum potassium concentration in the upper half of the reference interval and 1 dog that was hyperkalemic with a concurrent serum sodium concentration in the lower half of the reference interval. Fourteen dogs were treated with the initial label dosage of 2.2 mg/kg DOCP, and 15 dogs were treated with a lower dosage of 1.1 mg/kg DOCP. Adjustments of DOCP dosages were not performed in any dogs during the study period. All dogs were treated with PO prednisone, and the median final maintenance dosage was 0.1 mg/kg/day (IQR, 0.08 to 0.14 mg/kg/day).

Urine electrolytes based on DOCP dosage

Baseline features (median [IQR]) including age (3.0 yrs [IQR, 2 to 5.5 years] vs 4.0 years [IQR, 2.0

to 5.8 years]), weight (28.0 kg [IQR, 16.7 to 30.0 kg] vs 24.3 kg [IQR, 21.7 to 42.0 kg]), and serum Na:K ratio (16 [IQR, 15 to 21] vs 17.5 [IQR, 16 to 23]) were not significantly different between dogs that were treated with 1.1 mg/kg and 2.2 mg/kg DOCP (P = .785, P = 0.554, and P = .367, respectively). Urine potassium concentrations in dogs treated with 1.1 mg/kg DOCP were significantly higher (P = .049) than in dogs treated with 2.2 mg/kg DOCP 10 to 14 days after the third DOCP treatment, but no additional significant differences in urine potassium concentrations were observed at any other time point. Similarly, no significant differences in any of the other urine variables were observed between dogs treated with 1.1 mg/kg DOCP and dogs treated with 2.2 mg/kg DOCP at any of the evaluations **(Table 1)**.

Correlations of urine and serum electrolytes

Potential correlations between urine and serum variables were evaluated in 23 dogs at the 10- to 14-day time point after the initial DOCP injection and in 25 dogs at the 30-day time point after the initial DOCP injection. Urine K:Cr ratios were significantly and positively associated with serum potassium concentrations at both times **(Table 2)**, but the relationships were not strong (R^2 = 0.35 and R^2 = 0.17, respectively). Similarly weak, but negative, significant relationships between urine and serum sodium concentrations (R^2 = 0.18) 10 to 14 days after DOCP treatment and urine Na:Cr ratios and serum sodium concentrations (R^2 = 0.22) 30 days after DOCP treatment were identified. No significant associations between any of the other studied urine and serum variables were identified.

Potential associations of serum and urine electrolytes also were explored within 6 individual dogs. In a 5-year-old spayed female German Shorthaired Pointer, urine K:Cr ratios were significantly and negatively associated with serum potassium concentrations (R^2 = 0.62, P = .037), and urine Na:K ratios were significantly and negatively associated with serum Na:K ratios (R^2 = 0.70, P = .019). No other significant associations between any of the evaluated urine and serum variables were identified in this dog or in any other dog **(Supplementary Table S2)**.

Urine electrolyte comparisons based on mineralocorticoid adequacy

Twenty-three dogs underwent assessments of urine electrolytes and PRA 10 to 14 days after the initial DOCP injection; 9 of these dogs were in a state of mineralocorticoid deficiency (PRA > 3.73 ng/mL/h) and 12 of these dogs were in a state of mineralocorticoid excess (PRA < 0.41 ng/mL/h). Urine K:Cr ratios (median [IQR]) in dogs in a state of mineralocorticoid excess (1.3 [0.7 to 2.3]) were significantly higher than in dogs in a state of mineralocorticoid deficiency (0.8 [0.5 to 0.9]; P = .039) 10 to 14 days after DOCP treatment. The other studied urine variables were not different between dogs with low and high PRA values at the 10- to 14-day time point after the initial DOCP treatment **(Figure 1)**.

Table 1—Urine electrolyte measurements in dogs with HA that were treated with either a low (1.1 mg/kg) or standard (2.2 mg/kg) dosage of desoxycorticosterone pivalate (DOCP).

