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Use of Plasma Renin Activity to Monitor Mineralocorticoid Treatment in Dogs with Primary Hypoadrenocorticism: Desoxycorticosterone Versus Fludrocortisone

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Background: Measurement of plasma renin activity (PRA) is the gold standard for monitoring mineralocorticoid treatment in humans with primary hypoadrenocorticism (PH).

Objectives: To compare PRA in dogs with newly diagnosed PH, dogs with diseases mimicking PH, and healthy dogs, and evaluate measurement of PRA to monitor therapeutic effects in dogs with PH treated with different mineralocorticoids.

Animals: Eleven dogs with newly diagnosed PH (group 1), 10 dogs with diseases mimicking PH (group 2), 21 healthy dogs (group 3), 17 dogs with treated PH (group 4).

Methods: In group 1, PRA was measured before treatment and at different times after initiating treatment. In groups 2 and 3, PRA was measured at initial presentation only. In group 4, no baseline PRA was obtained but PRA was measured once or every 1–6 months during treatment. Mineralocorticoid treatment consisted of fludrocortisone acetate (FC) or desoxycorticosterone pivalate (DOCP).

Results: Plasma renin activity before treatment was increased in dogs with PH compared to normal dogs and dogs with diseases mimicking PH with median activity of 27, 0.8, and 1.0 ng/mL/h, respectively. In dogs with PH, PRA decreased and normalized with mineralocorticoid treatment using DOCP but not with FC. In dogs treated with DOCP, PRA was lower than in dogs treated with FC. Plasma sodium concentrations were higher and potassium concentrations were lower with DOCP treatment compared to FC treatment.

Conclusion and Clinical Importance: Plasma renin activity is a reliable tool for monitoring mineralocorticoid treatment. DOCP treatment more effectively suppresses PRA compared to FC in dogs with PH.

Key words: Adrenal insufficiency; Canine; Hormone replacement; Therapy.

Most dogs with primary hypoadrenocorticism (PH) suffer from immune-mediated destruction of the adrenal cortex, which results in absolute glucocorticoid and mineralocorticoid deficiency. Because of negative feedback, high concentrations of endogenous ACTH accompany glucocorticoid deficiency. Similarly, lack of aldosterone in patients with PH is accompanied by high concentrations of plasma angiotensin II that can be estimated indirectly by species-specific renin concentrations or by plasma renin activity (PRA) (ie, angiotensin generated by a plasma sample during timed incubation).[1]

Abbreviations:

DOCP	desoxycorticosterone pivalate
FC	fludrocortisone acetate
PH	primary hypoadrenocorticism
PRA	plasma renin activity

Treatment for PH consists of lifelong hormone replacement.[2] Mineralocorticoids usually are replaced by either fludrocortisone acetate (FC) or desoxycorticosterone pivalate (DOCP). Fludrocortisone acetate administered PO is the most commonly used treatment for humans with PH and has been recommended for dogs with PH for many years.[3] Fludrocortisone possesses potent mineralocorticoid activity and some glucocorticoid activity. Thus, in some cases there is no need for additional glucocorticoid supplementation. Signs of glucocorticoid overdosage can, however, occur, even when serum electrolyte concentrations still are not well controlled.[4]

Desoxycorticosterone pivalate is a parenterally administered long-acting mineralocorticoid alternative. DOCP has no glucocorticoid activity, and additional supplementation with glucocorticoids is recommended in all cases. The choice of mineralocorticoid replacement is based on several factors such as product availability, cost of treatment, and personal preference of the clinician and client.[3,5] Reports on the effectiveness and monitoring of mineralocorticoid treatment in dogs with PH are limited. Several authors report that DOCP is superior to FC, whereas in 1 large comparative clinical study no difference was seen with regard

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The study was done at the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich, Winterthurerstrasse 260, 8057 Zurich, Switzerland.

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to survival time and control of serum electrolyte concentrations.[3–6] The most important causes of poor response to treatment in dogs with PH are an inadequate mineralocorticoid dose or serious adverse glucocorticoid effects. Furthermore, the expense of mineralocorticoid supplementation may cause some owners to consider euthanasia.[7] In human medicine, standard monitoring of patients with PH consists of measurement of serum electrolyte concentrations, blood pressure, and PRA. PRA determination to control mineralocorticoid treatment was first described in 1975 and had been accepted as the gold standard since 1992.[8–11] PRA before treatment is increased in humans with PH and it decreases during treatment and correlates inversely with mineralocorticoid dose. Therefore, a target range for PRA is defined for optimal treatment in humans.[10]

In dogs with newly diagnosed PH, PRA is significantly higher than that in normal dogs.[1] The role of PRA in monitoring mineralocorticoid treatment in dogs with PH has not been investigated. Mineralocorticoid treatment currently is monitored mainly by serum potassium and sodium concentrations. The objectives of our study were, first, to measure and compare PRA in newly diagnosed PH dogs, in dogs with diseases mimicking PH, and in healthy dogs and, second, to evaluate PRA in dogs with PH during mineralocorticoid treatment. We hypothesized that PRA in dogs with PH would be significantly higher than that in dogs with diseases mimicking PH or in healthy dogs, that PRA would decrease during mineralocorticoid treatment and that it would be lower in well-controlled dogs than in poorly controlled dogs.

