

Standard Article

J Vet Intern Med 2017;31:1649–1657**Desoxycorticosterone Pivalate Duration of Action and Individualized Dosing Intervals in Dogs with Primary Hypoadrenocorticism**J.A. Jaffey , P. Nurre, A.B. Cannon, and A.E. DeClue

Background: Clinicians alter dosing for desoxycorticosterone pivalate (DOCP) to mitigate costs, but this practice has not been critically evaluated in a prospective clinical trial.

Hypothesis/Objectives: The duration of action of DOCP is longer than 30 days in dogs with primary hypoadrenocorticism (PH).

Animals: A total of 53 client-owned dogs with PH. Twenty-four dogs with newly diagnosed PH (Group 1) and 29 dogs with treated PH (Group 2).

Methods: Prospective, multicenter, clinical trial. For phase I, DOCP was administered and plasma sodium and potassium concentrations were measured until the dog developed hyponatremia or hyperkalemia at a planned evaluation, or displayed clinical signs with plasma electrolyte concentrations outside of the reference interval independent of a planned evaluation, thus defining DOCP duration of action. Plasma electrolyte concentrations then were assessed at the end of the individualized dosing interval (IDI; i.e., DOCP duration of action minus 7 days, phase II and at least 3 months after concluding phase II, phase III).

Results: The duration of action of DOCP in dogs in phase I with naïve PH (n = 24) ranged from 32 to 94 days (median, 62 days; 95% confidence interval [CI], 57, 65) and previously treated PH (n = 29) from 41 to 124 days (median, 67 days; CI, 56, 72). Overall, the final DOCP dosing interval for all dogs that completed phase II (n = 36) ranged from 38 days to 90 days (median, 58 days; CI, 53, 61). No dog that completed phase III (n = 15) required reduction in the IDI. The DOCP duration of action, independent of group, was not significantly associated with several baseline variables. The median drug cost reduction using IDI was approximately 57.5% per year.

Conclusion and Clinical Importance: The duration of action of DOCP in dogs with PH is >30 days, and plasma sodium and potassium concentrations can be maintained with an IDI >30 days long term.

Key words: addisons; desoxycorticosterone pivalate; mineralocorticoid.

The cost of DOCP treatment is a treatment-limiting factor for some clients. Clinicians have adopted various methods to decrease costs associated with long-term use of DOCP in dogs with PH. One common recommendation involves a 10% monthly DOCP dose reduction until plasma sodium and potassium concentrations start to trend outside of the reference interval, at which time the next dose is increased to the previous dose that resulted in plasma electrolyte concentrations within the reference interval.^{1,2} Another strategy is prolongation of the treatment interval. Because prolongation of the treatment interval by as little as 4 days would result in a greater cost reduction than a 10% dose decrease, we elected to investigate a dosing

Abbreviations:

ACTH	adrenocorticotrophic hormone
DOC	desoxycorticosterone
DOCP	desoxycorticosterone pivalate
IDI	individualized dosing interval
PH	primary hypoadrenocorticism
PRA	plasma renin activity

strategy that focused on extension of the DOCP treatment interval. In a retrospective study, dogs with PH were successfully managed with DOCP at intervals longer than the manufacturer recommended 25 days suggesting this strategy could be successful.³

The goal of our study was to identify if IDI could decrease the medication cost of DOCP for dogs with naïve and previously treated PH. For phase I of the study, we investigated the pharmacodynamic duration of action of DOCP. We hypothesized that the duration of action of DOCP is >30 days in dogs with PH. For phase II of the study, we hypothesized that administration of DOCP at an IDI (DOCP duration of action minus 7 days) would result in plasma sodium and potassium concentrations within the reference interval. Finally, for phase III of the study, we hypothesized that dogs treated with DOCP at IDIs will maintain plasma sodium and potassium concentrations within the reference interval on the last day of their dosing interval after at least 3 months of treatment. At the end of the study, a relative medication cost analysis was performed to determine if IDI decreased the per year DOCP cost. Finally, as a secondary objective, we wanted to

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The study was not supported by a grant.

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Submitted December 23, 2016; Revised July 31, 2017; Accepted August 9, 2017.

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DOI: 10.1111/jvim.14828

determine if there are clinical characteristics at baseline that predict the duration of action of DOCP.

Materials and Methods

Study Design

Our study was a prospective, multicenter, clinical trial conducted at 17 veterinary hospitals located in California, Colorado, New Mexico, Florida, Nevada, and Texas.

Inclusion and Exclusion Criteria

Dogs of any age, breed, or sex were enrolled between January 2011 and March 2015. The study protocol was reviewed and approved by the veterinarians and administration of each of the veterinary clinics involved, and informed consent of all pet owners was obtained before including the dogs in the study. Client-owned dogs with newly diagnosed PH naïve to DOCP treatment and dogs with PH that had previously been treated with DOCP were candidates for enrollment.

