Lack of association between clinical signs and laboratory parameters in dogs with hyperadrenocorticism before and during trilostane treatment

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Summary

Trilostane therapy, the treatment of choice for pituitary-dependent hyperadrenocorticism (HAC) in dogs, is monitored by assessing resolution of clinical signs and measuring adrenocortical reserve capacity with an ACTH-stimulation test. The aim of this prospective study was to evaluate agreement between clinical signs reported by owners and cortisol or ACTH concentrations before and during trilostane therapy (starting dose 1–2 mg/kg once daily). A questionnaire on signs of HAC was used and a clinical score calculated as the sum of the 9 questions. Eighteen questionnaires at diagnosis and 97 during therapy were filled out by owners of 32 dogs. An ACTH-stimulation test was performed at each reevaluation. There were weak correlations between abdominal girth, appetite or weight gain and cortisol concentrations during therapy. However, the clinical score did not correlate with cortisol or cACTH values. In 50% of dogs, trilostane application had to be changed from once daily to twice daily during the study. Clinical signs reported by owners matched poorly with cortisol or cACTH concentrations at any time point. If low-dose trilostane is used, treatment frequency often has to be increased.

Keywords: questionnaire, medical therapy, ACTH-stimulation test, cortisol, canine

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Fehlender Zusammenhang zwischen klinischen Symptomen und Laborwerten von Hunden mit Hyperadrenokortizismus vor und während der Trilostan-Behandlung

Die Behandlung mit Trilostan, dem Medikament der Wahl zur Therapie eines hypophysen-abhängigen Hyperadrenokortizismus (HAK) beim Hund, wird anhand des Verschwindens der klinischen Symptome und des Resultates des ACTH-Stimulationstestes beurteilt. Das Ziel dieser prospektiven Studie war die Übereinstimmung der klinischen Symptome (beurteilt durch Besitzer) mit den Kortisol- und endogenen ACTH-Konzentrationen vor und während der Trilostantherapie (Startdosis 1–2 mg/kg 1× täglich) zu untersuchen. Ein Fragebogen mit 9 Fragen zur Klinik des HAK wurde verwendet und ein klinischer Gesamtscore als Summe berechnet. Achtzehn Fragebögen zum Zeitpunkt der Diagnosestellung und 97 unter Therapie wurden von Besitzern von 32 Hunden ausgefüllt. Ein ACTH-Stimulationstest wurde zu jedem Kontrollzeitpunkt durchgeführt. Es fanden sich schwache Korrelationen von Bauchumfang, Appetit und Gewichtszunahme mit den Kortisolwerten während der Therapie. Der klinische Gesamtscore korrelierte aber nicht mit den Kortisol- oder ACTH-Konzentrationen. Bei 50% der Hunde musste die Trilostangabe während der Studie von ein- auf zweimal täglich umgestellt werden. Klinische Symptome beurteilt durch Besitzer zeigen eine schlechte Übereinstimmung mit Kortisol- und ACTH-Konzentrationen während der Trilostantherapie. Wird Trilostan tief-dosiert eingesetzt, muss die Applikationshäufigkeit oft erhöht werden.

Schlüsselwörter: Fragebogen, medikamentelle Therapie, ACTH-Stimulationstest, Kortiosl, Hund

Introduction

Trilostane is the treatment of choice for dogs with pituitary-dependent hyperadrenocorticism (HAC). Trilostane is a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase enzyme system and interferes with synthesis of glucocorticoids at the level of the adrenal glands. Trilostane has been shown to reduce the circulating concentrations of cortisol leading to substantial improvement of clinical signs in 70 to 96% of cases (Ruckstuhl et al., 2002; Braddock et al., 2003; Neiger et al., 2003). Since its first use in veterinary medicine, the recommended daily dose has been adjusted several times. Especially with the introduction of the veterinary product in the year 2002 in Europe, endocrinologists experienced a need to significantly reduce the daily dose from the originally prescribed >4–10 mg/kg to 1–2 mg/kg per day.

It is well known that the maximum effect of trilostane on glucocorticoid production is reached 2–4 hours after application and that trilostane does not normalize cortisol concentrations in dogs with HAC for 24 hours (Lehnert, 2007). Based on this, some authors postulate that using trilostane twice daily will increase the number of dogs with a good clinical response (Arenas et al., 2013). However, there is still no consensus on the optimal frequency of administration.

