**Effect of Trilostane on Hormone and Serum Electrolyte Concentrations in Dogs with Pituitary-Dependent Hyperadrenocorticism**

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**Background:** The effects of trilostane on key hormones and electrolytes over 24 hours in dogs with pituitary-dependent hyperadrenocorticism (PDH) are unknown.

**Objectives:** To determine the plasma concentration of cortisol, endogenous adrenocorticotropic hormone (ACTH), aldosterone, sodium, potassium, and ionized calcium concentrations, and plasma renin activity over a 24-hour period after administration of trilostane to dogs with well-controlled PDH.

**Animals:** Nine dogs (mean age 9.3 ± 0.67 years, mean weight 31.9 ± 6.4 kg) with confirmed PDH.

**Methods:** Prospective study. Thirty days after the first administration of trilostane, blood samples were taken at –30, 0 (baseline), 15, 30, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours after administration of trilostane and plasma cortisol concentration, endogenous ACTH, aldosterone, sodium, potassium, ionized calcium, and renin activity were determined.

**Results:** Cortisol concentrations decreased significantly ($P < .001$) 2–4 hours after trilostane administration. From baseline, there was a significant ($P < .001$) increase in endogenous ACTH concentrations between hours 3–12, a significant increase ($P < .001$) in aldosterone concentration between hours 16–20, and a significant ($P < .001$) increase in renin activity between hours 6–20. Potassium concentration decreased significantly ($P < .05$) between hours 0.5–2.

**Conclusion and Clinical Importance:** Treatment with trilostane did not cause clinically relevant alterations in plasma aldosterone and potassium concentration. Results suggest that in dogs with PDH, the optimal time point for an ACTH-stimulation test to be performed is 2–4 hours after trilostane dosing. Future studies are necessary to establish interpretation criteria for a 2- to 4-hour postpill ACTH-stimulation test.

**Key words:** Adrenal gland; Hypercortisolism; Treatment.

**Abbreviations:**

| Abbreviation | Description |
|--------------|-------------|
| ACTH         | adrenocorticotropic hormone |
| AT           | adrenocortical tumor |
| IM           | intramuscular |
| IRMA         | immunoradiometric assay |
| IV           | intravenous |
| LC-MS/MS     | liquid chromatographic-tandem mass spectrometry |
| PDH          | pituitary-dependent hyperadrenocorticism |
| PO           | peroral |
| RIA          | radioimmunoassay |

Pituitary-dependent hyperadrenocorticism (PDH) accounts for 80–85% of spontaneous hypercortisolism in dogs, which in most cases arises from hypersecretion of adrenocorticotropic hormone (ACTH) by a pituitary corticotroph adenoma. The aim of treatment is to eliminate the clinical signs caused by chronic glucocorticoid excess. This can be achieved by transsphenoidal hypophysectomy or medical treatment.

Trilostane is a synthetic steroid, which competitively inhibits the 3ß-hydroxysteroid dehydrogenase/isomerase system, an essential enzyme system for the synthesis of several steroids, including cortisol and aldosterone. Currently, trilostane is regarded as the medical treatment of choice in dogs with PDH.

The influence of trilostane on cortisol, endogenous ACTH, aldosterone, potassium concentration, and renin activity is well documented. There are no studies of these parameters over 24 hours after administration of trilostane.

The aims of this prospective study were to investigate the effect of trilostane on serum sodium, potassium, ionized calcium, endogenous ACTH, cortisol, and aldosterone concentration as well as its effect on renin activity over a 24-hour period after administration of trilostane in dogs with clinical signs of hypercortisolism were controlled.

**Materials and Methods**

**Study Population**

Dogs with confirmed PDH and body weight >15 kg without other concurrent diseases were enrolled. Hypercortisolism was diagnosed using an ACTH-stimulation test, low-dose dexamethasone suppression test, or both, and clinical signs and clinicopathologic findings. A diagnosis of hypercortisolism was supported by a cortisol concentration >600 nmol/L (22 μg/dL) 1 hour after IV or IM administration of 0.25 mg cosyntropin or inadequate suppression of cortisol concentration (>40 nmol/L [1.4 μg/dL]) 8 hours
after the IV administration of 0.01 mg/kg dexamethasone.©,14 Cortisol concentration was measured by a chemiluminescence method.© The results of the low-dose dexamethasone suppression test (cortisol concentration <40 nmol/L or less than 50% of the baseline cortisol concentration at 4 hours after dexamethasone administration diagnostic for the presence of PDH), endogenous ACTH (>28 pg/mL diagnostic for the presence of PDH), and ultrasound of the adrenal glands were used to differentiate between PDH and adrenal tumor (AT).© According to the governmental ethics committee consultation at the time of the study, no ethical approval was necessary to perform the study.