To be enrolled, each dog had to have a CBC, plasma biochemistry profile, urinalysis, ACTH stimulation test performed, and be otherwise healthy. Requirements for a diagnosis of PH were pre- and post-ACTH serum cortisol concentrations $<2 \mu\text{g/dL}$ and hyponatremia, hyperkalemia, or both. Dogs with iatrogenic primary hypoadrenocorticism (ie, due to mitotane or trilostane treatment or adrenalectomy), dogs treated with glucocorticoids within 30 days before the diagnosis of hypoadrenocorticism and dogs with known comorbidities (known history of chronic renal failure, congestive heart failure, liver failure, portal hypoplasia, protein-losing enteropathy, protein-losing nephropathy, or portosystemic shunt) were excluded. Additionally, dogs were excluded if they were receiving angiotensin-converting enzyme inhibitors, diuretics, insulin, or beta-blockers to treat a comorbid condition. These comorbidities and medications were chosen because of the unknown effect they may have when evaluating the duration of action of DOCP because each may alter carrier proteins, blood volume, or plasma electrolyte concentrations. Failure of owner compliance was defined as missing >2 (phase I) or 1 (phase II and III) scheduled evaluations or refusal to follow the DOCP dosing protocol. The development of adverse effects consistent with poor control and death was not reasons for exclusion.

Study Protocol

Dogs that were newly diagnosed with PH and were naïve to treatment with DOCP^a were assigned to Group 1. Dogs with PH that had been treated previously with DOCP were assigned to Group 2. A standardized questionnaire and physical examination checklist were not utilized, but at each evaluation, owners were asked standard history questions in addition to questions pertaining directly to clinical signs that may be related to PH including vomiting, diarrhea, anorexia, lethargy, trembling, or collapse.

Phase I

For phase I, dogs from Group 1 were treated with DOCP at the attending clinician's discretion (2.1–2.6 mg/kg), and dogs from Group 2 were treated with DOCP at dosages used before study enrollment (1.4–2.4 mg/kg). Plasma sodium and potassium concentrations then were measured 30 days post-administration of DOCP. Dogs with plasma sodium and potassium concentrations within the reference interval at the first evaluation postadministration of DOCP 30 days post-treatment had plasma sodium and potassium concentrations measured once every 7 days until

hyponatremia or hyperkalemia developed at a planned evaluation or the dog exhibited clinical signs associated with PH (eg, vomiting, diarrhea, anorexia, lethargy, trembling, collapse)² and had concurrent plasma electrolyte concentrations outside of the reference interval on a day outside of a scheduled evaluation. If a dog was evaluated for clinical signs believed to be related to PH and plasma electrolyte concentrations were within the reference interval, DOCP was not administered and the dog was evaluated at the next planned evaluation. The duration of action of DOCP was recorded as the duration of time from DOCP administration to the time that either hyponatremia or hyperkalemia developed. Desoxycorticosterone pivalate was administered at the conclusion of phase I at the same dose utilized at the start of phase I, and dogs were evaluated next at the end of their IDI (ie, individual dog duration of action of DOCP determined in phase I minus 7 days). The severity of hyponatremia at the conclusion of phase I was described according to deviation from the lower end of the reference interval: borderline ($\leq 5 \text{ mEq/L}$), mild (6–10 mEq/L), moderate (11–15 mEq/L), and severe ($\geq 16 \text{ mEq/L}$).⁴ The severity of hyperkalemia at the conclusion of phase I was described according to deviation from the upper end of the reference interval: mild (5.5–6.5 mEq/L), moderate (6.5–7.5 mEq/L), and severe ($>7.5 \text{ mEq/L}$).⁵

Phase II

The goal for phase II was to determine whether, at the end of the IDI, the plasma sodium and potassium concentrations were within the reference interval. The plasma sodium and potassium concentrations were evaluated on the last day of the IDI. If hyponatremia, hyperkalemia, or clinical signs associated with PH along with hyponatremia, hyperkalemia, or both were noted at any time from the end of phase I to the last day of the IDI, DOCP was administered, and the IDI was decreased by 7 days. If a dog was evaluated for clinical signs believed to be related to PH and the plasma electrolyte concentrations were within the reference interval, DOCP was not administered and the dog was evaluated on the last day of the IDI. In dogs with decreased IDI, plasma sodium and potassium concentrations were evaluated again at the end of the new adjusted IDI. This process continued until the plasma sodium and potassium concentrations were within the reference interval on the last day of the IDI marking the end of phase II. The conclusion of phase II defined the final DOCP treatment interval.

Phase III

To determine if dogs with PH could be managed long term with DOCP administered with an IDI, plasma sodium and potassium concentrations as well as clinical signs were evaluated on the last day of the IDI established by phase II (final DOCP treatment interval), at least 3 months after the conclusion of phase II.

Analytical Procedures

Plasma sodium and potassium concentrations for each dog were evaluated on a biochemistry profile or venous blood gas analyzer located on the premises at each institution.^{b-i} There were multiple analyzers used in the study, but each dog was evaluated with the same analyzer throughout the study and follow-up period. Reference intervals were determined based on the individual analyzer.

Statistical Analysis

Statistical analysis was performed by commercial software.^j Data were expressed as median, range, and CI. A Shapiro–Wilk

test was used to assess normality. Differences in baseline variables between Group 1 and 2 were evaluated by a Mann–Whitney *U*-test. Multiple linear regression analysis was used to evaluate associations between DOCP duration of action (dependent variable) and baseline characteristics (independent variables: DOCP dose, prednisone dose, weight, age, and time treated with DOCP before phase I). The variance inflation factor for all predictors was <2. The level of significance was set at $P < 0.05$.