Material and Methods

Animals

Group 1: Eleven client-owned dogs with newly diagnosed PH were prospectively enrolled between January 2011 and August 2013. One of these dogs had been part of a previous study.[12] Diagnostic evaluation included CBC, serum biochemical profile, urinalysis, ACTH stimulation test, measurement of endogenous plasma ACTH concentration, and abdominal ultrasonography (with particular attention to the adrenal glands) in all dogs. PH was confirmed if serum cortisol concentrations after synthetic ACTH administration did not increase adequately (<1 μg/dL) and if endogenous baseline plasma ACTH concentrations were increased (cACTH > 130 pmol/L). Dogs were enrolled in the study if their serum sodium concentration was <152 mmol/L, their serum potassium concentration was >5.3 mmol/L, or both. Dogs with normal electrolyte concentrations and dogs with iatrogenic PH (ie, previous corticosteroid or trilostane treatment) were excluded from the study.

Group 2: Ten dogs with diseases mimicking PH diagnosed between June 2010 and February 2012 were prospectively enrolled in the study. All dogs initially had been suspected of having PH but finally were determined to have a different disease; all had post-ACTH serum cortisol concentrations ≥4.5 μg/dL. Diseases mimicking PH were associated with clinical signs, laboratory findings, or both routinely seen in dogs with PH, such as vomiting, diarrhea, weakness, lethargy, hyperkalemia, hyponatremia, or some combination of these.

Group 3: Twenty-one privately owned dogs were used as controls. The dogs were considered to be healthy on the basis of normal history and physical examination, as well as unremarkable hematology and serum biochemistry profile results.

Group 4: Seventeen client-owned dogs with PH that had already been treated for PH were prospectively enrolled between June 2010 and July 2013. PH had been diagnosed between 2 weeks and 7 years previously based on typical electrolyte abnormalities and an inadequate post-ACTH serum cortisol concentration (<1 μg/dL). All of these dogs were being treated with mineralocorticoid and glucocorticoid supplementation at the time of inclusion into the study.

All procedures were approved by the Cantonal Veterinary Office of Zurich (permission number, TVB 72/2011) and conducted in accordance with guidelines established by the Animal Welfare Act of Switzerland. In addition, informed consent was obtained from the owners of the healthy dogs.

Analytical Procedures

For the ACTH simulation test, blood samples were collected before and 60 minutes after IV injection of 250 μg synthetic ACTH.[a] Cortisol concentrations were measured by chemiluminescence assay.[b] The sensitivity of the cortisol assay was 0.2 μg/dL. Endogenous plasma ACTH concentration before ACTH stimulation was determined by a chemiluminescence assay.[b] Blood for cACTH determination was collected into chilled EDTA-coated tubes placed on ice and centrifuged at 4°C. Cortisol and cACTH measurements were performed in-house twice a week; plasma was stored either at −20°C (cortisol) or at −80°C (ACTH) until assayed.

Plasma renin activity was measured with an enzymatic assay in the Division of Angiology and Hypertension, Department of Medicine, Lausanne University Hospital, Lausanne, Switzerland. The method is based on trapping of angiotensin I generated in plasma during incubation at 37°C and subsequent radioimmunoassay.[13] The detection limit was 0.025 ng AngI/mL/h. The within- and between-assay precisions were characterized by coefficients of variation of 5.1 and 13.0%, respectively. The reference values (5 and 95% percentiles) for healthy dogs were 0.1–1.7 ng AngI/mL/h and were virtually identical to human normal values (0.05–2.4 ng AngI/mL/h) and they were (unlike in human subjects) independent of the postprandial time.[14] Blood was collected into chilled EDTA-coated tubes, placed on ice and centrifuged immediately at 4°C. Plasma samples were batched and stored at −80°C before analysis.

Study Design

In dogs with newly diagnosed PH (group 1, n = 11), PRA was measured before treatment. Subsequently, in 8 of these dogs, follow-up PRA measurements were obtained at different time points during hormone replacement treatment (n = 37). The results in these 8 dogs later were included in the calculations for Figures 3, 4.