**Trial Procedure**

Baseline (pretreatment) blood samples for hematology and biochemistry were analyzed at the central laboratory of the Small Animal Clinic, Justus-Liebig-University, Giessen, Germany. After written consent was obtained from the owners, treatment was initiated with 60 mg (for dogs of body weight <20 kg), 120 mg (20–40 kg), or 180 mg (>40 kg) trilostane© once daily, PO with food.

A clinical evaluation was performed 10 days after the start of the treatment and included evaluation of possible adverse effects, improvement of hypercortisolism-related clinical signs, and performance of an ACTH-stimulation test 4–6 hours after trilostane administration. If cortisol concentrations were >250 nmol/L (>9 μg/dL),© or if the dog had clinical signs of hypercortisolism, the trilostane dose was increased by 60 mg. If the cortisol concentration was <50 nmol/L (<2 μg/dL) and the dog was clinically unwell, the trilostane dose was reduced. If the dog showed adverse effects (lethargy, diarrhea, or vomiting), trilostane treatment was stopped and re-instituted after a few days at half of the previous dose. Ten days after an alteration in the trilostane dose, the clinical evaluation was repeated.

Twenty days after the final dose change (improvement of clinical signs of hypercortisolism and cortisol within or below reference ranges on ACTH-stimulation test), the dogs’ 24-hour sampling procedure was carried out. Dogs were hospitalized the day before sampling was due to start. On admission, a central venous catheter was inserted either into a jugular vein or into a femoral vein. Trilostane was administered the next morning, with food. Blood samples were taken −30, 0 (within x minutes of administration), 15, 30, 60, and 90 minutes, and 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours, after administration of trilostane. Blood was drawn from the central venous catheter. After aspiration of 10 mL blood, 1.2 mL blood was put into each of the following tubes: 2 EDTA tubes were used for measurement of ACTH and renin; 1 heparin tube for serum electrolytes; and 2 tubes without additive for cortisol and aldosterone. The 10 mL of aspirated blood was returned into the central venous catheter, which was then flushed with 1 mL heparinized sodium chloride solution (10 IU/mL). Serum electrolytes were measured immediately from whole blood, and the other blood samples were immediately centrifuged and separated. The samples were stored at −80°C and shipped overnight on dry ice to the analytical laboratories. Renin activity, ACTH, cortisol and aldosterone concentrations were measured at Cambridge Specialist Laboratories, Wallsend, UK.

**Laboratory Evaluation**

Serum cortisol concentrations were measured using a radioimmunoassay (RIA), which has been previously validated in dogs over the concentration range 20–1,656 nmol/L (0.7–60 μg/dL) (clinicalopathologic data). Normal dogs have serum cortisol concentrations up to 250 nmol/L (9 μg/dL).© An immunoradiometric assay (IRMA) was used to measure endogenous ACTH in EDTA plasma. A sandwich assay with solid-phase bead system was performed. The test has been validated for use in dogs.© Sensitivity was 5 pg/mL, upper limit at 600 pg/mL and reference range for dogs between 20 and 80 pg/mL.©,13 For serum aldosterone measurement, an RIA was performed, with solid-phase–coated tube separation, validated for use in dogs.© The sensitivity was 20 pmol/L; the upper limit is 3,300 pmol/L; and reference range in dogs is up to 960 pmol/L.© Renin activity was measured using an RIA, with solid-phase–coated tube separation, validated for use in dogs.© The sensitivity was 0.08 and the upper limit at 5.0 ng/tube© with a reference range in dogs of 0.22–2.4 ng/mL/h.©

Serum electrolytes were measured with an ion-selective electrode system,© which has been used extensively in veterinary medicine. Reference ranges in normal dogs for sodium are 141–152 mmol/L, for potassium are 3.6–5.4 mmol/L, and for ionized calcium are 1.2–1.45 mmol/L.