Treatment response is monitored by assessing improvement or resolution of clinical signs and by measuring the adrenocortical reserve capacity with an ACTH-stimulation test (Ruckstuhl et al., 2002; Neiger et al., 2003). However, this test is time consuming and expensive. Moreover, concerns have been raised that synthetic ACTH, if applied in excessive amounts, could have deleterious effects on adrenal glands (Burkhardt et al., 2011). Therefore a monitoring system without the need for ACTH-stimulation, but with which both over- and underdosed animals could be safely and timely identified, would be preferable. The assessment of clinical signs as an alternative to monitoring trilostane treatment has been investigated by two groups (Wehner et al., 2013; Ramsey et al., 2015). Results, however, are only available as abstracts and are somewhat contradictory. While in the first study, no correlation between clinical signs and ACTH-stimulation test results during trilostane therapy were observed (Wehner et al., 2013), in the second, a weak correlation between clinical signs and cortisol concentrations could be shown (Ramsey et al., 2015).

Both research groups included dogs solely during therapy but not at the time of diagnosis (Wehner et al., 2013; Ramsey et al., 2015). The latter, however, would be an interesting time point to evaluate a possible correlation between clinical signs and cortisol or ACTH concentrations, as one could hypothesize that clinical signs reported by owners would be more severe in dogs with higher cortisol or ACTH concentrations. Still, no studies have addressed this hypothesis.

Therefore, the objectives of the study were multiple. First, we wanted to evaluate the agreement between clinical signs reported by the owners and cortisol and cACTH concentrations at the time of diagnosis as well as during trilostane therapy. Second, we wanted to assess the number of dogs in which the treatment regimen had to be changed from once to twice daily during therapy.

Animals, Material and Methods

Animals

Thirty-two client-owned dogs with HAC were included in the study. Age ranged from 6 to 14 years (median, 11 years) and bodyweight from 2.1 to 39.7 kg (median, 14.5 kg). There were 16 females (13 spayed) and 16 males (11 castrated). The most frequently represented breeds were mixed breed (5), Dachshund (n=2) and Dandie Dinmont Terrier (2). There was 1 Australian Cattle Dog, Basset Hound, Bedlington Terrier, Bichon Frisé, Border Collie, Boxer, Cairn Terrier, Dalmatian, Doberman, Flat Coated Retriever, Eurasier, French Bulldog, Labrador Retriever, Maltese, Nova Scotia Duck Tolling Retriever, Papillon, Parson Jack Russell Terrier, Pekingese, Pomeranian, Tibetan Terrier, Toy Poodle, West Highland White Terrier and Yorkshire Terrier. Twenty-nine dogs were diagnosed with pituitary-dependent hyperadrenocorticism (PDH) and 2 with adrenal-dependent hyperadrenocorticism (ADH). In 1 dog differentiation between PDH and ADH was not possible.

Study design

The prospective study was conducted between December 2010 and October 2014 at our facility.

Dogs suspected of having hyperadrenocorticism underwent a thorough clinical examination. Blood and urine samples were collected for a CBC, biochemical profile, urinalysis and urine culture. Further work-up included an ACTH-stimulation test, a low-dose dexamethasone suppression test (LDDS) and/or measurement of the urinary corticoid:creatinine ratio (UCCR) and ultrasonographic examination of the adrenal glands. PDH or ADH was diagnosed on the basis of the dog's concentration of endogenous ACTH (cACTH) and/or the ultrasonographic appearance of the adrenal glands.

Dogs were included in the study when consistent clinical and laboratory findings for HAC were present, the LDDS and/or the ACTH-stimulation test and/or the urinary UCCR were positive, the dog had not received other

treatments (radiation treatment or mitotane) and at least one owner questionnaire had been filled out. Dogs with concurrent diseases (e.g. diabetes mellitus, chronic renal disease) were excluded from the study. Informed consent was obtained from the owners of all dogs. Their use complied with the guidelines and directives established by the Animal Welfare Act of Switzerland.