In dogs with diseases mimicking PH (group 2, n = 10), PRA was measured once at initial presentation.

In healthy dogs (group 3, n = 21), PRA was measured before and 2 hours after feeding.

In dogs with previously diagnosed PH and included in the study during ongoing hormone replacement treatment (group 4, n = 17), PRA was measured once (5 dogs) or repeatedly at 1- to 6-month interval (12 dogs) for a total of 72 plasma samples. The results in these 17 dogs later were included in the calculations for Figures 3, 4.

Treatments

Mineralocorticoid replacement treatment of confirmed PH consisted of fludrocortisone acetate (FC) or DOCP. The starting dosage of fludrocortisone acetate[c] was 0.01–0.02 mg/kg/d PO divided twice daily. Efficacy of FC treatment was assessed regularly by monitoring clinical signs, renal function (BUN and serum creatinine concentration) and serum electrolyte concentrations (sodium, potassium, phosphorus). The FC dosage was adjusted mainly according to the serum potassium concentration. Dose adjustments were made in increments of 0.025–0.1 mg/dog depending on the size of the dog. The starting dosage and starting injection interval of DOCP[d] was 2 mg/kg SC q25 days. Depending on electrolyte concentrations 14 days after injection, the DOCP dosage was adjusted. In the event of normal serum electrolyte concentrations, the DOCP dose was slightly decreased (5–10%) at the next injection. In the case of normal serum electrolyte concentrations at the time of the next injection, the injection interval was increased stepwise by 1 day.

Seven of the dogs with newly diagnosed PH were started on FC treatment and 4 of them on DOCP treatment. Two of the dogs started on FC treatment were later changed to DOCP treatment.

Fifteen of the dogs with previously treated PH were on FC treatment and 2 on DOCP treatment at the time of their inclusion in the study. Three dogs treated with FC later were changed to DOCP treatment.

All dogs also were treated with glucocorticoids. The following standardized protocol was used for guiding glucocorticoid treatment: starting dosage of 2 mg/kg prednisolone IV after the ACTH stimulation test; then, 1 mg/kg prednisolone IV q6h during the first 24 hours. If the dogs seemed stable after 24 hours, the glucocorticoid dosage was decreased to 0.5 mg/kg prednisolone IV q12h. Prednisolone treatment was changed to PO as soon as the dogs ate and vomiting had stopped. At the time of discharge, the prednisolone dosage was decreased to 0.5 mg/kg PO q24h. Additional glucocorticoid reduction was individualized based on clinical signs (eg, appetite, activity level, diarrhea, vomiting, polyuria, polydipsia, weight gain) and on the assessment of the clinician. In general, the goal was to reach a glucocorticoid dosage of no more than 0.1–0.2 mg/kg PO q24h. In dogs with signs of glucocorticoid over dosage (eg, polyuria, polydipsia, weight gain), glucocorticoid treatment was decreased further and in dogs treated with FC stopped if possible.

Statistical Analysis

Statistical analysis was performed with commercial software by using nonparametric tests.[e,f] Data are expressed as median and range. Differences in PRA before or after feeding were tested by using the Wilcoxon signed rank test. Differences in PRA among groups were tested by using the Kruskal-Wallis *H*-test and Dunn's posttest. Changes in PRA during treatment were tested by Friedman's repeated measures test and Dunn's posttest. Differences in PRA as well as in sodium and potassium concentrations between dogs on FC and DOCP treatment were tested by the Mann-Whitney test. For dogs with repeated measurements, mean PRA, and serum sodium and potassium concentrations during FC or DOCP treatment were determined and analyzed statistically. Differences in the numbers of dogs with normal or abnormal electrolyte concentrations between the 2 treatment groups were tested by the Fisher's exact test. Linear correlation between PRA and serum sodium and potassium concentrations was calculated by Spearman nonparametric correlation. As above, for dogs with repeated measurements, mean PRA, and serum sodium and potassium concentrations during FC or DOCP treatment were analyzed. The level of significance was set at $P < .05$.

Results

Animals

Group 1: in the dogs with newly diagnosed PH, the age range was 1–10 years (median, 5 years) and the body weight ranged from 1.9 to 28.8 kg (median, 8.5 kg). There were 5 males (2 castrated) and 6 females (5 spayed). Nine purebred dogs and 2 mixed-breed dogs were included. No breed was overrepresented.