**Data Analysis**

Normality of the data was analyzed by visual inspection of the Q-Q-Plots of the residuals for each variable (program BMDP1R). Logarithmic transformation was performed for those variables whose distributions were skewed to the right. An analysis of variance (ANOVA) with repeated measures over time (program BMDP2V) was performed for 15 time points for the transformed and nontransformed data to look for global changes over time. To assess at which time point a statistical significant change in comparison with the initial value could be detected, a Dunnett-test was used subsequently. For variables with several values below the detection limit (which were not normally distributed even after logarithmic transformation), the Friedman test was used instead of an ANOVA. Significant global differences in pair-wise comparisons between later time points and the initial value were detected by the Wilcoxon and Wilcoxon multiple comparison method for correlated samples. Data analysis was performed by the statistical program package BMDP.©

For statistical analysis, data points below the detection limit of the assay were replaced by the arithmetic mean between the lowest quantifiable concentration and zero. A significance level of α = 0.05 was chosen; so, P values less or equal .05 were considered to indicate statistical significant changes.

**Results**

Ten dogs (3 male, 2 male neutered, 1 female, 4 female neutered of various breeds) with PDH were enrolled initially. The mean (±SD) age and weight of the dogs were 9.7 ± 1.4 years and 30.3 ± 8.0 kg, respectively. The initial dose of trilostane ranged from 3.3 to 5.2 mg/kg (mean 4.2 ± 0.55 mg/kg), administered once daily. It was not necessary to change the dose in any dog, so that the 24-hour sampling period was performed 30 days after the start of treatment in all dogs. One dog was removed from the study before collection of samples because of unexplained collapse. All timings are relative to time of trilostane administration. There were significant changes over time in all variables, except plasma sodium and ionized calcium concentrations.

Cortisol concentrations decreased significantly 2 hours after trilostane administration (P < .001).
Pair-wise comparison between baseline value and time points showed a significant negative difference between hours 2 and 4 ($P < .05$) (Fig 1). In 6 dogs, the lowest cortisol concentration was below the detection limit of the assay at least once during the day.

Endogenous ACTH plasma concentrations increased significantly 3 hours after trilostane administration ($P < .001$). By Dunnett's comparison, a significant peak was reached between hours 3 and 12 (Fig 2), and decreased to baseline after hour 12.

In the first 6–8 hours after trilostane administration, the aldosterone concentration remained constant in all dogs (Fig 3). There was a significant increase in aldosterone concentration between hours 16 and 20 ($P < .01$) (Fig 3). In 2 dogs, serum aldosterone concentrations were below the detection limit of the assay at a few time points throughout the day.

Plasma renin activity increased significantly after trilostane administration ($P < .001$) by hour 6 and reached peak activity after hour 8 (Fig 4). While there was only minimal change for the next 12 hours, plasma renin activity decreased slightly after hour 20.

Plasma sodium concentrations remained within the reference range (141–152 mmol/L) throughout the day in all but 4 dogs. These dogs had short episodes each of mild hyponatremia shortly before or after trilostane administration. Hyponatremia was not detected in any of the dogs. Throughout the study period, there was only mild fluctuation of the sodium concentration ($P = .582$); however, there was quite a marked interindividual variation.

There was a significant decrease in the potassium concentration (Fig 5) between hours 0.5 and 2 ($P < .05$). Two dogs had excursions of potassium concentrations above the reference range, one at hours $-0.5, 0$, and 24, the other at hour $-0.5$; no dog became hypokalemic. Three dogs had a sodium:potassium ratio below 27 at varying time points after

![Fig 1. Cortisol concentrations in 9 dogs with pituitary-dependent hypercortisolism on day 30 of treatment with trilostane. The not normally distributed data were initially logarithmized and mean and standard deviation of these values were calculated. For graphical representation, these results were retransformed yielding the geometric mean and dispersion factor (=geometric SD). Positive whiskers indicate geometric mean times dispersion factor, whereas negative whiskers show geometric mean divided by dispersion factor. Asterisks show significant changes from baseline concentrations.](image1)

![Fig 2. Concentrations of endogenous ACTH in 9 dogs with pituitary-dependent hypercortisolism on day 30 of treatment with trilostane. For explanation of graphical presentation, see Figure 1.](image2)

![Fig 3. Aldosterone concentrations in 9 dogs with pituitary-dependent hypercortisolism on day 30 of treatment with trilostane. For explanation of graphical presentation, see Figure 1.](image3)

![Fig 4. Plasma renin activity in 9 dogs with pituitary-dependent hypercortisolism on day 30 of treatment with trilostane. For explanation of graphical presentation, see Figure 1.](image4)
trilostane administration. While potassium concentrations decreased during the first 2 hours after trilostane administration, aldosterone concentrations showed a mild insignificant increase at hour 1. After this time point, potassium concentrations showed a slight increase back to baseline.