Relative Cost Analysis

A relative cost analysis was performed to demonstrate the expected cost savings utilizing the individualized DOCP treatment interval protocol determined in the study compared to the manufacturer recommended 25-day treatment interval. Estimates of the unit costs of DOCP were derived from an analysis of the current market price of DOCP (\$ 2.00 per milligram) using a dosage of 2.2 mg/kg. Expected costs were calculated using the median weight of the dogs that completed phase II of the study. The number of DOCP treatment intervals per year was defined as either manufacturer recommended $365/25 = 14.6$, or by the 95% CI for the median DOCP treatment interval determined in the study.

Results

Sixty-two dogs were enrolled in the study (Fig. 1). Nine dogs (Group 1, $n = 4$; Group 2, $n = 5$) were excluded from analysis of phase I because of owner preference or failure to comply with the study evaluation schedule. Seventeen dogs (Group 1, $n = 7$; Group 2, $n = 10$) were excluded from analysis of phase II because of owner preference or failure to comply with the study evaluation schedule. A total of 21 dogs (Group 1, $n = 7$; Group 2, $n = 14$) was excluded from analysis of phase III because of owner preference or failure to comply with the study evaluation schedule.

Animals

Group 1

Twenty-four dogs were included in Group 1. The age range was 0.4–11.2 years (median, 4.5 years), and the body weight ranged from 3.3 to 32 kg (mean, 16.25 kg). There were 14 spayed females and 10 castrated males. Seventeen purebred dogs and 7 mixed-breed dogs were included; Standard Poodle ($n = 4$), Beagle ($n = 2$), Labrador Retriever ($n = 5$), Maltese ($n = 2$), and 1 of each Miniature Poodle, Toy Poodle, Rat Terrier, and Doberman Pinscher.

Group 2

Twenty-nine dogs were included in Group 2. The age range was 0.8–13 years (median, 6.5 years), and the body weight ranged from 3.0 to 63 kg (median, 24.2 kg). There were 18 spayed females and 11 castrated males. Twenty-four purebred dogs and 5 mixed-breed dogs were included; Standard Poodle ($n = 6$), Labrador Retriever ($n = 5$), West Highland White Terrier ($n = 3$), Great Dane ($n = 2$), and 1 of each Miniature Poodle, English Springer Spaniel, Rottweiler, Shih Tzu, Pomeranian, Bearded Collie, Pit Bull Terrier and Yorkshire Terrier. The number of days from initial diagnosis of PH to enrollment ranged from 30 to 2,450 days (median, 431 days).

Phase I

Group 1

All 24 dogs in Group 1 completed phase I, and no dogs required evaluation at a time other than the scheduled evaluation. Two dogs exhibited clinical signs that might have been attributable to PH on the day their sodium or potassium concentrations or both fell outside of the reference interval (ie, lethargy and hyponatremia [$n = 1$]; trembling and hyperkalemia [$n = 1$]). No other dogs had clinical signs of PH during the treatment period. The duration of action of DOCP ranged from 32 to 94 days (median, 62; 95% CI, 57, 65; Fig. 2). Dogs received DOCP at dosages that ranged from 2.1 to 2.6 mg/kg (median, 2.2 mg/kg). Eighteen dogs from Group 1 received DOCP at 2.2 mg/kg, 1 dog received 2.6 mg/kg, 3 dogs received 2.3 mg/kg, and 2 dogs received 2.1 mg/kg. There were deviations from the proposed evaluation schedule as a consequence of owner compliance. The actual evaluation timing for dogs from Group 1 was first evaluation 21–36 days post-DOCP administration and once every 5–17 days thereafter.

Group 2

All 29 dogs in Group 2 completed phase I, and no dogs required evaluation at a time other than the scheduled evaluation. Three dogs exhibited clinical signs that might have been attributable to PH on the day their sodium or potassium concentrations or both fell outside of the reference interval (ie, trembling and hyperkalemia [$n = 1$]; trembling and hyponatremia [$n = 1$]; hypoxemia and hyponatremia [$n = 1$]). The duration of action of DOCP ranged from 41 to 124 days (median, 67; 95% CI, 56, 72; Fig. 2). Dogs received DOCP at dosages that ranged from 1.4 mg/kg to 2.4 mg/kg (median, 2.1 mg/kg). Eleven dogs from Group 2 received DOCP at 2.2 mg/kg, 1 dog received 2.4 mg/kg, 4 dogs received 2.1 mg/kg, 3 dogs received 2.0 mg/kg, 1 dog received 1.9 mg/kg, 4 dogs received 1.8 mg/kg, 1 dog received 1.7 mg/kg, 2 dogs received 1.6 mg/kg, 1 dog received 1.5 mg/kg, and 1 dog received 1.4 mg/kg. There were some deviations from the proposed evaluation schedule as a consequence of owner compliance. The actual evaluation timing for dogs from Group 2 was first evaluation 24–37 days post-DOCP administration and once every 6–21 days thereafter.