Group 2: in the dogs with diseases mimicking PH, the age range was 1–13 years (median, 3.5 years) and the body weight ranged from 6.7 to 42 kg (median, 19.9 kg). There were 5 males (3 castrated) and 5 females (3 spayed). Eight purebred dogs and 2 mixed-breed dogs were included. The final diagnoses were acute gastroenteritis (2), food-responsive enteropathy (2), inflammatory bowel disease (1), gastric ulceration (1), idiopathic megaesophagus (1), hypothyroidism (1), primary hyperparathyroidism (1) dirofilariasis, and leishmaniasis (1).

Group 3: in the healthy dogs, the age range was 1–12 years (median, 4 years) and the body weight ranged from 5 to 35 kg (median, 22 kg). There were 8 males (2 castrated) and 13 females (11 spayed). Sixteen purebred dogs and 5 mixed-breed dogs were included.

Group 4: in the dogs with already treated PH, the age range was 1–14 years (median, 8 years) and the body weight ranged from 3.6 to 34 kg (median, 10.6 kg). There were 7 males (4 castrated) and 10 females (9 spayed). Eleven purebred dogs and 6 mixed-breed dogs were included. No breed was overrepresented.

PRA in Healthy Dogs

There was no influence of feeding on PRA in healthy dogs ($P = .44$). Fasted PRA in healthy dogs ranged from 0.1 to 1.3 ng/mL/h (median, 0.6 ng/mL/h) and postprandial PRA ranged from 0.1 to 1.7 ng/mL/h (median, 0.75 ng/mL/h). The 5 and 95% percentiles of fasted PRA were 0.1 and 1.3 and those of postprandial PRA were 0.1 and 1.7 ng/mL/h, respectively.

Comparison of PRA in Dogs with Newly Diagnosed PH, Dogs with Diseases Mimicking PH, and Healthy Dogs

Plasma renin activity before treatment was significantly higher in dogs with PH (2.9–89 ng/mL/h; median, 27 ng/mL/h) than in dogs with diseases mimicking PH (0.5–2.8 ng/mL/h; median, 1.0 ng/mL/h; $P < .001$) and in healthy dogs (0.1–1.7 ng/mL/h; median, 0.8 ng/mL/h; $P < .0001$; Fig 1). PRA did not differ significantly between dogs with diseases mimicking PH and healthy dogs ($P = .13$).

PRA in Dogs with PH Before and After Initiation of Mineralocorticoid Treatment

Plasma renin activity decreased significantly after the start of mineralocorticoid treatment ($P = .04$;

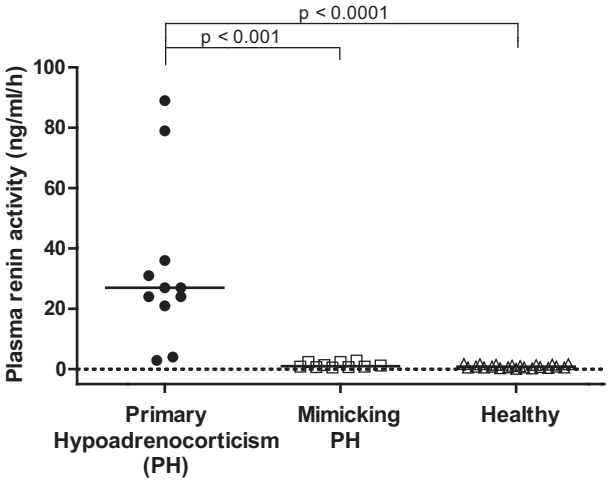

Fig 1. Plasma renin activity (PRA) of dogs with primary hypoadrenocorticism (PH, n = 11), dogs with diseases mimicking PH (n = 10), and healthy dogs (n = 21). The horizontal bars represent the medians of each group.

Fig 2A). However, the PRA response was different for the 2 treatments: PRA of dogs treated with FC remained very high and was unchanged. In contrast, in dogs treated with DOCP, PRA decreased into the reference range and even lower during treatment (Fig 2B). Comparison of the treatment groups at each follow-up evaluation was not possible because of the low numbers of dogs.