Urine variable	DOCP dosage	Baseline (n = 19)	10–14 d post-tx 1 (n = 23)	30 d post-tx 1 (n = 25)	10–14 d post-tx 2 (n = 23)	30 d post-tx 2 (n = 26)	10–14 d post-tx 3 (n = 23)	30 d post-tx 3 (n = 28)
Na (mmol/L)	1.1	59 (40–128)	89 (44–147)	85 (57–104)	83 (56–109)	97 (65–153)	66 (37–114)	95 (62–134)
	2.2	75 (35–102)	55 (34–97)	75 (49–104)	78 (33–90)	136 (33–167)	75 (19–85)	80 (52–119)
K (mmol/L)	1.1	52 (24–73)	112 (46–233)	136 (70–165)	104 (84–143)	145 (89–194)	82[a] (54–158)	162 (88–226)
	2.2	57 (22–81)	58 (36–76)	89 (76–168)	94 (60–135)	110 (60–166)	52[a] (40–76)	114 (66–191)
Na:K	1.1	2.0 (0.5–4.0)	1.1 (0.6–1.2)	0.7 (0.5–1.2)	0.8 (0.6–1.1)	0.9 (0.4–1.0)	0.9 (0.5–1.1)	0.8 (0.5–1.0)
	2.2	1.4 (0.8–1.7)	1.2 (0.5–1.5)	0.6 (0.3–1.3)	0.8 (0.3–1.1)	1.1 (0.8–1.2)	0.9 (0.6–1.3)	0.7 (0.4–1.2)
Na:Cr	1.1	0.6 (0.2–1.8)	1.0 (0.5–1.4)	0.8 (0.4–1.2)	1.0 (0.6–1.7)	0.8 (0.6–1.1)	0.8 (0.3–1.2)	0.7 (0.3–1.0)
	2.2	0.6 (0.4–0.9)	1.1 (0.4–2.0)	0.7 (0.3–1.3)	0.6 (0.1–1.3)	0.9 (0.7–1.6)	0.7 (0.2–1.8)	0.8 (0.3–2.0)
K:Cr	1.1	0.3 (0.3–0.40)	0.9 (0.8–1.5)	1.1 (0.7–1.5)	1.0 (0.8–2.0)	0.9 (0.8–1.3)	1.0 (0.7–1.1)	1.0 (0.7–1.3)
	2.2	0.4 (0.3–0.5)	0.8 (0.6–2.1)	1.1 (0.9–1.4)	0.9 (0.5–1.4)	0.7 (0.6–1.5)	0.9 (0.4–1.3)	1.2 (0.6–1.6)

Results for each of the studied variables are depicted as median and interquartile (25th–75th percentile) range, with electrolyte concentrations shown in mmol/L and ratios as absolute numbers. Data are further classified based on DOCP dosage (1.1 mg/kg or 2.2 mg/kg). The initial column time point depicts baseline values before the initiation of DOCP, with subsequent columns representing 10 to 14 days or approximately 30 days after (d post) each of the 3 total DOCP treatments (tx).

[a]P = 0.049.

K = Potassium. K:Cr = Potassium-to-creatinine ratio. Na = Sodium. Na:Cr = Sodium-to-creatinine ratio.

Table 2—Associations of urine and serum electrolytes in DOCP-treated dogs.

	10–14 days post-DOCP (n = 23)			30 days post-DOCP (n = 25)		
Association	**Equation**	***R*²**	***P***	**Equation**	***R*²**	***P***
Urine Na and serum Na	Y = 0.0278 • X + 144.9	0.18	.029[a]	Y = −0.00581 • X + 146.7	0.01	.594
Urine Na:Cr and serum Na	Y = 1.307 • X + 145.8	0.11	.102	Y = −2.038 • X + 147.8	0.22	.011[a]
Urine K and serum K	Y = 0.000597 • X + 4.2	0.01	.606	Y = 0.00024 • X + 4.4	< 0.01	.849
Urine K:Cr and serum K	Y = 0.4001 • X + 3.8	0.35	.002[a]	Y = 0.357 • X + 4.1	0.17	.027[a]
Urine Na:K and serum Na:K	Y = 0.986 • X + 33.9	0.02	.542	Y = −0.312 • X + 33.2	< 0.01	.847

The equation, coefficient of determination (R^2), and *P* value from linear regression analyses are shown for each of the possible associations, which were explored 10–14 days after the initial desoxycorticosterone pivalate (DOCP) injection and again at approximately 30 days after the initial DOCP injection. The units of measure for the electrolyte concentrations were mmol/L, and the ratios were absolute numbers. For each equation, Y = serum analyte and X = urine analyte.

[a]Significant ($P < 0.05$).

See Table 1 for remainder of key.