Group 1 versus Group 2: DOCP Duration of Action and Baseline Characteristics

There was no significant difference between groups with respect to DOCP duration of action defined by phase I ($P = 0.421$; Table 1). Dogs from Group 1 received a higher dose of DOCP ($P < 0.001$) and prednisone ($P = 0.01$) than dogs from Group 2 (Table 1). Dogs from Group 2 were older ($P = 0.049$) than dogs from Group 1 (Table 1).

Plasma Sodium and Potassium Concentration at the End of Phase I

Upon completion of phase I, 16 of 53 dogs had plasma sodium concentrations within the reference interval. Of the remaining dogs, the severity of hyponatremia was borderline in 33 of 53 and mild in 4 of 53 dogs at the end of phase I. Additionally, 29 of 53 dogs

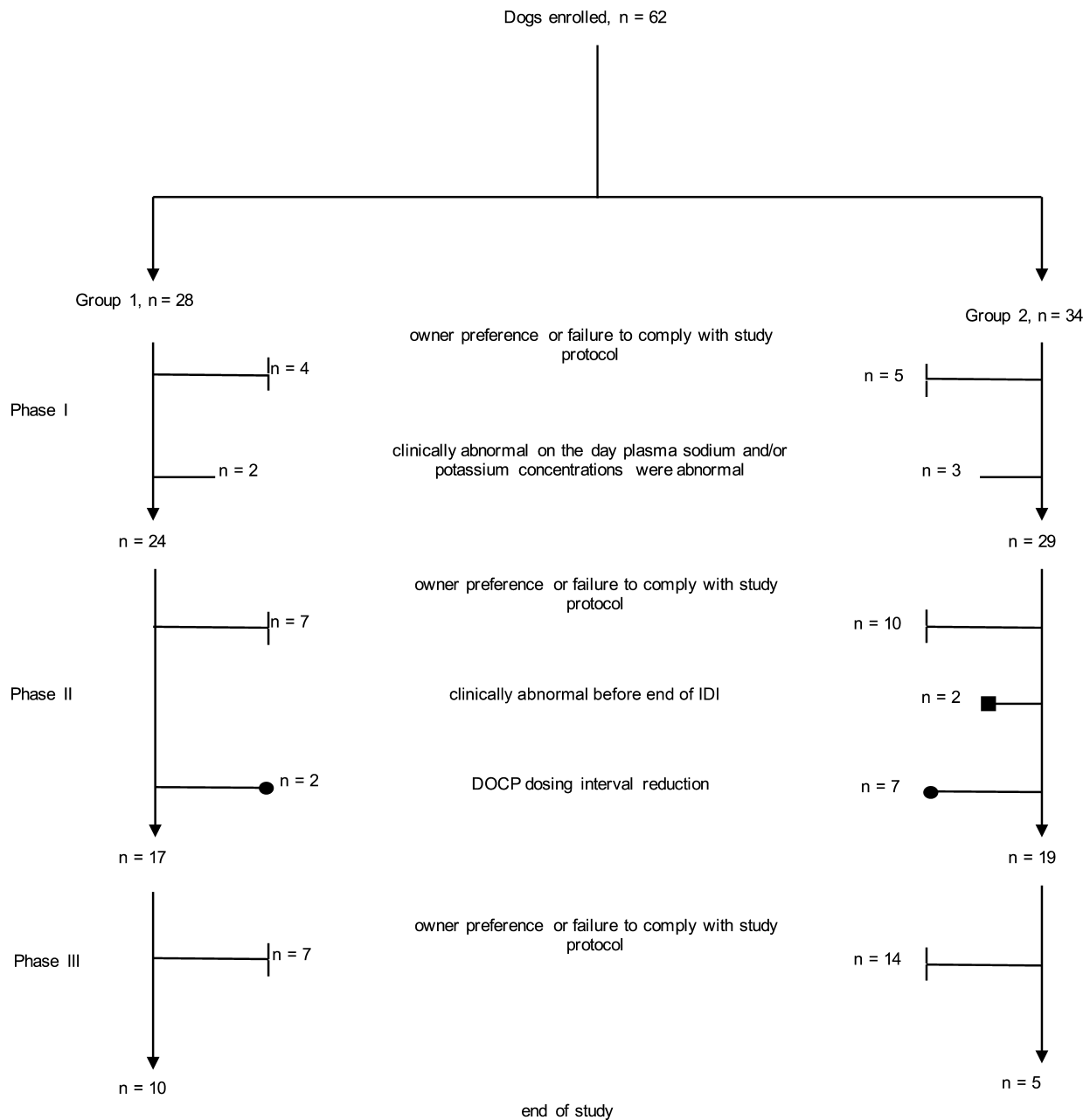


Fig 1. Allocation of treatment groups for dogs with naïve (Group 1) and previously treated (Group 2) PH. Lines with arrows indicate progression of dogs that entered the study, phase I, phase II, and phase III. Lines with terminal ends indicate when dogs were excluded from the study. Lines with open ends indicate when dogs exhibited clinical signs that may have been associated with PH on the day the plasma sodium and/or potassium concentrations were outside of the reference interval. The line with a terminal box indicates dogs that displayed clinical signs that may have been associated with PH before the last day of the IDI. Lines with a terminal circle indicate dogs that required a DOCP dosing interval reduction. DOCP, desoxycorticosterone pivalate; IDI, individualized dosing interval; n, number of dogs in group.

had plasma potassium concentrations within the reference interval at the end of phase I. Of the remaining dogs, the severity of hyperkalemia was mild in 23 of 53 and moderate in 1 of 53 dogs at the completion of phase I. A total of 3 of 53 dogs had plasma sodium and potassium concentrations characterized as borderline hyponatremia with mild hyperkalemia, and 1 dog each was described as having mild hyponatremia with mild hyperkalemia and borderline hyponatremia with

moderate hyperkalemia. Lastly, at the end of phase I, 33 of 53 dogs had a Na-to-K ratio of <27 : 1.