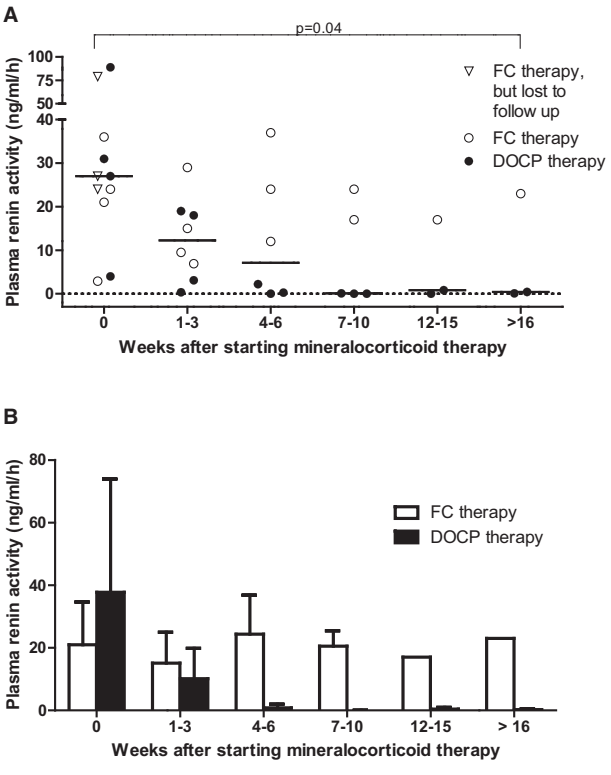

Fig 2. **(A)** Plasma renin activity (PRA) of dogs with primary hypoadrenocorticism (PH) treated with fludrocortisone acetate (FC, open circles) or with desoxycorticosterone pivalate (DOCP, closed circles). Three dogs were lost to follow-up (triangles). **(B)** Bar graphs showing mean (SD) PRA of dogs with PH treated with FC (white bars) and DOCP (black bars).

PRA and Correlation with Serum Sodium or Potassium Concentrations

There was a significant, negative correlation of PRA and sodium concentrations ($r = -0.74$, $P < .0001$) and a significant positive correlation of PRA and potassium concentrations ($r = .71$, $P < .0001$) in dogs with PH (groups 1 and 4) before and during treatment.

PRA and Serum Electrolyte Concentrations in Dogs with PH Already Treated for PH

For these calculations, 8 dogs from group 1 (4 on FC and 4 on DOCP treatment) and 17 dogs from group 4 (15 on FC and 2 on DOCP treatment) were used. In 2 dogs of group 1 and in 3 dogs of group 4, mineralocorticoid treatment was changed from FC to DOCP during the study, leading to 2 and 3 additional results in the DOCP group. Therefore, a total of 19 results (4 from group 1 and 15 from group 4) in the FC group and 11 results (6 from group 1 and 5 from group 4) in the DOCP group were included.

Plasma renin activity was significantly lower in dogs on DOCP treatment (0.04–6.13 ng/mL/h; median, 0.04 ng/mL/h) than in dogs on FC treatment (8.7–47.5 ng/mL/h; median, 16.8 ng/mL/h; $P < .0001$; Fig 3).

Serum sodium concentrations of dogs treated with DOCP were significantly higher (154–158 mmol/L; median, 156 mmol/L) than those of dogs treated with FC (138–155 mmol/L; median, 147 mmol/L; $P < .0001$; Fig 4A). Serum potassium concentrations of dogs treated with DOCP were significantly lower (4.3–5.1 mmol/L; median, 4.6 mmol/L) than those of dogs treated with FC (5.1–6.3 mmol/L; median, 5.4 mmol/L; $P < .0001$; Fig 4B).

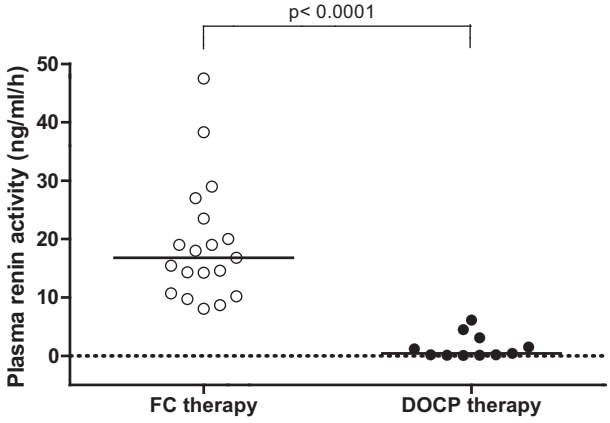

Fig 3. Plasma renin activity (PRA) of dogs with primary hypoadrenocorticism on fludrocortisone acetate treatment (FC, n = 19) and on desoxycorticosterone pivalate treatment (DOCP, n = 11). The horizontal bars represent the medians.