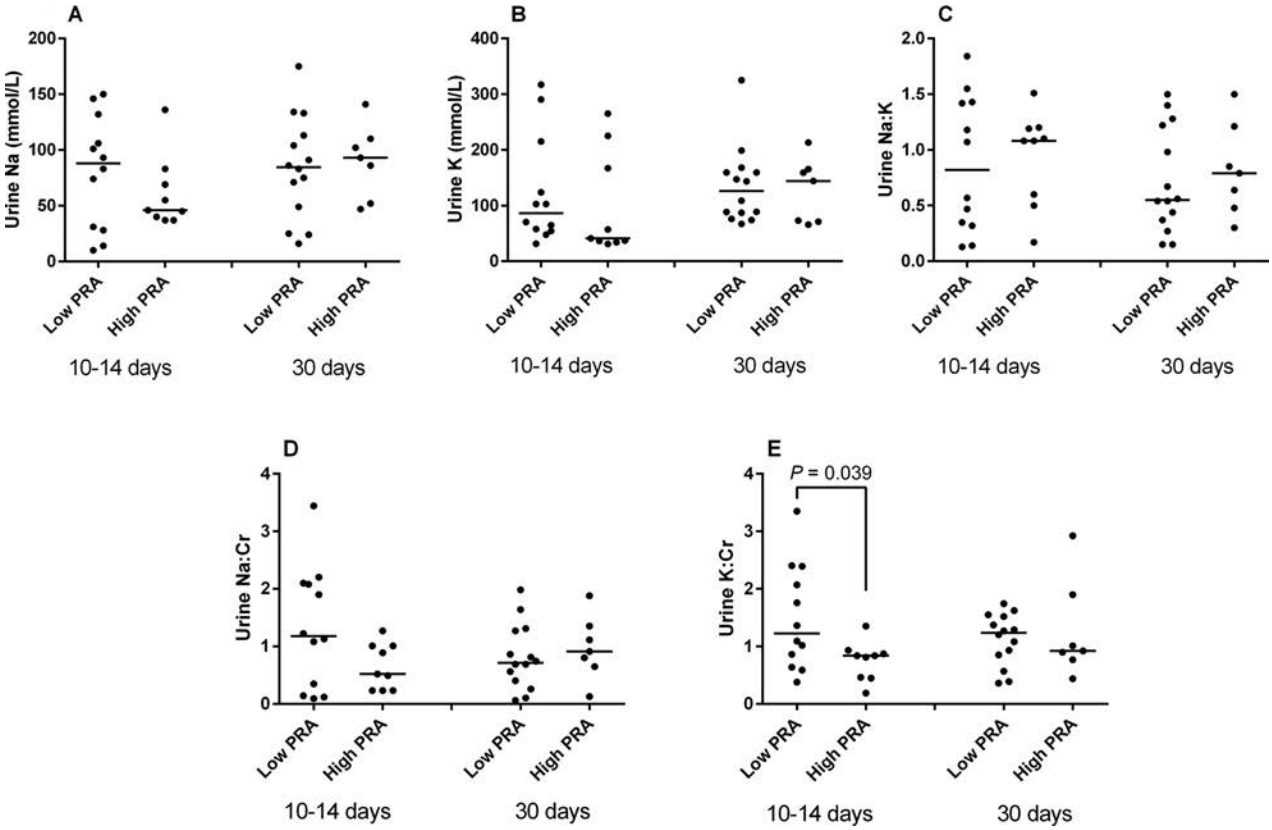

Figure 1—Scatterplots depicting urine sodium (Na) concentrations (A), urine potassium (K) concentrations (B), urine sodium-to-potassium (Na:K) ratios (C), urine sodium-to-creatinine (Na:Cr) ratios (D), and urine potassium-to-creatinine (K:Cr) ratios (E) in dogs with primary hypoadrenocorticism that were overtreated or undertreated with desoxycorticosterone pivalate (DOCP). Treatment adequacy was based on plasma renin activity (PRA) measurements, with low PRA values considered indicative of overtreatment and high PRA values considered indicative of undertreatment. Each variable was evaluated at 2 time points, which included 10 to 14 days after the initial DOCP injection and 30 days after the initial DOCP injection. The horizontal line within each scatter represents the median.

Twenty-five dogs underwent assessments of urine electrolytes and PRA 30 days after the initial DOCP injection, which included 7 dogs that were in a state of mineralocorticoid deficiency and 14 dogs that were in a state of mineralocorticoid excess. None of the studied urine variables were different between dogs with low and high PRA values at the 30-day time point.