Phase II

Group 1

Two of the 17 dogs from Group 1 included in analysis of phase II required a single DOCP dosing interval reduction before completion of phase II. No dogs

required evaluation at a time other than scheduled visits, and no dogs exhibited clinical signs of PH during the treatment period. The number of days the DOCP dosing interval was decreased in the 2 dogs from Group 1 upon completion of phase II was 5 and 19 days.

Group 2

Seven of the 19 dogs from Group 2 included in analysis of phase II required DOCP dosing interval reductions before completion of phase II. Four of those dogs needed 1 interval reduction, and 3 dogs required 2 interval reductions. A total of 2 of 19 dogs from Group 2 required evaluation before the end of their IDI. The primary complaints included lethargy ($n = 2$), trembling ($n = 1$), and hyporexia ($n = 2$). The aforementioned dogs presented 35 and 38 days before the end of their IDI after completion of phase I. Both dogs had plasma sodium and potassium concentrations outside of their respective reference intervals, but did not experience a hypotensive crisis and did not require hospitalization. The number of days the DOCP dosing interval was shortened in the 7 dogs from Group 2 upon completion of phase II ranged from 7 to 42 days (median, 35 days).

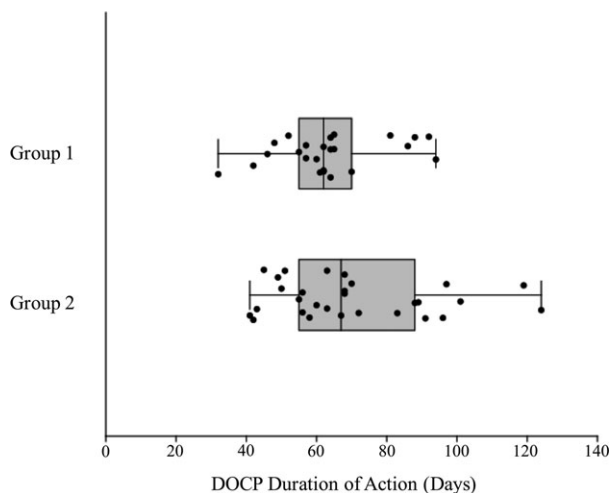


Fig 2. Box-and-whisker plots of the duration of action of DOCP in dogs newly diagnosed with hypoadrenocorticism (Group 1), and dogs previously diagnosed and treated with DOCP (Group 2). The boxes represent the 25th and 75th quartiles with the horizontal line representing the median. The whiskers represent the range of the data. The black circles represent dogs from Group 1, $n = 24$, and Group 2, $n = 29$.

Final DOCP Dosing Intervals

The final DOCP dosing interval for dogs from Group 1 ranged from 41 to 85 days (median, 56 days; 95% CI, 53, 60; Fig. 3). The final DOCP dosing interval for dogs from Group 2 ranged from 38 to 90 days (median, 59; 95% CI, 53, 67; Fig. 3). There was no significant difference between Group 1 and Group 2 with respect to the final DOCP dosing interval defined by completion of phase II ($P = 0.612$). The final DOCP dosing interval, independent of group, ranged from 38 days to 90 days (median, 58; 95% CI, 53, 61; Fig. 3).

Phase III

A total of 15 dogs (Group 1, $n = 10$; Group 2, $n = 5$) completed phase III. The number of days from conclusion of phase II to the last evaluation at which plasma electrolyte concentrations were determined on the last day of the IDI defined by this study, ranged from 110 days to 1,285 days (median, 274; CI 95%, 189, 591). None of 15 dogs required DOCP treatment interval reductions after completion of phase II.

Predictive Variables Associated with DOCP Duration of Action

Multiple linear regression was used to identify variables that predicted DOCP duration of action. For Group 1, the DOCP duration of action could not be significantly predicted by weight, prednisone dosage (mg/kg/d), DOCP dosage (mg/kg), or age (years; $R^2 = 0.192$, $F(4,19) = 1.127$, $P = 0.373$). For Group 2, the DOCP duration of action could not be significantly predicted by weight, prednisone dosage (mg/kg/d), DOCP dosage (mg/kg), age (years), or duration of treatment ($R^2 = 0.0883$, $F(5,23) = 0.446$, $P = 0.812$; Table 2).

Relative Cost Analysis

Expected costs were calculated using the median weight (18.1 kg) of the 36 dogs that completed phase I and phase II. Additionally, the number of DOCP treatment intervals per year was defined as either manufacturer recommended $365/25 = 14.6$ or by the DOCP dosing interval (58 days; 95% CI, 53, 61) defined by our study populations: $365/58 = 6.2$, $365/53 = 6.8$, $365/61 = 5.9$, respectively. The dosage used in both comparisons was 2.2 mg/kg. This analysis was performed

Table 1. Comparison of baseline variables between Group 1 and 2 by a Mann–Whitney U -test.