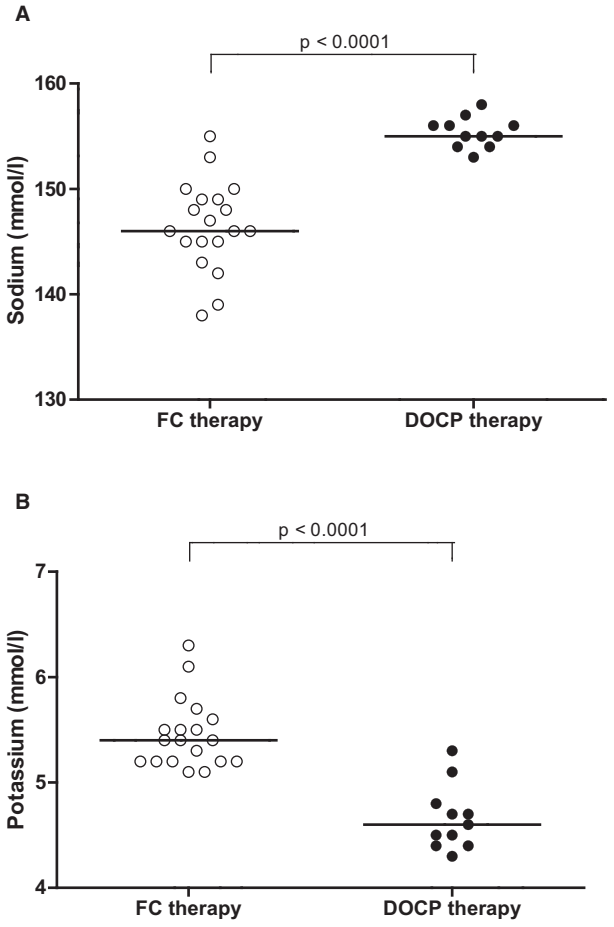

Fig 4. Serum sodium **(A)** and potassium **(B)** concentrations of dogs with primary hypoadrenocorticism on fludrocortisone acetate treatment (FC, n = 19) and on desoxycorticosterone pivalate treatment (DOCP, n = 11). The horizontal bars represent the medians.

Significantly more dogs treated with DOCP had serum sodium ($P < .0001$) or potassium ($P < .0001$) concentrations within the reference range than did dogs treated with FC.

Change in Mineralocorticoid Treatment

Five dogs were changed from FC to DOCP treatment because of adverse glucocorticoid effects, lack of normalization of serum electrolyte concentrations, or both. The FC dosage and the prednisolone dosage at the time of treatment change ranged from 0.013 to 0.026 mg/kg/d (median, 0.017 mg/kg/d) divided q12h and from 0 to 0.2 mg/kg/d (median, 0.06 mg/kg/d), respectively.

In 4 of the dogs, follow-up samples on either FC or DOCP treatment could be obtained. The PRA and serum sodium and potassium concentrations in the 4 dogs on FC ranged from 2.8 to 37 ng/mL/h (median, 17 ng/mL/h), 135 to 156 mmol/L (median, 146 mmol/L), and 4.2 to 7.1 mmol/L (median, 5.6 mmol/L), respectively. After changing to DOCP treatment, PRA and serum sodium and potassium concentrations in the 4 dogs ranged from 0.03 to 2.2 ng/mL/h (median, 0.12 ng/mL/h), 151 to 160 mmol/L (median, 156 mmol/L), and 4.2 to 5.3 mmol/L (median, 4.6 mmol/L), respectively (Fig 5A–C).

Discussion

Dogs with PH have higher PRA than do healthy dogs. These results confirm previous observations.[1]