Urine variables were further explored when mineralocorticoid adequacy was based on the serum Na:K ratio, and these results are available as supplementary information **(Supplementary Figure S1)**.

Discussion

Measures of urinary sodium and potassium were investigated as potential markers for mineralocorticoid adequacy in DOCP-treated dogs. Given the role of aldosterone in renal tubular electrolyte processing,

we anticipated that urine analytes would strongly correlate with serum counterparts and provide an alternative method for monitoring mineralocorticoid replacement therapy. Indeed, urine electrolyte testing in humans is used for the screening and monitoring of various kidney and endocrine disorders, and urine Na:K ratios have even been suggested as a possible screening test for aldosterone-related disturbances.[29–31] However, only weak associations or no associations at all between urine and serum electrolytes were observed in our study population despite evaluating absolute urine electrolyte concentrations, urine Na:K ratios, and urine electrolyte-to-creatinine ratios. These findings were true for the analyses of the grouped dogs at each of the study visits as well as when regressions were performed within individual dogs. The reasons why correlations were either weak or nonexistent are unknown. Dogs were not fed a uniform diet, and dietary salt intake would be expected to influence urine sodium and potassium concentrations.[32,33] The feeding of a standardized diet was considered, but this was not likely to be practical nor would it be reflective of typical clinical practice. Even if large differences in dietary salt levels were present across the study population, this would not explain the lack of correlations within individual dogs that were presumably consuming the same diet throughout the study period. It is likely that the myriad physiologic factors and adaptive responses involved in renal electrolyte processing contributed to heterogeneous findings, but investigation of these factors was beyond the scope of this study.[34,35]

The potential utility of urine electrolytes was further explored by comparing values based on treatment targets. Similar to the correlation analyses, there were not any findings with potential clinical applicability. Values in dogs that were undertreated overlapped with the values of dogs that were overtreated (Figure 1). We used PRA to assess the degree of control because this is the well-established standard in humans with primary adrenal insufficiency.[27,28] Perhaps differences would have been observed had we used serum electrolyte concentrations for classification. There were only a few instances of hyperkalemia, hyponatremia, and abnormal serum Na:K ratios during the entire study period, which precluded meaningful statistical comparisons. Furthermore, the presence of normal serum electrolyte concentrations does not necessarily indicate mineralocorticoid adequacy as most HA dogs are deficient in aldosterone even when serum electrolytes are normal at the time of diagnosis (eg, dogs with "atypical" HA).[7] In further support of this, both high and low PRA values have been observed in DOCP-treated dogs with normal serum electrolyte concentrations.[19,26] Independent of the method in which clinical control is assessed, the notable variability in urine electrolytes suggests that no cut points will be useful for accurately determining whether or not DOCP dosing adjustments are needed in dogs with HA. This is further supported by the substantial overlap in urine electrolyte measures between dogs treated with 2.2 mg/kg DOCP and dogs treated with half of that dosage.

Although the collective findings reported herein suggest that urine electrolyte measurements are unlikely to aid in HA monitoring in dogs, there are some study limitations that warrant consideration. A larger study population with an extended monitoring period might have facilitated the detection of more subtle relationships between serum and urine electrolytes. However, even if additional statistical differences were to exist, the degree of overlap between overtreated and undertreated dogs would still preclude clinical relevance. Another limitation is that there were very few instances in which serum electrolyte abnormalities consistent with DOCP undertreatment were observed, and in no instance was hyperkalemia severe enough to warrant clinical concern. It is possible that urine electrolyte measures would be predictive of more severe disturbances in serum electrolyte concentrations. Our study did not capture such a population of dogs, but available evidence suggests that severe electrolyte abnormalities during DOCP treatment are exceedingly rare, even across a wide range of DOCP dosing protocols.[16–19] Finally, the DOCP protocols utilized in this study differed from the manufacturer-recommended protocol, and it is unknown how this could have influenced study results.

In summary, we documented that urine electrolytes are not strongly correlated with serum electrolytes in DOCP-treated dogs. There were no discriminatory cut points for any of the evaluated urine analytes that would permit practitioners to accurately monitor and adjust DOCP dosing protocols. In the absence of commercially available PRA assays, the monitoring of DOCP therapy in dogs with glucocorticoid- and mineralocorticoid-deficient HA should still be based on routine assessments of serum electrolyte concentrations. Strategies such as lower DOCP doses or DOCP interval prolongation remain the most effective way to reduce management costs in dogs with HA.