	Group 1	Group 2	P Value
DOA (days)	Median = 62, (range: 32–94)	Median = 67, (range: 41–124)	$P = 0.421$
DOCP dosage (mg/kg)	Median = 2.2, (range: 2.1–2.6)	Median = 2.1, (range: 1.4–2.4)	$P < 0.001$
Prednisone (mg/kg/d)	Median = 0.16, (range: 0.04–0.39)	Median = 0.10, (range: 0.02–0.30)	$P = 0.01$
Age (year)	Median = 4.5, (range: 0.4–11.2)	Median = 6.5, (range: 0.8–13)	$P = 0.049$
Weight (kg)	Median = 16.25, (range: 3.3–32)	Median = 24.2, (range: 3–63)	$P = 0.102$

DOA, duration of action; DOCP, desoxycorticosterone pivalate; mg, milligram; kg, kilogram.

assuming the current average market price of DOCP of approximately \$2.00 per milligram.

The total savings per year based on the median weight (18.1 kg) and by the 95% CI for the median DOCP treatment interval determined in this study (58 days; 95% CI, 53, 61), ranged from 54% to 60% (median, 57.5%).

Discussion

Ours is the first study to evaluate the duration of action of DOCP clinically and to determine if plasma sodium and potassium concentrations can be maintained using DOCP dosing intervals >30 days. In agreement with our hypothesis, the duration of action of DOCP is >30 days in dogs with newly diagnosed PH and in dogs with PH that previously have been treated with DOCP. In addition, our results were consistent with our hypothesis that administration of DOCP at an IDI (individual dog duration of action of DOCP determined in phase I minus 7 days) would result in plasma sodium and potassium concentrations within the reference interval on the last day of the dosing interval.

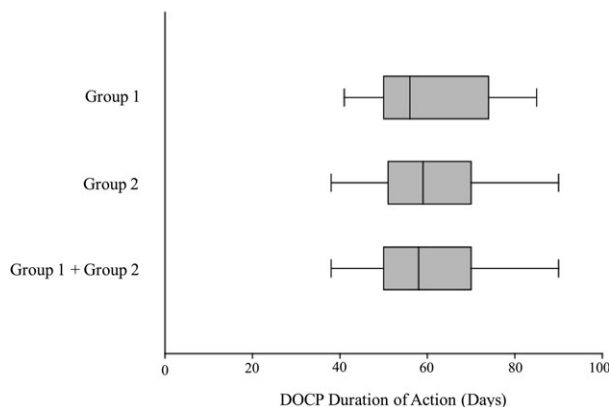


Fig 3. Box-and-whisker plots of the final individualized DOCP dosing intervals in dogs from Group 1 (n = 17), Group 2 (n = 19), and all dogs independent of group (Group 1 + Group 2, n = 36). The boxes represent the 25th and 75th quartiles with the horizontal line representing the median. The whiskers represent the range of the data.

Furthermore, our results were consistent with our hypothesis that dogs treated with DOCP with an IDI would maintain plasma sodium and potassium concentrations within the reference interval. We did not identify an association between glucocorticoid dosage, DOCP dosage, weight, age, or time treated with DOCP before enrollment (Group 2) and the duration of action of DOCP. Our results indicate that the duration of action of DOCP (Group 1 median = 62; Group 2 median = 67) is >30 days.

Limited information is available regarding the pharmacokinetics of DOCP in dogs.⁶ Our results suggest that the half-life of DOCP in dogs is longer than what was determined from initial clinical efficacy studies, on which current dosing recommendations are based.^{7,8}

Alternatively, the results from phase I of our study may reflect a spectrum of processes to maintain electrolyte balance including DOCP initially, followed by physiologic compensatory mechanisms. In humans with PH, it is not uncommon to have serum sodium and potassium concentrations (10%) within the reference interval or just serum potassium concentrations (25%) within the reference interval.⁹ Increased plasma renin activity (PRA) in the aforementioned people indicates compromised plasma volume suggesting concurrent mineralocorticoid deficiency despite serum electrolyte concentrations being within the reference interval.¹⁰ This phenomenon also has been investigated in dogs with PH.¹¹ It has been postulated that dogs with PH can maintain serum electrolyte concentrations within the reference interval if sodium intake is sufficient to maintain extracellular volume and adequate distal tubular flow rate to excrete sufficient potassium.¹² This theory is supported by an early experiment that evaluated serum sodium and potassium concentrations as well as plasma volume in adrenalectomized dogs receiving PO sodium chloride and sodium bicarbonate in the absence of hormone substitution.¹³ Dogs in the aforementioned study maintained serum electrolyte concentrations within the reference interval and normal plasma volume with PO sodium supplementation alone for over 150 days.¹³ However, dogs commonly refused to eat the heavily salted food and thus a stomach tube was used for administration. Diet was not controlled for in our study, and additional studies evaluating its effect on IDI are warranted.