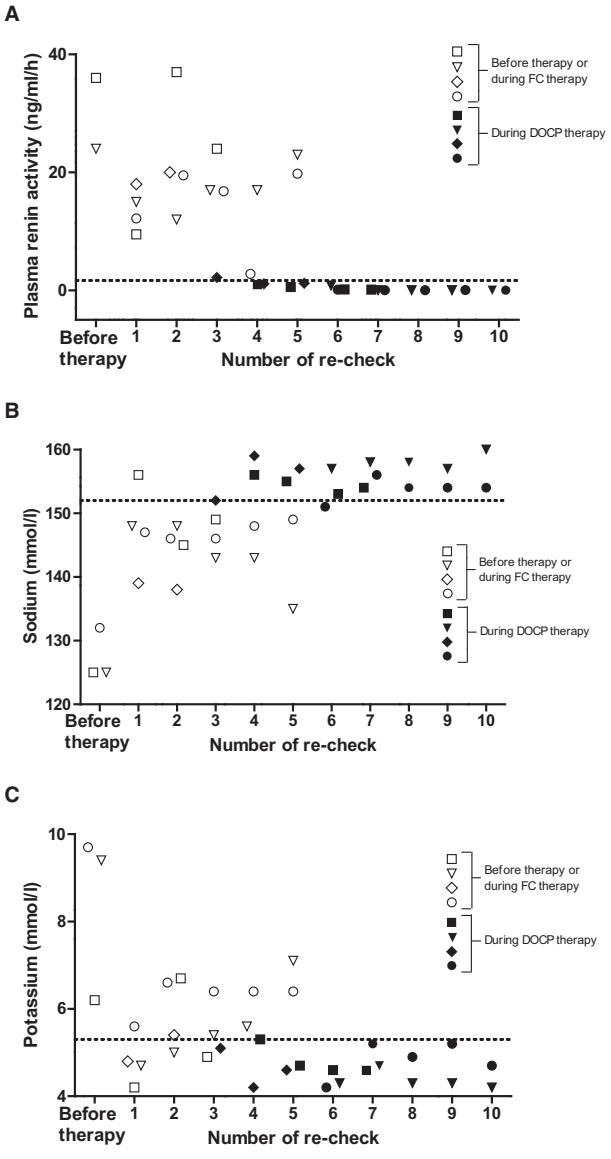

Fig 5. Effects of switching hormone replacement treatment in 4 dogs with primary hypoadrenocorticism (square, triangle, rhombus, and circle) from fludrocortisone acetate (FC, open symbols) to desoxycorticosterone pivalate (DOCP, closed symbols). Plasma renin activity **(A)**, serum sodium concentrations **(B),** and serum potassium concentrations **(C)**: All normalize after switching from initial FC to final DOCP treatment. The dotted lines in figures A and C represent the upper limit of normal values. The dotted line in figure B represents the lower limit of normal values.

Renal renin secretion apparently is enhanced in an attempt to try and further stimulate adrenal mineralocorticoid secretion, which is lacking in PH. In contrast, PRA was not increased in dogs with diseases mimicking PH. Dogs with diseases mimicking PH were included because of clinical signs or laboratory findings commonly seen in dogs with PH (eg, gastrointestinal illness, hyponatremia, hyperkalemia). Many of these dogs presented with decreased plasma volume (eg, signs of dehydration, low blood pressure, or both) and were classified as being critically ill. Thus, they would have been expected to have high PRA. Possibly, in contrast to true PH, fluid therapy at the time of PRA sampling may already have corrected factors (eg, volume depletion) that would have stimulated renin secretion in dogs with diseases mimicking PH. Alternatively, hepatic or renal insufficiency may have prevented an increase in PRA.

Plasma renin activity in dogs with PH decreased during mineralocorticoid treatment. This observation is similar to the situation in humans with PH, in whom PRA is increased before treatment and decreases during treatment.[10] In human medicine, PRA is the most sensitive marker for identifying insufficient or excessive mineralocorticoid replacement treatment.[10] For optimal treatment control of PH, PRA should be within the reference range of healthy humans.[10] Our results confirm that, in dogs, reference PRA results are very similar to those of humans when individuals with or without PH are compared.[1,10,13] In addition, PRA of healthy dogs and dogs with PH on successful treatment were very similar to those results in healthy humans.[1,10,13] We therefore hypothesize that PRA can be used to titrate mineralocorticoid treatment in dogs as well as in humans. Interestingly, based on our PRA results, SC DOCP treatment seemed to be more effective than PO FC treatment. This observation was confirmed by serum sodium and potassium concentrations and also by clinical observations (data not shown). More dogs treated with DOCP had normal serum sodium and potassium serum concentrations when compared to dogs treated with FC. PRA of dogs treated with FC was higher than PRA of dogs treated with DOCP. Moreover, in the dogs that were changed from FC to DOCP treatment, pathologically increased PRA and serum potassium concentrations and pathologically decreased serum sodium concentrations observed during FC treatment were normalized after changing to DOCP treatment. Our findings suggest that DOCP lowers PRA and normalizes serum electrolyte concentrations in a more predictable way than does FC. Possible explanations for a lesser effect of FC treatment in dogs could be decreased absorption of FC from the gastrointestinal tract, lower mineralocorticoid activity of FC compared to DOCP, or decreased owner compliance with PO administered medication. Certainly, owner compliance could have influenced treatment control in some dogs on FC. However, owners of dogs with PH understood that they were treating with a life-threatening disease in their dogs, and thus poor owner compliance seems an unlikely explanation. In humans, the mineralocorticoid replacement treatment of choice in patients with PH is PO FC. Normalization of serum sodium and potassium concentrations and of PRA seems very consistent during treatment.[10] It is evident however that serum sodium and potassium concentrations require a smaller FC dosage for normalization than does PRA.[10] The FC dosage leading to PRA in the desired range shows considerable interindividual variability.[10,15] The primary problem of FC treatment in dogs is the risk of adverse glucocorticoid effects. In some dogs, adverse glucocorticoid effects seem to occur before an FC dosage adequate for normalization of serum electrolyte concentrations and PRA can be achieved. Possibly, dogs are more sensitive to adverse glucocorticoid effects or FC may have higher glucocorticoid activity or lower mineralocorticoid activity in dogs than in humans.