Acknowledgments

This study was supported by the American College of Veterinary Internal Medicine and the Purina Institute.

The authors declare that there were no conflicts of interest.

Dr. Langlois is a member of the *Journal of the American Veterinary Medical Association* (*JAVMA*) scientific review board. He declares that he had no role in the editorial direction of this manuscript.

References

1. Church DB. Canine hypoadrenocorticism. In: Mooney CT, Peterson ME, eds. *BSAVA Manual of Canine and Feline Endocrinology.* 4th ed. British Small Animal Veterinary Association; 2012;156–167.
2. Hess RS. Hypoadrenocorticism. In: Ettinger S, Feldman E, Cote E, eds. *Textbook of Veterinary Internal Medicine.* 8th. Vol 2. Elsevier; 2017:1825–1832.
3. Willard MD, Schall WD, McCaw DE, Nachreiner RF. Canine hypoadrenocorticism: report of 37 cases and review of 39 previously reported cases. *J Am Vet Med Assoc.* 1982;180(1):59–62.

4. Boag AM, Catchpole B. A review of the genetics of hypoadrenocorticism. *Top Companion Anim Med.* 2014;29(4):96–101. doi:10.1053/j.tcam.2015.01.001
5. Hauck C, Schmitz SS, Burgener IA, et al. Prevalence and characterization of hypoadrenocorticism in dogs with signs of chronic gastrointestinal disease: a multicenter study. *J Vet Intern Med.* 2020;34(4):1399–1405. doi:10.1111/jvim.15752
6. Peterson ME, Kintzer PP, Kass PH. Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism: 225 cases (1979–1993). *J Am Vet Med Assoc.* 1996;208(1):85–91.
7. Baumstark ME, Sieber-Ruckstuhl NS, Müller C, Wenger M, Boretti FS, Reusch CE. Evaluation of aldosterone concentrations in dogs with hypoadrenocorticism. *J Vet Intern Med.* 2014;28(1):154–159. doi:10.1111/jvim.12243
8. DiBartola SP. Disorders of sodium and water: hypernatremia and hyponatremia. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice.* 4th ed. Elsevier; 2012:45–79.
9. DiBartola SP, Autran De Morais H. Disorders of potassium: hypokalemia and hyperkalemia. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice.* 4th ed. Elsevier; 2012:92–119.
10. Kemppainen RJ, Behrend EN. Adrenal physiology. *Vet Clin North Am Small Anim Pract.* 1997;27(2):173–186. doi:10.1016/S0195-5616(97)50026-X
11. Haviland RL, Toaff-Rosenstein RL, Reeves MP, Littman MP. Clinical features of hypoadrenocorticism in soft-coated wheaten terrier dogs: 82 cases (1979–2013). *Can Vet J.* 2016;57(4):387–394.
12. Kintzer PP, Peterson ME. Treatment and long-term follow-up of 205 dogs with hypoadrenocorticism. *J Vet Intern Med.* 1997;11(2):43–49. doi:10.1111/j.1939-1676.1997.tb00072.x
13. Lynn RC, Feldman EC, Nelson RW. Efficacy of microcrystalline desoxycorticosterone pivalate for treatment of hypoadrenocorticism in dogs. *J Am Vet Med Assoc.* 1993;202(3):392–396.
14. Lathan P, Thompson AL. Management of hypoadrenocorticism (Addison's disease) in dogs. *Vet Med (Auckl).* 2018;9:1–10. doi:10.2147/VMRR.S125617
15. Dechra Veterinary Products. Package insert for Zycortal. Accessed January 2, 2023. https://www.dechra-us.com/Files/Files/SupportMaterialDownloads/US/ZYC21001-PI-0221-Final.pdf
16. Bates JA, Shott S, Schall WD. Lower initial dose desoxycorticosterone pivalate for treatment of canine primary hypoadrenocorticism. *Aust Vet J.* 2013;91(3):77–82. doi:10.1111/avj.12019
17. Jaffey JA, Nurre P, Cannon AB, DeClue AE. Desoxycorticosterone pivalate duration of action and individualized dosing intervals in dogs with primary hypoadrenocorticism. *J Vet Intern Med.* 2017;31(6):1649–1657. doi:10.1111/jvim.14828
18. Sieber-Ruckstuhl NS, Reusch CE, Hofer-Inteeworn N, et al. Evaluation of a low-dose desoxycorticosterone pivalate treatment protocol for long-term management of dogs with primary hypoadrenocorticism. *J Vet Intern Med.* 2019;33(3):1266–1271. doi:10.1111/jvim.15475