Table 2. Multiple linear regression analysis to evaluate associations between DOCP duration of action (dependent variable) and baseline characteristics (independent variables: DOCP dosage, prednisone dosage, weight, age, and time treated with DOCP before phase I).

	Group 1			Group 2		
	Coefficient	SE	P Value	Coefficient	SE	P Value
DOCP dosage	59.179	35.546	0.112	25.618	21.969	0.256
Prednisone dosage	3.742	35.827	0.918	31.169	64.848	0.635
Age	-0.0356	1.273	0.978	-0.409	1.61	0.802
Weight	0.559	0.377	0.155	0.199	0.378	0.604
Duration of treatment				0.005	0.007	0.502

DOCP, desoxycorticosterone pivalate.

Mineralocorticoid replacement treatment in people with PH is titrated according to clinical signs as well as measurement of PRA.¹⁴ In human medicine, PRA is the most sensitive marker of mineralocorticoid dosing.¹⁵ Although it is controversial where within the reference interval ideal PRA falls in people with PH, it is uniformly accepted that complete suppression of PRA is suggestive of excessive mineralocorticoid treatment.^{10,14,16} A recent study evaluated PRA in dogs with PH treated with fludrocortisone acetate or DOCP.¹⁷ All of the dogs treated with DOCP in that study exhibited a progressive decrease in PRA leading to complete suppression.¹⁷ Results from the aforementioned study emphasize the need to identify an alternative DOCP strategy to treat dogs with PH. Our results demonstrate that the use of an IDI longer than 30 days may be an effective option for the treatment of dogs with PH long term. Admittedly, the use of plasma electrolyte concentrations and clinical signs as markers of clinical control may not reflect adequate plasma volume. In humans with PH, PRA is negatively correlated with plasma volume.¹⁸ The utilization of PRA as a marker for DOCP treatment would have been ideal, but the complexity of blood sampling and sparse availability of this test make it impractical for most practitioners to use in management of dogs with PH.¹⁷ A total of 15 dogs completed phase III, and thus a conclusion related to the safety and efficacy of using IDI for the long-term management of dogs with PH cannot be made. Additional studies incorporating a large number of dogs with PH treated with the IDI protocol and followed long term are needed to evaluate long-term safety.

Interestingly, 13 of the 36 dogs that completed phase II had IDI >30 days while using dosages lower than the manufacturer recommended 2.2 mg/kg. It is unclear why these dogs were treated with lower dosages, because dosing was left to the discretion of the overseeing clinician. Our study results suggest that dogs with PH may be capable of being maintained with a DOCP treatment protocol that combines IDI with a dosage lower than that recommended by the manufacturer. Future studies critically evaluating DOCP dose reduction after identification of the IDI are needed to confirm this possibility. We caution against simultaneously decreasing the dose of DOCP and increasing the treatment interval because this approach was not evaluated in our study and might be dangerous.

The dogs in Group 1 were treated with significantly higher doses of prednisone during the study when compared to dogs from Group 2. The prednisone dosage used in newly diagnosed dogs is commonly higher than that used in dogs with established treatment regimens.^{1,2,19,20} The initial prednisone dosage is gradually tapered until the lowest dose that will control clinical signs has been identified. The lack of significant difference in DOCP duration of action defined by phase I between the groups in our study suggests that the dosage of glucocorticoid supplementation does not substantially influence DOCP treatment interval. Furthermore, glucocorticoids have variable amounts of mineralocorticoid activity depending on their structures and metabolites.²¹ In humans, high doses of

hydrocortisone (in excess of 100 mg/d) have been shown to have marked mineralocorticoid effects, causing excessive sodium retention and potassium wasting.²¹ Although hydrocortisone is not typically used in the long-term management of hypoadrenocorticism in veterinary medicine, it can be used as a benchmark for comparison showing that the low dosages of prednisone used to treat dogs with PH should not substantially influence the DOCP treatment interval. Additionally, dogs from Group 1 were treated with a significantly higher dosage of DOCP than dogs in Group 2. Although this difference was statistically significant, the difference is not believed to be clinically relevant. This supposition is supported by the lack of difference in the duration of action of DOCP between the groups.

We were interested in knowing if there were characteristics at baseline that could predict the duration of action of DOCP and thus the expected IDI. To investigate this, we performed a multiple linear regression analysis and did not identify a baseline characteristic predictive of DOCP duration of action. However, we only evaluated glucocorticoid dosage, DOCP dosage, weight, age, and time treated with DOCP before enrollment (Group 2). Furthermore, the duration of time dogs from Group 2 was treated with DOCP before enrollment was not significantly associated with DOCP duration of action. This finding is interesting because 7 of 19 dogs from Group 2 required a DOCP dosing interval reduction before the completion of phase II. The magnitude of drug plasma protein binding substantially affects the pharmacokinetics and pharmacodynamics of a drug because only the unbound fraction can exert its biological effect or be available for metabolism or excretion.²² The plasma protein-bound drug in plasma also can serve as a reservoir for free drug, slowing its elimination and prolonging its duration of action.²² Desoxycorticosterone (DOC) is 90% bound to plasma proteins, thus only 10% of DOC is unbound and available to exert a biological effect or be eliminated.²³ It is therefore reasonable to suspect that dogs previously treated with DOCP at 2.2 mg/kg every 25 days accumulate a supraphysiologic plasma reserve of DOC (bound to plasma proteins), which results in prolongation of the duration of action initially and as the plasma reserve decreases, so does the duration of action. Additional studies focusing on the pharmacokinetics and pharmacodynamics of DOCP in dogs with PH are needed to confirm this hypothesis.

