Received: 20 December 2018 | Accepted: 21 February 2019

DOI: 10.1111/jvim.15475

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Evaluation of a low-dose desoxycorticosterone pivalate treatment protocol for long-term management of dogs with primary hypoadrenocorticism

Nadia S. Sieber-Ruckstuhl[1] | Claudia E. Reusch[1] | Nathalie Hofer-Inteeworn[1] | Claudia Kuemmerle-Fraune[1] | Claudia Müller[1] | Regina Hofmann-Lehmann[2] | Felicitas S. Boretti[1]

[1]Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

[2]Clinical Laboratory, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

Correspondence
Claudia E. Reusch, Vetsuisse Faculty, Clinic for Small Animal Internal Medicine, University of Zurich, Winterthurerstrasse 260, Zurich 8057, Switzerland.
Email: creusch@vetclinics.uzh.ch

Abstract

Background: Lowering the dose of desoxycorticosterone pivalate (DOCP) for the treatment of dogs with primary hypoadrenocorticism (PH) decreases costs and could lead to increased owner motivation to treat their affected dogs.

Objective: To evaluate the efficacy of a low-dose DOCP treatment protocol in dogs with PH.

Animals: Prospective study, 17 client-owned dogs with naturally occurring PH (12 newly diagnosed, 5 previously treated with fludrocortisone acetate [FC]).

Methods: Dogs with newly diagnosed PH were started on 1.5 mg/kg DOCP SC; dogs previously treated with FC were started on 1.0-1.8 mg/kg DOCP SC. Reevaluations took place at regular intervals for a minimum of 3 months and included clinical examination and determination of serum sodium and potassium concentrations. The DOCP dosage was adjusted to obtain an injection interval of 28-30 days and to keep serum electrolyte concentrations within the reference interval.

Results: Median (range) follow-up was 16.2 months (4.5-32.3 months). The starting dosage was sufficient in all but 2 dogs and had to be significantly decreased after 2-3 months to a median dosage (range) of 1.1 mg/kg (0.7-1.8). Dogs 3 years of age or younger needed significantly higher dosages compared to older dogs. None of them, however, needed the 2.2 mg/kg DOCP dosage, recommended by the manufacturer.

Conclusions and Clinical Importance: A starting dosage of 1.5 mg/kg DOCP is effective in controlling clinical signs and serum electrolyte concentrations in the majority of dogs with PH. An additional dose reduction often is needed to maintain an injection interval of 28-30 days. Young and growing animals seem to need higher dosages.

KEYWORDS

adrenal insufficiency, canine, mineralocorticoid

Abbreviations: DOCP, desoxycorticosterone pivalate; FC, fludrocortisone acetate; FDA, Food and Drug Administration; PH, primary hypoadrenocorticism; PRA, plasma renin activity.

1 | INTRODUCTION

Most dogs with primary hypoadrenocorticism (PH) suffer from immune-mediated destruction of the adrenal cortex, which results in absolute glucocorticoid and mineralocorticoid deficiency. Treatment of PH consists of life-long replacement with both hormones. Mineralocorticoids usually are replaced by either PO fludrocortisone acetate (FC) or SC injection of desoxycorticosterone pivalate (DOCP). The latter is a parenteral long-acting mineralocorticoid with no glucocorticoid activity. In 1998, the US Food and Drug Administration (FDA) approved DOCP (Percorten-V; Novartis Animal Health US, Greensboro, North Carolina) for mineralocorticoid replacement treatment in dogs with PH.[1] An alternative DOCP product (Zycortal; Dechra Pharmaceuticals, Overland Park, Kansas) was approved in 2015 by the European Medicines Agency and in 2016 by the FDA.[2,3] Zycortal is produced by a different manufacturer than Percorten-V and differs slightly from the latter with regard to the preservative (chlorocresol rather than thimerosal) and the surfactant (polysorbate-60 rather than polysorbate-80). It is the only product licensed in Europe for the treatment of PH. In July 2018, because of a shortage of Percorten-V, the FDA proposed Zycortal as an alternative. In pharmacological studies, the effectiveness of Zycortal was shown to be "noninferior" to that of Percorten-V and the same starting dosage of 2.2 mg/kg every 25 days was recommended by the manufacturer.