19. Vincent AM, Okonkowski LK, Brudvig JM, et al. Low-dose desoxycorticosterone pivalate treatment of hypoadrenocorticism in dogs: a randomized controlled clinical trial. *J Vet Intern Med.* 2021;35(4):1720–1728. doi:10.1111/jvim.16195
20. Dropkin CA, Kruger JM, Langlois DK. Evaluation of urine electrolytes for the diagnosis of hypoadrenocorticism in dogs. *Vet Clin Pathol.* 2021;50(4):507–514. doi:10.1111/vcp.13018
21. Lennon EM, Hummel JB, Vaden SL. Urine sodium concentrations are predictive of hypoadrenocorticism in hyponatraemic dogs: a retrospective pilot study. *J Small Anim Pract.* 2018;59(4):228–231. doi:10.1111/jsap.12792
22. Gold AJ, Langlois DK, Refsal KR. Evaluation of basal serum or plasma cortisol concentrations for the diagnosis of hypoadrenocorticism in dogs. *J Vet Intern Med.* 2016;30(6):1798–1805. doi:10.1111/jvim.14589
23. Moore GE, Hoenig M. Duration of pituitary and adrenocortical suppression after long-term administration of anti-inflammatory doses of prednisone in dogs. *Am J Vet Res.* 1992;53(5):716–720.
24. Sullivant AM, Lathan P. Ketoconazole-induced transient hypoadrenocorticism in a dog. *Can Vet J.* 2020;61(4):407–410.
25. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med.* 2019;33(2):363–382. doi:10.1111/jvim.15454
26. Baumstark ME, Nussberger J, Boretti FS, et al. Use of plasma renin activity to monitor mineralocorticoid treatment in dogs with primary hypoadrenocorticism: desoxycorticosterone versus fludrocortisone. *J Vet Intern Med.* 2014;28(5):1471–1478. doi:10.1111/jvim.12426
27. Flad TM, Conway JD, Cunningham SK, McKenna TJ. The role of plasma renin activity in evaluating the adequacy of mineralocorticoid replacement in primary adrenal insufficiency. *Clin Endocrinol (Oxf).* 1996;45(5):529–534. doi:10.1046/j.1365-2265.1996.00838.x
28. Reisch N, Arlt W. Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin North Am.* 2009;38(2):407–418. doi:10.1016/j.ecl.2009.01.008
29. Beer-Borst S, Hayoz S, Gréa Krause C, Strazzullo P. Validation of salt intake measurements: comparisons of a food record checklist and spot-urine collection to 24-h urine collection. *Public Health Nutr.* 2022;25(11):2983–2994. doi:10.1017/S1368980022001537
30. Kamel KS, Ethier JH, Richardson RM, Bear RA, Halperin ML. Urine electrolytes and osmolality: when and how to use them. *Am J Nephrol.* 1990;10(2):89–102. doi:10.1159/000168062
31. Segawa H, Higashi A, Masuda I, Yoshii K, Iwahori T, Ueshima H. Urinary sodium/potassium ratio as a screening tool for hyperaldosteronism in men with hypertension. *Hypertens Res.* 2021;44(9):1129–1137. doi:10.1038/s41440-021-00663-9
32. Salman E, Kadota A, Okami Y, et al. Investigation of the urinary sodium-to-potassium ratio target level based on the recommended dietary intake goals for the Japanese population: the INTERMAP Japan. *Hypertens Res.* 2022;45(12):1850–1860. doi:10.1038/s41440-022-01007-x
33. Santos JA, Bolton KA, Rosewarne E, et al. Agreement between 24-hour urine and 24-hour food recall in measuring salt intake in primary school children in Australia. *Nutr J.* 2022;21(1):68. doi:10.1186/s12937-022-00823-8
34. Tabibzadeh N, Crambert G. Mechanistic insights into the primary and secondary alterations of renal ion and water transport in the distal nephron. *J Intern Med.* 2023;293(1):4–22. doi:10.1111/joim.13552
35. Waldrop JE. Urinary electrolytes, solutes, and osmolality. *Vet Clin North Am Small Anim Pract.* 2008;38(3):503–512 doi:10.1016/j.cvsm.2008.01.011

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.