Our study had several potential limitations. One limitation is that blood samples were analyzed at different laboratories. To account for this variation, treatment decisions were based on the reference intervals for the laboratory of each dog, as would be expected in standard clinical practice. Additionally, for each individual dog, the analytical methodology was kept consistent during the duration of the study to maintain individual consistency. A second limitation is the inconsistent DOCP dosages used, although the dosage remained the same for each dog through the duration of the study. Our results may underestimate the DOCP dosing interval because not every dog was treated with the

manufacturer-recommended dosage of 2.2 mg/kg/d. However, our regression analysis did not find an association between DOCP dosage and DOCP dosing interval. Another limitation is that plasma electrolyte concentrations were not assessed at the time of maximal effect. However, because of the lack of pharmacokinetic information, the time of maximal effect is unknown. Based on previous clinical efficacy studies, the time related to maximum effect can be estimated to be 10–14 days post-DOCP administration. Logistically, it was unreasonable to attempt to investigate the maximum effect of DOCP, because doing so would have required plasma electrolyte concentrations to be measured once a day on days 10–14 post-DOCP administration. An additional limitation is that electrolyte evaluations were recommended to occur weekly after the first evaluation, but as a result of owner compliance the interval ranged from 5 to 21 days. Repeated evaluations with plasma electrolyte concentrations within the reference interval may have influenced clients to not adhere firmly to the scheduled appointments. If these methods are adopted in clinical practice, weekly electrolyte evaluations after the first assessment are suggested. We did not utilize a specific questionnaire to collect subjective data from owners, nor was there a standard methodology in which clinicians collected data pertaining to physical examination and vital parameters. However, at each evaluation, owners were asked standard history questions in addition to questions pertaining directly to clinical signs that may be related to PH including vomiting, diarrhea, anorexia, lethargy, trembling, or collapse. Sodium-to-potassium ratios were not utilized to monitor electrolyte changes, nor were clinical decisions made using this metric, which should be used with caution. The fact that only 33 of 53 dogs had a Na-to-K ratio of <27 : 1 at the time that hyponatremia, hyperkalemia, or both were identified at the end of phase I highlights the importance of avoiding the use of this ratio as a sole evaluative tool for determining IDI. Had the Na-to-K ratio been used exclusively to determine the IDI, 38% of dogs with electrolyte abnormalities would have been missed. An additional limitation is that we relied on the evaluation of plasma electrolyte concentrations and clinical signs rather than determination of PRA to monitor mineralocorticoid treatment. Reliance on the aforementioned variables instead of PRA may have overestimated mineralocorticoid control. A final limitation is that only 15 of 36 dogs that completed phase II were available for analysis of phase III. Therefore, it is possible a dog's IDI may require adjustment over time if there are changes in drug metabolism, decrease in the concentration of carrier proteins, or if a dog develops a comorbidity that influences the renin angiotensin aldosterone system or plasma electrolyte concentrations (eg, congestive heart failure, liver failure, chronic renal failure).

We conclude that individual dosing interval can be evaluated by measuring plasma sodium and potassium concentrations weekly starting 25–30 days post-DOCP administration to identify the duration of action. The IDI then is determined by subtracting 7 days from

the duration of action. Using this method, the duration of action of DOCP in dogs with PH is >30 days and plasma sodium and potassium concentrations can be maintained with an IDI >30 days long term. This new approach to long-term mineralocorticoid replacement treatment will decrease the cost of treatment as a result of a decreased total yearly dose of DOCP and possibly less frequent hospital visits for injections. The application of these data to the management of client-owned dogs with PH should be on a case-by-case basis as deemed appropriate. We acknowledge the possibility that use of plasma electrolyte concentrations and the absence of clinical signs as markers of clinical control may not equate to pharmacokinetic control and more extensive, longer term studies are needed to confirm the safety and efficacy of this management approach.

Footnotes

- ^a Percorten-V, Novartis Animal Health., Greensboro, NC
 - ^b IMMULITE 2000 Immunoassay System, Siemens AG Corp., Munich, Germany
 - ^c ABL800 Flex blood gas analyzer, Radiometer Medical ApS, Brea, CA
 - ^d VetStat Electrolyte and Blood Gas Analyzer, IDEXX Laboratories, Inc., Westbrook, ME
 - ^e VetScan Vspro, Abaxis, Union City, CA
 - ^f Catalyst Dx Chemistry Analyzer, IDEXX Laboratories, Inc., Westbrook, ME
 - ^g DRI-CHEM 7000 Veterinary Chemistry Analyzer, Heska Corp., Loveland, CO
 - ^h Stat Profile pHox Ultra, Nova Biomedical Corp., Waltham, MA
 - ⁱ VetScan i-STAT 1 300V, Abaxis, Union City, CA
 - ^j SigmaPlot, Systate Software
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Acknowledgment

The authors thank Kate Anderson for her help with the literature review.

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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