Because the expense of DOCP can be a limiting factor for some owners, finding the lowest effective dose for each dog is important. In previous studies using the originally licensed DOCP (Percorten-V), it was shown that in the majority of dogs the clinical disease can be well controlled with substantially lower dosages than the recommended 2.2 mg/kg.[4–6] Another strategy to decrease treatment costs is prolongation of the injection interval.[6] The duration of action of DOCP (Percorten-V) has been shown to range from 32 to 94 days in dogs newly diagnosed with PH.[6]

However, in no published study has a fixed starting dosage of DOCP been evaluated. Furthermore, to our knowledge, no studies have evaluated whether, using the newly registered DOCP product (Zycortal), lower doses than recommended by the manufacturer are effective in controlling clinical signs.

Thus, the aims of our study were to evaluate a low-dose treatment protocol using the new DOCP product (Zycortal) in dogs with naturally occurring PH and to identify the lowest possible dose needed to obtain a monthly injection interval of 28-30 days.

2 | MATERIALS AND METHODS

2.1 | Animals

Seventeen client-owned dogs with naturally occurring PH were prospectively enrolled between May 2016 and March 2018. Primary hypoadrenocorticism was diagnosed based on a post-ACTH serum cortisol concentration of <1 μg/dL, abnormal serum sodium (Na) and potassium (K) concentrations, increased plasma endogenous ACTH concentrations, or all.

Ages ranged from 0.3 to 9 years (median, 3.8) and body weight from 3.2-74.2 kg (median, 25.7). There were 6 males (4 castrated) and 11 females (7 spayed). Eleven purebred dogs (Bearded Collie [1], Dachshund [1], German Shepherd dog [1], Golden Retriever [1], Great St. Bernard [2], Labradoodle [1], Labrador Retriever [3], Miniature Poodle [1]) and 6 mixed-breed dogs were included. Presenting clinical signs included vomiting, diarrhea, anorexia or hyporexia, weight loss, weakness, lethargy, polyuria, polydipsia, or some combination of these. Blood urea nitrogen concentration was increased in 12 of 17 dogs.

2.2 | Analytical procedures

For the ACTH stimulation test, blood samples were taken before and 60 minutes after IV injection of 5 μg/kg synthetic ACTH (Synacthen; Future Health Pharma GmbH, Wetzikon, Switzerland). Serum cortisol concentrations were measured by a competitive immunoassay (DPC Immulite 2000; Siemens Schweiz AG, Zurich, Switzerland), previously validated in dogs and performed according to the manufacturer's instructions.[7] As reported by the manufacturer, the sensitivity of the assay is 0.2 μg/dL and the intra-assay coefficients of variation were 10% and 6% at cortisol concentrations of 2.7 and 18.9 μg/dL, respectively. For the determination of plasma endogenous ACTH, blood was collected before ACTH administration into chilled EDTA-coated tubes, placed on ice, and centrifuged at 4°C within 30 minutes. Plasma ACTH concentrations were determined using a 2-site solid-phase chemiluminescent immunometric assay (DPC Immulite 2000; Siemens Schweiz AG), previously validated for dogs.[8,9] Cortisol and endogenous ACTH measurements were performed in house by a commercial laboratory; plasma was stored either at −20°C (cortisol) or at −80°C (ACTH) if not assayed. Plasma Na and K concentrations were determined by a commercial laboratory using a Roche Hitachi 501 chemistry analyzer (Roche Pharma Schweiz AG, Reinach, Switzerland).