Disease-specific questionnaires

The disease-specific questionnaire included 9 questions about polyuria, polydipsia, appetite, panting, amount of sleep, body weight increase, abdominal girth, activity level, and general attitude. For each question the owner could rate the severity of a symptom between 1–10 (5=normal, 10=severe). Symptom scores were recorded and a total clinical score calculated by adding the scores for each clinical symptom. A total clinical score of 45 represented a well-controlled dog. Total clinical scores >45–90 represented dogs with mild (46) to severe (90) clinical signs of HAC. The clinical scores derived from the owner questionnaire were then categorized into one of 3 groups: excessive (<45), adequate (45–50) or inadequate (>50) control of HAC.

Diagnostic testing and hormone analysis

The ACTH-stimulation tests were performed by collecting blood samples for determination of serum cortisol before and 1 hour after intravenous or intramuscular injection of 5 ug/kg of synthetic ACTH (Synacthen®, Novartis Pharma Schweiz AG, Bern, Switzerland). A cortisol concentration of >17 ug/dl was considered consistent with HAC. The LDDS test was performed as described previously (Braun et al., 2013). A cortisol concentration of ≥1.0 ug/dl at 8 hours or of ≥1 ug/dl at 4 hours and <1 ug/dl at 8 hours (inverse result, Mueller et al., 2006) after dexamethasone administration was considered consistent with HAC. Serum cortisol concentrations were determined by use of chemiluminescence assays (DPC Immulite® 1000, Siemens AG, Zurich, Switzerland). Urinary corticoid concentrations were measured by use of a radioimmunoassay (RIA Beckmann, Unilabs Dr. Weber, St. Gallen, Switzerland). A UCCR of $>10\times10^{-6}$ was considered abnormal. Endogenous ACTH was determined before ACTH-stimulation by collecting blood into chilled EDTA-coated tubes placed on ice. After centrifugation at 4 °C, plasma was stored at −80 °C until assayed. Measurement was performed by a chemiluminescence assay (DPC Immulite® 1000, Siemens AG, Zurich, Switzerland).

Trilostane therapy

The initial dose of trilostane was 1–2 mg/kg bodyweight orally q24h. Efficacy of trilostane treatment was assessed at each re-evaluation based on the clinical signs documented by the attending clinician and the results of ACTH-stimulation testing. ACTH-stimulation tests were performed at the time of diagnosis and after 2 (t1), 4 (t2), 8 (t3), 12 weeks (t4), 4–7 months (t5), and 8–12 (t6) months of trilostane treatment. At t1-t3, t5 and t6 the test was performed 2–3 h after the daily dose of trilostane. At t4 the ACTH-stimulation test was performed 24 hours after the last trilostane application. The treatment goal at t1–t3, t5 and t6 was a serum cortisol concentration between 1.5 and 5 ug/dl after ACTH-stimulation (Burkhardt et al., 2013). In dogs with post-ACTH cortisol concentration lower or higher than the target range, the trilostane dose was reduced or increased, respectively. The dose adjustments were made in increments of 2.5–10 mg/dog/day depending on the dog's size. The treatment goal at t4 was a post-ACTH cortisol concentration ≤10 ug/dl. In dogs with a post-ACTH cortisol concentration >10 ug/dl and in which the owner complained of polydipsia, polyuria, panting or restlessness in the late afternoon or at night, the treatment was changed to twice daily therapy (dividing the daily trilostane dose to q12h). Control of cortisol release was classified according to the post-ACTH cortisol concentrations as: excessive (<1.5 ug/dl), adequate (1.5–5 ug/dl) or inadequate (>5 ug/dl).

Statistical analysis

Variables were tested for normality by use of the Shapiro-Wilk test and analyzed by means of non-parametric statistical methods (GraphPad Prism6, GraphPad Software, San Diego, CA, USA; SPSS 22.0 for Windows; SPSS Inc, Chicago, IL, USA). At the time point of diagnosis the scores of each clinical sign and the total clinical score were correlated with baseline cortisol, post-ACTH cortisol, cACTH, baseline/4h/8h cortisol values of the LDDS test, thrombocyte count, serum alkaline phosphatase (ALP) and serum lipase concentrations. During reevaluations the scores of each clinical sign and the total clinical score were compared with baseline cortisol, post-ACTH cortisol and cACTH concentrations. Ranges and median values are reported. Linear correlations between clinical scores and laboratory values were calculated by Spearman rank non-parametric correlation. Weighted kappa was calculated to assess the agreement between categorization according to the clinical score and post-ACTH cortisol. Differences between groups were tested by the Kruskal-Wallis test and Dunn's post test. Differences were considered significant at values of $p < 0.05$.