Throughout the study period, there were only mild nonsignificant fluctuations of ionized calcium concentration. Ionized calcium concentrations remained within the reference range in all but 1 dog throughout the day. This dog was mildly hypercalcemic between hours 0.25 and 0.5, and again at hours 4–24; the maximum calcium concentration was 1.55 mmol/L at hour 12. None of the dogs were hypocalcemic. No adverse effects were observed in any dog during the study.

Discussion

Results of this study indicate that cortisol concentrations are significantly suppressed only between 2 and 4 hours after trilostane administration, indicating that an ACTH-stimulation test to assess the adrenal reserve capacity should be carried out during this time frame. The effect of trilostane on electrolyte concentrations was of sufficiently small magnitude to not result in adverse clinical effects.

The maximum effect of trilostane on glucocorticoid production is reached 2–4 hours after oral administration. Accordingly, at this time point, minimal cortisol concentrations occur. As a result, endogenous ACTH concentrations increase 4–8 hours after trilostane administration because of negative feedback, which also influences the secretion of ACTH from the pituitary adenoma.

Cortisol concentrations were low in all dogs, and below the detection limit of the assay in most of the dogs on at least one occasion (in total on 18 occasions), but none of the dogs showed any adverse clinical effects. This could be caused by the brief period of hypocortisolemia, which might be too short to cause overt clinical signs. On the other hand, the signs might have been too mild to be detectable clinically. Nevertheless, in some dogs, this could lead to signs of hypocortisolism. In essence, the trilostane dosage could have been too high when given once daily. ACTH-stimulation test performed 4–6 hours after trilostane administration showed good control of the hypercortisolism. However, minimum cortisol concentrations were reached 2–4 hours after trilostane administration. An ACTH-stimulation test performed 4–6 hours after trilostane administration might miss brief periods of hypocortisolism during that time period (2–4 hours). It would be interesting to determine cortisol concentrations over 24 hours after twice-daily administration of trilostane as suggested in previous studies to determine if hypocortisolism could be avoided by administration of a lower dose every 12 hours.

Reduction in plasma cortisol after trilostane administration relieves the negative feedback on ACTH secretion. Dogs with PDH undergoing treatment with trilostane have marked elevations of plasma ACTH. The peak plasma ACTH concentration in dogs in this study occurred shortly after the lowest cortisol concentration. In this study, all blood samples had endogenous ACTH concentrations above the reference range. There was a marked interindividual variation in endogenous ACTH concentrations over the 24 hours and changes in endogenous ACTH concentrations were only minimal in some dogs; therefore, measurement of endogenous ACTH seems unhelpful for the evaluation of the therapeutic success of trilostane, as has been suggested previously. As no dog in this study showed signs of hypoadrenocorticism, the usefulness of basal plasma ACTH concentration to detect trilostane overdosage could not be evaluated.

Although there was no significant decrease in serum aldosterone concentration 2–4 hours after trilostane administration when plasma cortisol was at its lowest concentration, 2 dogs had aldosterone concentrations below the detection limit of the assay. This small decrease in aldosterone is similar to that reported by others, and is an expected result of the 3ß-hydroxysteroid dehydrogenase inhibition by trilostane that affects synthesis of all steroid hormones in the adrenal cortex. Aldosterone concentrations increased significantly after hour 16. However, it increased above the reference range in only 1 dog on hour 20. This is consistent with the results of 1 study in which a significant increase in basal aldosterone concentrations in dogs with PDH treated with trilostane was found, and in contrast to another study in which aldosterone concentrations were unaltered. However, both studies measured aldosterone concentration 2–6 hours after trilostane administration and did not determine its concentration 16 hours after trilostane making it difficult to compare it with our study. On the other hand, both noticed that trilostane’s effect on serum aldosterone concentration is less pronounced than on serum cortisol concentration. Although only playing a minor role, ACTH is nevertheless known to influence serum aldosterone concentrations. However, prolonged elevations of ACTH do not have the stimulatory effect on secretion that is noted after brief exposure to increased ACTH. Plasma
aldosterone concentration was lower in dogs with PDH and higher in dogs with AT than normal dogs.22