2.3 | Treatments

In 12 dogs, PH was newly diagnosed at the time of inclusion in the study. Mineralocorticoid replacement treatment was started with DOCP (Zycortal) after an individualized stabilization period that included among other treatments, IV fluids, management of hyperkalemia by glucose infusion, and prednisolone administration. The starting dosage of DOCP was 1.5 mg/kg SC and the target injection interval was q28-30 days. Efficacy of DOCP treatment was assessed on days 14 and 28 after the first injection by monitoring clinical signs and serum K and Na concentrations. Depending on serum K and Na concentrations 14 and 28 days after injection, DOCP dosage was adjusted and the injection interval changed to arrive at serum K and Na concentrations within the reference interval. If the serum K concentration was below the reference interval (4.3-5.3 mmol/L) and the serum Na concentration was within the reference interval (145-152 mmol/L) 14 days after DOCP injection, the dosage was decreased by 5%-10% at the next injection. If the serum K concentration was <4.3 mmol/L 28 days

after injection, the next injection was postponed and serum electrolyte concentrations evaluated at a weekly interval. As soon as serum K concentration was within the reference interval, the next DOCP dose was again administered at decreased dosage (5%-10% reduction for every week of delayed injection). With this approach, we aimed for an injection interval of 28-30 days and a target dose of DOCP at which serum Na and K concentrations remained within the reference interval.

Five dogs previously had been diagnosed with PH and PO FC (Florinef; Bristol-Myers Squibb SA, Baar, Switzerland) treatment had been started 1 to 18 months (median, 6 months) before inclusion in the study. At the time of inclusion, mineralocorticoid treatment was changed from PO FC to SC DOCP. The starting dosage of DOCP was 1.8 mg/kg in 1 dog, 1.5 mg/kg in 1 dog, 1.2 mg/kg in 2 dogs, and 1 mg/kg in 1 dog. The DOCP dosage for these dogs was determined, among other things, on actual serum electrolyte concentrations and owner financial concerns and was adjusted as described above.

All dogs were treated with prednisolone, and starting dosages in the dogs with newly diagnosed PH ranged between 0.5 and 1 mg/kg IV q6h to q12h for a duration of 12-48 hours, depending on the severity of clinical signs and the condition of the dog. Prednisolone treatment was changed to PO as soon as the dogs ate and vomiting stopped. At the time of discharge, the prednisolone dosage was decreased to 0.5 mg/kg PO q24h and further reduction was individualized based on clinical signs (eg, appetite, activity level, diarrhea, vomiting, polyuria, polydipsia, weight gain) and on assessment by the clinician. In general, the goal was to reach a glucocorticoid dosage ≤0.1 mg/kg PO q24h with no signs of glucocorticoid excess (eg, polyuria, polydipsia, polyphagia, muscle loss).

In dogs previously treated with PO FC, the starting dosage of prednisolone was 0.1 mg/kg per day.

2.4 | Study design

A minimum follow-up period of >3 months was necessary to be included in the study. The DOCP dosage and serum Na and K concentrations were recorded at the time of inclusion and after 1-2, 2-3, 3-6, 6-12, 12-18, 18-24, and >24 months during follow-up. All variables were recorded on the day of the DOCP injection.

All procedures were conducted in accordance with guidelines established by the Animal Welfare Act of Switzerland. In addition, informed consent of the pet owners was obtained before including dogs in the study.

2.5 | Statistical analysis

Statistical analysis was performed by means of nonparametric tests using commercial software (SPSS, Statistical Package for the Social Science, Software Packets for Windows, Version 23; GraphPad Prism6, GraphPad Software, San Diego, California). Data are expressed as median and range. Changes in DOCP dosage and changes in serum K and Na concentrations during treatment were evaluated by Friedman's repeated-measures test and Dunn's post-test. Zycortal dosages between age groups and between dogs previously treated with FC and those initially treated with DOCP were tested by Mann-Whitney *U* test. The level of significance was set at $P < .05$.