Results

Comparing clinical signs and laboratory parameters

Time of diagnosis

Eighteen owner questionnaires were filled out at the time of diagnosing HAC. There was no significant correlation

between any of the cortisol values (baseline or post-ACTH cortisol, 0/4/8h LDDST cortisol value) or the cACTH concentration with the score for any clinical parameter or with the total clinical score (Fig. 1). Comparing scores for the clinical signs of dogs with a positive ACTH-stimulation test with those with a negative test result did not reveal any significant differences.

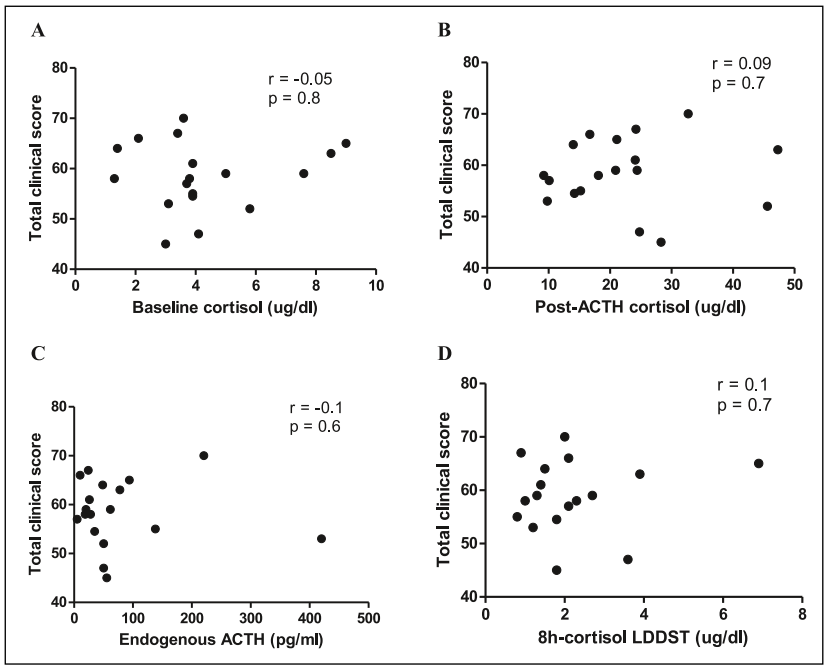

Figure 1: Correlation of the total clinical score with the baseline cortisol concentration (A), the post-ACTH cortisol concentration (B), the cACTH concentration (C) and the 8h cortisol oncentration during the low-dose dexamethasone suppression (LDDST) (D) at the time of diagnosing HAC in 18 dogs.

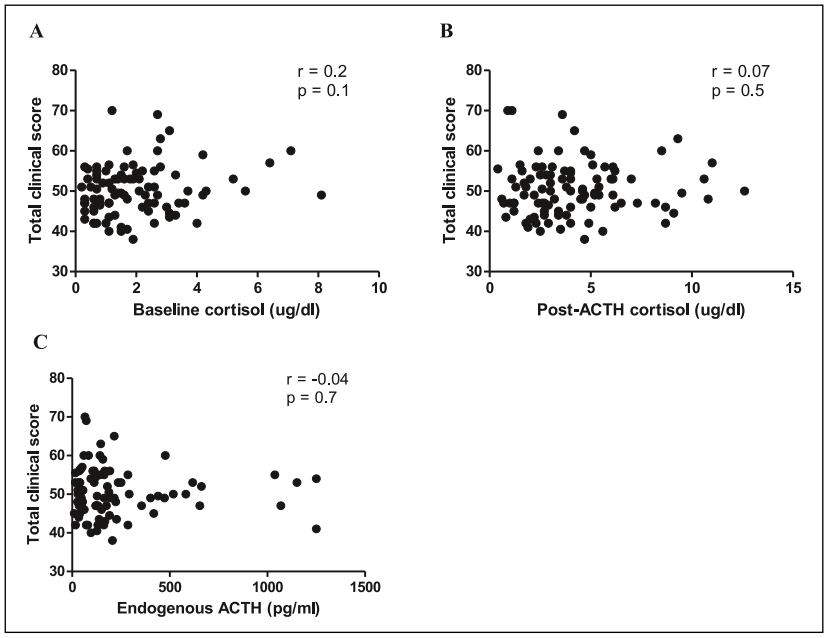

Figure 2: Correlation of the total clinical score with the baseline cortisol concentration (A), the post-ACTH cortisol concentration (B) and the cACTH concentration (C) at 97 re-evaluations during trilostane therapy in 32 dogs.