In the only larger study[3] comparing FC and DOCP treatment in dogs, no difference was seen between FC and DOCP with regard to control of serum electrolyte concentrations and survival time. However, the authors reported that 14% of dogs with PH that initially were treated with FC had to be changed to DOCP because of adverse effects, poor response to treatment, owner convenience, or financial considerations.[3] In this study as well as in our study, no dog had to be changed from DOCP to FC. Several other authors reported that an inadequate mineralocorticoid dosage was more commonly seen with FC than with DOCP.[4,5]

In all of our dogs treated with DOCP, PRA was completely suppressed, which in human medicine indicates excessive treatment with mineralocorticoids.[10] This observation is in agreement with the clinical experience of several authors that most dogs are well controlled with lower doses of DOCP.[3,16,17] In 1 study, only 18.2% of dogs required the recommended dosage of 2.2 mg/kg.[3] In a recent study, no significant differences in survival time or serum electrolyte concentrations were seen in dogs treated with different dosages of DOCP (0.4–3.8 mg/kg).[17] The authors concluded that initial DOCP dosages <2.2 mg/kg may be effective in controlling serum electrolyte concentrations in dogs with PH without adversely affecting survival.[17] Our finding of completely suppressed PRA in dogs on DOCP further substantiates this hypothesis. We hypothesize that it would be possible to decrease DOCP dosage until PRA is detectable while serum electrolytes concentrations are still normal. This would allow calibrations of mineralocorticoid treatment. In the dogs in which we decreased the DOCP dosage, PRA still was completely suppressed except in 1 case. In human medicine, 1 problem of mineralocorticoid overdosage is the risk of iatrogenic hypertension and potential long-term complications.[17,18] In dogs treated with 2.2 mg/kg DOCP every 30 days for 3 months, there was no effect on blood pressure.[19] However, when overdosed up to 15-fold over a period of 6 months, dogs developed polyuria, polydipsia, decreased serum potassium concentrations, and increased serum sodium

concentrations.[20] These findings clearly indicate the need for additional dosing studies for the long-term management of dogs with PH using DOCP.

In most dogs treated with FC, PRA remained increased. The renin-angiotensin system is integral in the maintenance of cardiovascular homeostasis. Increased renin activity leads to enhanced production of angiotensin I and angiotensin II. Angiotensins have important effects on vascular endothelium and vascular smooth muscle (eg, vasoconstriction, vascular smooth muscle cell proliferation, and atherosclerosis).[21] In humans, PRA (or more precisely angiotensin II) is a well known cardiovascular risk factor.[22–25] Strokes and myocardial infarctions are more frequent in patients with increased PRA. Effects of increased PRA and the enhanced growth effects of angiotensin II on the cardiovascular system and other cell systems in patients with PH are likely and await further investigation.

In view of these observations, we prefer to start dogs with PH on DOCP instead of FC. We follow an approach similar to that suggested by Klein and Peterson and adjust the dosage individually as described above.[26]

We acknowledge that measurement of PRA is not widely available for the management of dogs with PH, mostly because the method is not commonly available and blood sampling as described above is not possible for most practitioners. Measuring renin with an immunoassay could be considered as an alternative. The advantage of this method is an easier sampling procedure. In human medicine, renin concentrations correlate with PRA in healthy humans and patients with hypertension, but not in patients with other conditions.[27,28] So far, no information about the correlation of PRA and renin concentrations in dogs with different diseases is available. Renin concentrations in dogs would have to be measured indirectly (ie, generation of angiotensin in the presence of added excess angiotensinogen), because no specific antibody for canine renin is commercially available.

We conclude that measurement of PRA is a promising tool for establishing dosage and monitoring mineralocorticoid treatment in dogs with PH. Based on our results, DOCP treatment more effectively suppresses PRA compared to FC treatment and therefore is the preferred mineralocorticoid treatment in dogs.

Footnotes

[a] Synacthen; Novartis Pharma Schweiz AG, Bern, Switzerland (During this study 250 μg ACTH/dog were used for the ACTH stimulation test. Today the authors use only 5 μg/kg ACTH for the ACTH stimulation test)
[b] DPC Immulite 1000; Siemens Schweiz AG, Zurich, Switzerland
[c] Florinef; Bristol-Myers Squibb SA, 6340 Baar, Switzerland
[d] Percorten-V; Novartis Animal Health US, Greensboro, NC
[e] GraphPad Prism5; GraphPad Software, San Diego, CA
[f] SPSS 18.0 for Windows; SPSS Inc, Chicago, IL

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

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