3 | RESULTS

3.1 | DOCP dosage

Median (range) follow-up period on DOCP treatment of all 17 dogs was 16.2 months (4.5-32.3 months); all except 1 dog were still alive at the end of the study period. This 1 dog had to be euthanized after 28.5 months of DOCP treatment because of gastric dilatation and volvulus. All except 1 dog were still on DOCP treatment at the end of the observation period; 1 dog had to be changed to PO FC after 15.4 months of DOCP treatment, despite excellent clinical control, because the owner was no longer able to give the injections.

For all dogs, results at inclusion and after 1-2, 2-3 and 3-6 months were available. After 6-12, 12-18, 18-24 and >24 months, results of 14, 13, 6, and 4 dogs, respectively, could be included. Overall, a significant decrease in the DOCP dosage was observed during the study ($P = .03$; Table 1; Figure 1).

At the first reevaluation, the DOCP dose was decreased and the injection interval increased because of hypokalemia in 15 dogs. At the second reevaluation, the DOCP dose was decreased in 7 dogs, and in 5 of the 7 dogs, the injection interval was increased. Injection intervals for the first 3 months of treatment of all dogs are presented in Table 2. In 2 dogs, the DOCP dose first had to be increased and later during the follow-up period decreased again. One of the 2 dogs was a 4-month-old Dachshund. In this dog, the DOCP dosage was increased 2.4 months after inclusion from 1.5 to 1.7 mg/kg. Nine months after inclusion (at the age of 13 months), however, the DOCP dosage had to be decreased to 1.5 mg/kg again and 2 months later to 1.0 mg/kg. The second dog was a 3-year-old Great St. Bernard, which, because of financial concerns, first had been treated with PO FC. The FC dose had to be continually increased because of serum electrolyte concentrations outside the reference interval. After 6 months, treatment was finally changed to DOCP because of glucocorticoid-associated adverse effects (polyuria, polydipsia, muscle loss) despite discontinuation of prednisolone. The dog was started on a DOCP dosage of 1.2 mg/kg, but the dosage had to be increased to 1.3 and 1.6 mg/kg after 1.7 and 2.7 months, respectively. After 4.3 months, the DOCP dosage was steadily decreased to a final dosage of 0.7 mg/kg, which was reached after 28.5 months of treatment.

In dogs with ≤3 years of age (7 dogs), the DOCP dose 3 months after starting treatment was significantly higher compared to dogs >3 years of age (10 dogs; $P = .03$).

No significant difference in Zycortal dosage was found between dogs previously treated with FC and those that were immediately started on Zycortal.

3.2 | Serum K concentrations

Serum K concentrations decreased during DOCP treatment. The decrease compared over all reevaluations, however, was not statistically

TABLE 1 Dosage of DOCP, serum potassium (mmol/L), and serum sodium concentrations (mmol/L) (median and range) at different time points

	Diagnosis	Start DOCP	1-2 mo	2-3 mo	3-6 mo	6-12 mo	12-18 mo	18-24 mo	>24 mo
Dosage DOCP	NA	1.5[a] (1-1.8)	1.2[a,c] (0.9-1.8)	1.1[a] (0.7-1.8)	1 (0.6-1.7)	0.8 (0.6-1.7)	0.8[b,c] (0.4-1.5)	0.7[b,c] (0.35-0.75)	0.7[b,c] (0.35-0.75)
Potassium concentration	7.6[a] (4.1-8.9)	5.2[b] (4.3-6.6)	4.7 (4.1-5.7)	4.5 (4.1-6.5)	4.6 (3.9-5)	4.5 (4.2-4.9)	4.7 (3.5-5.3)	4.4 (4.3-4.8)	4.2 (4.1-4.2)
Sodium concentration	131[a] (111-139)	141[b] (130-147)	147 (139-149)	146 (131-152)	148 (140-153)	147 (143-150)	147 (142-152)	147 (143-148)	149

Reference interval of sodium: 145-152 mmol/L; potassium: 4.3-5.3 mmol/L.
Within a row different superscript letters indicate statistical differences between the time points ($P < .05$).
Abbreviation: DOCP: desoxycorticosterone pivalate.