Reevaluations

Ninety-seven owner questionnaires were filled out during reevaluations. The median number of owner questionnaires filled out per dog was 3 (1–7). There was no significant correlation of the total clinical score with the cortisol values of the ACTH-stimulation test or the cACTH (Fig. 2). The following significant, but weak correlations between laboratory parameters and clinical scores were found: baseline cortisol and abdominal girth ($r=0.3$, $p=0.01$, $n=88$), post-ACTH cortisol and appetite ($r=0.2$, $p=0.04$, $n=97$), post-ACTH cortisol and body weight increase ($r=0.2$, $p=0.03$, $n=94$). Grouping dogs according to their control of cortisol release (excessive, adequate, inadequate), revealed no significant difference in the scores of the clinical signs between the 3 groups (Fig. 3). The weighted kappa for post-ACTH cortisol compared to the total clinical score categories was 0.058 (poor agreement).

Dosing of trilostane

In 24 dogs a follow-up of more than 3 months was available. In 12 of them (50%) the trilostane treatment regimen was changed from once to twice daily during the evaluation period. The reason for the change was a worsening of the clinical signs (polydipsia, polyuria, panting and restlessness) in the late afternoon or at night and/or a post-ACTH cortisol concentration >10 ug/dl 24h after the last trilostane dose. At the time of the treatment change the total daily trilostane dose was divided, and in selected cases slightly increased by about 5%. In the twice-daily treated group, all except one of the dogs had a positive ACTH-stimulation test at the time point of diagnosis, whereas in the once-daily treated group, only 6 had a positive ACTH-stimulation test. This difference was not significant ($p=0.07$) (Fig. 4).

Discussion

In the present study we were able to show for the first time that, at the time point of diagnosis, owner-reported clinical signs of dogs with HAC correlated neither with cortisol concentrations of the tests to confirm the diagnosis nor with the cACTH concentration. This finding was fairly surprising, as one would expect that cases with only mild clinical signs would have a lower degree of cortisol hypersecretion and a less decreased hypothalamic-pituitary-adrenal axis sensitivity than cases with more severe clinical signs (Behrend et al., 2013). On the one hand, the lack of correlation could be due to the subjectivity of the owner questionnaires. On the other hand, individual sensitivity to cortisol could play a role, meaning that some dogs show moderate to severe signs even though their cortisol hypersecretion is only mild. This phenomenon has been described in human medicine and, although not yet documented in veterinary

medicine, could also exist in dogs (Nieman et al., 2008; Zografos et al., 2014). It is also possible that not only cortisol concentrations contribute to clinical signs, but also cortisol precursor concentrations and that therefore correlation of clinical signs with a cortisol-based monitoring method is less favourable (Behrend et al., 2005). Another aim of the study was to evaluate the agreement between clinical signs reported by owners and cortisol and cACTH concentrations during trilostane therapy. Some owners were highly satisfied and documented substantial improvement, although the post-ACTH cortisol levels were still fairly increased and accordingly, there was no significant correlation between the total clinical score and the cortisol concentrations (basal, post-ACTH). This observation is in agreement with a study by Wehner and coworkers (2013) who were also not able to show a significant correlation between the absolute clinical score and the baseline or post-ACTH cortisol concentration in their trilostane-treated dogs. In the study by Ramsey et al. (2015) the correlation between clinical signs and ACTH-test results was weak but still significant. This discrepancy is difficult to explain, but the higher case number in the latter study or differences within the owner questionnaires could account for the different results. Several other explanations for the lack of correlation between clinical signs and cortisol values in our and in the study of Wehner and coworkers have to be considered. As noted above, this could be due to the subjectivity inherent in the owner questionnaires. Further, in our study, owners were not aware of their answers to the previous questionnaires, which could, however, have helped them to assess the improvement of clinical signs between the first and further rechecks. On the other hand, clinical signs might not only be related to the extent but also to the duration of cortisol excess, a phenomenon which has been documented in human medicine (Nieman, 2015). Finally, timing of the ACTH-stimulation test in relation to trilostane administration has an influence on the magnitude of the cortisol concentration and stimulation, which in turn could lead to a lack of correlation between clinical signs and cortisol concentrations. This explanation, however, can be excluded in this study, as the test protocol was standardized and the ACTH-stimulation always performed 2–3 h after the daily dose of trilostane.