Six to 20 hours after trilostane administration, renin plasma activity was significantly increased. As peak aldosterone concentrations were found 16–24 hours after drug dosing, increased renin activity may be responsible for the increase in aldosterone concentration as it has a much larger physiologic role in aldosterone control than ACTH. In 1 study, a significant increase in median plasma renin activities and an insignificant decrease in aldosterone concentration 3.5 hours after trilostane administration were found.11 In this study, plasma renin activity showed an unstable profile in the first hours after trilostane uptake, which is consistent with the maximum effect of trilostane. At this time point, aldosterone reached its lowest concentration. Renin might increase because of a decrease in blood flow to the kidneys secondary to low aldosterone concentrations and, therefore, increased loss of fluids via the urine. This represents one of the 2 main mechanisms through which renin activity is regulated. The second trigger of an increased renin activity is increased plasma potassium concentrations. At the time point of maximum effect of trilostane, potassium concentrations were decreased and should cause low renin activity concentrations.

A significant decrease in potassium concentrations, albeit within the reference range, was unexpectedly found. No correlation between serum aldosterone and potassium concentrations during treatment with trilostane, found. No correlation between serum aldosterone and potassium concentrations during treatment with trilostane was found previously.10 Because of the effect of potassium concentrations during treatment with trilostane, potassium concentrations were decreased and increased renin activity is increased plasma potassium concentrations. At the time point of maximum effect of trilostane, potassium concentrations were decreased and should cause low renin activity concentrations.

The sodium:potassium ratio was above 27 on all but 3 occasions throughout the day. As serum potassium concentrations were decreased rather than increased, and serum sodium concentration fluctuated little throughout the day, it seems that the electrolyte abnormalities that occur in hypoadrenocorticism are uncommon in dogs with PDH treated with trilostane. Hypoadrenocorticoid crises can still occur,6,11,23,24 but might be more likely caused by an adrenal necrosis, which, in rats, has been reported to result from long-standing increased concentrations of ACTH,25 than to abnormally low aldosterone concentrations.

In summary, this study confirms that trilostane is an effective drug in the treatment of PDH in dogs. As cortisol concentrations decreased significantly 2–4 hours after trilostane administration, it seems reasonable to perform an ACTH-stimulation test at this time. However, future studies are necessary to establish interpretation criteria for a 2–4 hour after trilostane administration ACTH-stimulation test. Aldosterone abnormalities did not occur throughout the day, and serum potassium concentrations decreased rather than increased shortly after trilostane administration. Some of the reasons for changes in hormones and electrolyte concentrations remain unclear. A possible explanation may be diurnal variation in the hormones. Further studies with a greater caseload would be interesting.

Footnotes

* Hurley K, Sturgess K, Cauvin A, et al. The use of trilostane for the treatment of hyperadrenocorticism in dogs. J Vet Intern Med 1998; 12:210 (abstract)

† Synaetken; Novartis, Aulendorf, Germany

‡ Dexasel; Selectavet, Weyarn-Holzolling, Germany

§ Advia Centaur; Siemens Healthcare, Munich, Germany

‖ Vetoryl Hard Capsules; Dechra Limited, Shropshire, UK

¶ Radioimmunoassay (RIA), Solid-phase component system (coated tube separation); Cambridge Specialist Laboratory Services, Cambridge, UK; Manufacturer: MP Biomedicals, London, UK

‖ Immunoradiometric-assay (IRMA), sandwich assay with solid-phase bead system; Cambridge Specialist Laboratory Services, Cambridge, UK; Manufacturer: Nichols Institute Diagnostics, San Juan Capistrano, CA

‡ Radioimmunoassay (RIA), Solid-phase with coated tube separation; Cambridge Specialist Laboratory Services, Cambridge, UK; Manufacturer: EURO/DPC Ltd, Gwynedd, UK

§ Radioimmunoassay (RIA), Solid-phase with coated tube separation; Cambridge Specialist Laboratory Services, Cambridge, UK; Manufacturer: DiaSorin, Stillwater, MA

‖ AVL; Roche

∥ Neiger R, Campbell E. 24-hour cortisol values after trilostane therapy in dogs with hyperadrenocorticism. Proceedings of the 10th ESVIM Congress, 14–16 September 2000, Neuchâtel, Switzerland; pp. 31–32 (abstract)
Acknowledgments

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Conflict of Interest Declaration: Greg Williams is an employee of Dechra Limited, the marketing authorization holder for Vetoryl hard capsules (trilostane).

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