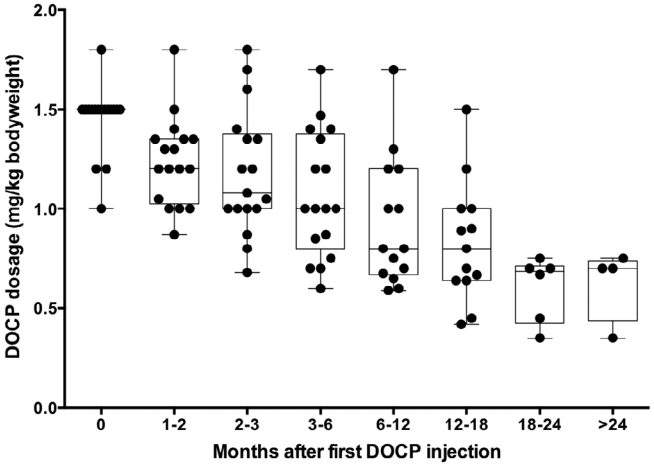

FIGURE 1 Desoxycorticosterone pivalate dosage (mg/kg body weight) at the time of first injection (0) and at selected time points during the follow-up period of each dog

significant (Friedman test, $P = .81$). Results (median, range) at different time points during reevaluation are presented in Table 1 and Figure 2.

3.3 | Serum Na concentration

Serum Na concentrations increased during DOCP treatment. The increase compared over all reevaluations, however, was not statistically significant (Friedman test, $P = .16$). Results (median, range) at different time points during reevaluation are presented in Table 1 and Figure 3. Selected dogs had mild hyponatremia at different time points during treatment despite their serum K concentrations being within the reference interval. Mild hypernatremia was observed in 1 dog 3 months after starting treatment.

4 | DISCUSSION

We were able to show that all dogs with PH, started on a lower DOCP dosage than recommended by the manufacturer, could be effectively treated and stabilized.

Pharmacological studies by the manufacturer had shown that DOCP (Zycortal) administered at the dosage of 2.2 mg/kg was well tolerated in purpose-breed beagle dogs. Even dose increases up to as much as 5-fold the labeled dosage for 6 months did not seem harmful.[2,3] At first consideration, there may be no indication to recommend a lower starting dose except cost reduction. However, our data show

TABLE 2 Injection intervals after starting desoxycorticosterone pivalate treatment given in days counted from the last injection up to the next following injection

	Days after 1st injection	Days after 2nd injection	Days after 3rd injection
Median	33	29	30
Minimum	27	25	27
Maximum	49	71	40

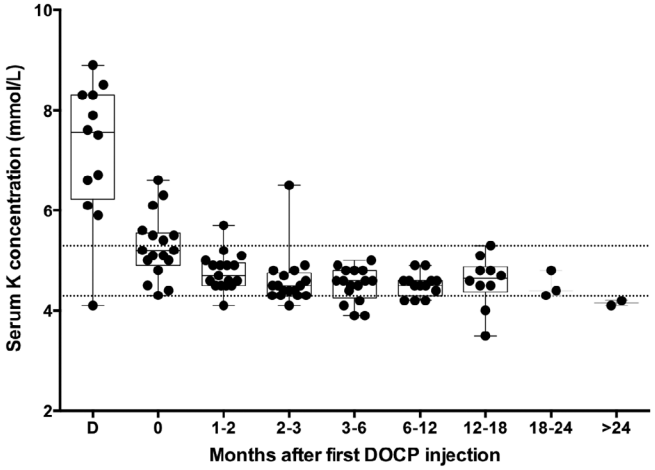

FIGURE 2 Serum Na concentrations (mmol/L) at the time point of diagnosis (D), on the day of desoxycorticosterone pivalate injection (0) and at selected time points during the follow-up period of each dog. The area between the dotted lines represents the reference range of the serum Na concentration