Classifying the dogs of this study into excessively-, adequately- or inadequately-controlled groups according to their cortisol release during the ACTH-stimulation test revealed no difference in their total clinical score. The weighted kappa even defined the agreement between post-ACTH cortisol and the total clinical score as poor. This was surprising and incongruent with our clinical experience. Although the ACTH-stimulation test certainly can be discussed as a gold standard in monitoring trilostane therapy, it has been proven to objectively assess the therapeutic response. Treatment monitoring with the use of the ACTH-stimulation test is very often successful and helpful in identifying excessively-controlled dogs (Sieber-Ruckstuhl et al., 2006; Galac et al., 2009; Burkhardt et al., 2013). Again, the problem could be the subjectivity of owner questionnaires, which may even increase when owners are not able to look back at their answers on previous questionnaires. In addition, the owners' perception of clinical signs may not reflect the clinical status assessed by the veterinarian in charge. The agreement of the clinical

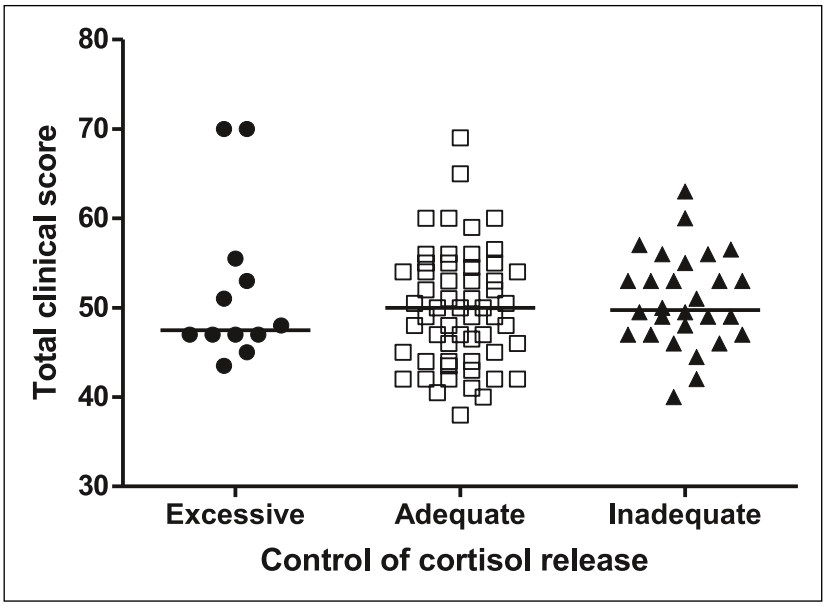

Figure 3: The total clinical score from 97 re-evaluations during trilostane therapy in 32 dogs. Control of cortisol release is classified according to the post-ACTH cortisol concentrations as: excessive (<1.5 ug/dl), adequate (1.5–5 ug/dl) or inadequate (>5 ug/dl).