that even with a lower starting dosage of 1.5 mg/kg, hypokalemia seems to be a common observation 28 days after the first injection, necessitating not only dose reduction but also prolongation of the injection interval. Clearly, hypokalemia is far less dangerous than the hyperkalemia of untreated dogs with PH, but, clinical signs such as weakness still might be observed in dogs with hypokalemia associated with inappropriately high doses of DOCP. Moreover, another aspect of treatment monitoring must be taken into consideration. Dose adjustment of DOCP in our study, but also in previous studies, was only based on clinical signs and serum Na and K concentrations. Determination of plasma renin activity (PRA) is the most sensitive marker in human medicine for identifying insufficient as well as excessive mineralocorticoid replacement.[10] In a previous study, we found completely suppressed (ie, below the detection limit of the assay) PRA

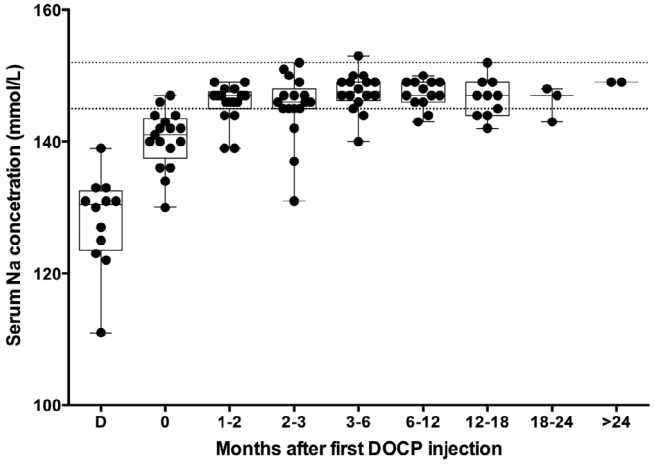

FIGURE 3 Serum K concentrations (mmol/L) at the time point of diagnosis (D), on the day of desoxycorticosterone pivalate injection (0) and at selected time points during the follow-up period of each dog. The area between the dotted lines represents the reference range of the serum K concentration

concentrations in dogs with PH treated with the original DOCP product (Percorten-V).[11] In human medicine, this is a clear indication of excessive treatment with mineralocorticoids and can indicate a risk for iatrogenic hypertension and potential long-term complications in these patients.[10] Short-term treatment of dogs with 2.2 mg/kg DOCP (Percorten-V) did not lead to hypertension,[12] but long-term studies including determination of PRA as a monitoring tool and measurement of blood pressure during treatment have not yet been performed in dogs.[12] Therefore, in our study, despite serum Na and K concentrations within the reference interval, dogs still could have been exposed to inappropriately high doses of DOCP. Hence, veterinarians should strive to find the lowest possible dose of DOCP, not only to achieve lower treatment costs but also for safety reasons to avoid possible, as yet undescribed, adverse effects of long-term overtreatment.

Despite decreases in serum K concentrations below the reference interval, development of severe hypernatremia has not been described, neither in our study (only 1 dog with mildly increased serum Na concentration 3 months after starting treatment) nor in previous studies using the original DOCP product (Percorten-V). This is not surprising, because in healthy Beagle dogs receiving up to 5 times the labeled dosage of Zycortal, either normonatremia or only mild hypernatremia was observed.[2] Mineralocorticoid excess is known to lead to "aldosterone escape," characterized by increased renal perfusion and natriuresis, which prevents nonphysiologically high increases in serum Na concentration.[13,14]

A DOCP dose increase was necessary in only 2 dogs. One dog was a puppy in which the dosage had to be increased to 1.7 mg/kg. Interestingly, at the ages of 13 and 15 months (at the time of manuscript preparation), the dosage could be decreased to 1.5 and 1 mg/kg, respectively. We assume that this change corresponded with the end of the dog's growth period. Also, in another study, the DOCP dose had to be increased in a 4-month old dog, which was attributed to the dog's continued growth.[5] However, it also could be a sign of young age independent of growth, meaning that at older ages, lower dosages are needed. In fact, we were able to show a significant difference in the DOCP dose when comparing younger to older dogs. This phenomenon also has been observed in another study using the original DOCP product (ie, a higher dosage was needed in younger than in older dogs).[6] Interestingly, registration and approval documents of the manufacturer show that their healthy research Beagle dogs were between 5 and 6 months of age.[1,3] This seems a likely explanation for the manufacturer's recommendation of a relatively high 2.2 mg/kg starting dosage.

In a double-blinded 180-day field study by the manufacturer, Zycortal was found to be "noninferior" to Percorten-V, and a mean injection interval of 38.5 ± 12.5 days with a range of 20-99 days was observed.[2] Also in a study using Percorten-V in dogs newly diagnosed with PH, the investigators were able to show that serum K and Na concentrations could be maintained within the reference interval for a median duration of 62 days, with a range of 32-94 days, using a dosage of 2.2 mg/kg.[6] Based on these results, the injection interval using a high starting dosage, may be highly variable with both products and may be as long as 99 days. For owners, however, considerable

variation in the injection interval might lead to poor compliance, which could be dangerous or life-threatening for the dog. A treatment interval of 28-30 days corresponds to 1 injection per month, which is easier for owners to remember and likely would result in improved compliance. However, even with our low-dose starting protocol, major variations in the injection interval were observed within the first 3 months, necessitating a dose reduction in all but 2 dogs.

All owners were satisfied with the treatment response using DOCP, including those whose dogs were changed from PO FC to SC DOCP because of adverse glucocorticoid effects or lack of normalization of serum electrolyte concentrations. No difference was observed in the DOCP dosage in dogs previously treated with FC compared to newly diagnosed dogs treated with DOCP. In addition, DOCP treatment was superior to the prior FC treatment in terms of owner satisfaction, improvement of clinical signs, fewer or no adverse effects, and improved control of serum Na concentrations. This observation also was made in earlier studies using Percorten-V.[4,11]

Potential limitations of our study are the low number of dogs and the lack of PRA determination as a monitoring tool, as discussed above. Considering the case number, we can say that, although low, in none of the dogs was the high dosage of 2.2 mg/kg needed. Moreover, a significantly lower dosage than our already low starting dosage of 1.5 mg/kg was needed, with decreases to dosages as low as 0.35 mg/kg. Therefore, the 2.2 mg/kg dosage recommended by the manufacturer seems too high to maintain dogs at a targeted injection interval of 28-30 days.

In conclusion, DOCP dosage is highly variable and should be titrated to the needs of each individual animal. A starting dosage of 1.5 mg/kg seems adequate in the majority of dogs. In all but 2 dogs, decreasing doses were necessary to obtain an injection interval of 28-30 days and to avoid overdosing as assessed by serum electrolyte concentrations outside the reference interval. Dosages higher than 1.5 mg/kg may be needed in young growing dogs. Further studies are needed to confirm this suspicion.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

All procedures were conducted in accordance with guidelines established by the Animal welfare Act of Switzerland. In addition, informed consent of the pet owners was obtained before including the dogs in the study.

HUMAN ETHICS APPROVAL DECLARATION

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

ORCID

Nadia S. Sieber-Ruckstuhl https://orcid.org/0000-0002-8256-0137
Regina Hofmann-Lehmann https://orcid.org/0000-0001-9750-4296
Felicitas S. Boretti https://orcid.org/0000-0001-6793-8464

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How to cite this article: 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;33:1266–1271. https://doi.org/10.1111/jvim.15475