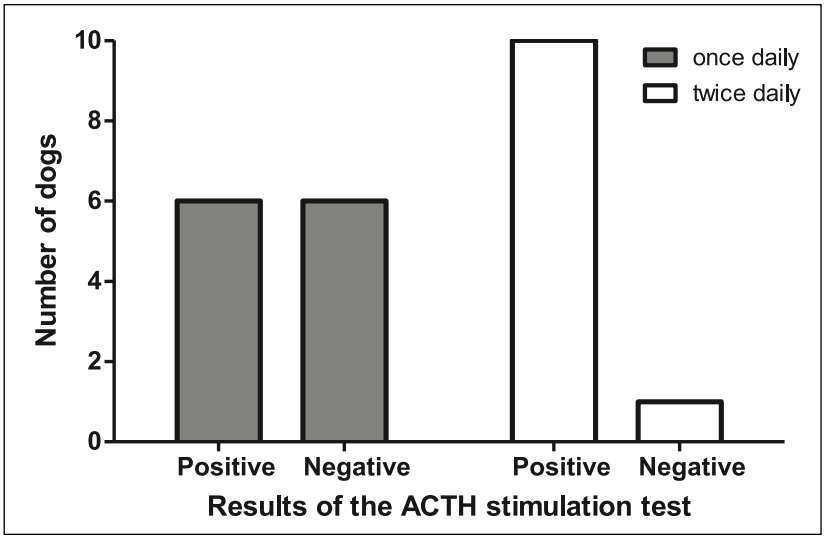

Figure 4: Number of dogs with a positive (post-ACTH cortisol ≥17 ug/dl) or negative (post-ACTH cortisol <17 ug/dl) ACTH-stimulation test at the time of diagnosis in relation to their trilostane treatment frequency (once versus twice daily).

score with the cortisol concentrations might possibly be improved if the clinical assessment of a veterinarian were to be included in the score. However, to increase the reliability of the clinical score in this way, the same veterinarian would have to judge each patient at each recheck, which is hardly possible in a large clinical institution.

Trilostane does not normalize cortisol concentrations in dogs with HAC for a period of 24 hours (Lehnert et al., 2007). It has been suggested that using trilostane twice daily might increase the number of dogs with a good clinical response compared to only once-daily therapy (Arenas et al., 2013). In the present study, the treatment regimen had been changed from once to twice daily in 12 of 24 dogs during the evaluation period. Reasons for the change were worsening of the clinical signs late in the afternoon or at night and/or increased post-ACTH cortisol concentrations 24h after the last trilostane dose. This number is much higher than in earlier years. We believe that the main reason for this is the substantially lower trilostane starting dose used nowadays (1–2 mg/kg compared to >4 mg/kg). However, for this study we can assess neither which treatment regimen is more favourable nor whether the twice-daily treatment would lead to a better correlation between the cortisol values and the total clinical score. Interestingly, all except one dog in which the trilostane treatment frequency was changed from once- to twice- daily therapy had a positive ACTH-stimulation test at the time point of diagnosis. In contrast, for dogs controlled with the once-daily trilostane treatment, the same number had a positive as a negative ACTH-stimulation test. A positive ACTH-stimulation test reflects an increased capacity to synthesize and secrete excessive amounts of cortisol. Therefore, one could argue that dogs with a positive ACTH-stimulation test, reflecting a greater capacity to synthesize cortisol, would need more frequent trilostane application to control the disease. This interesting finding should be further addressed in future studies.

A limitation of this and also other trilostane studies is the lack of a gold standard with which to classify dogs as excessively-, adequately- or inadequately-controlled. This is reflected in the discrepant results between the studies, due to the fact that there are different monitoring standards: clinical signs and cortisol values. All studies, including ours, reflect however that neither cortisol nor clinical parameters should be judged separately. Of interest are the results of a very recent study (Ramsey et al., 2015) comparing 4 different cortisol-based monitoring methods with the clinical score. Two cortisol-based monitoring methods (one using the pre-trilostane cortisol value and the other the pre-trilostane in combination with the 3 hours post-trilostane cortisol) seemed to reflect clinical control better than results of the ACTH-stimulation test (Ramsey et al., 2015). Future studies should therefore include such cortisol-based monitoring methods, possibly in combination with an optimized clinical evaluation sheet.

In summary, comparing the score of the clinical signs reported by owners with the results of the ACTH-stimulation test 2-3 hours after trilostane application revealed no significant correlation of the cortisol values with the clinical signs. Therefore we conclude that monitoring of trilostane therapy based on clinical signs assessed by owners is only partially helpful in differentiating excessively-, adequately- or inadequately-controlled dogs. Neither under- nor overdosing could be identified based on the clinical score. If trilostane is used in a low-dose (1–2 mg/kg), treatment frequency often has to be changed from once to twice daily.

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Absence de corrélation entre les symptômes cliniques et les valeurs de laboratoire chez les chiens souffrant d'hyperadrénocorticisme avant et durant un traitement au trilostane

Le traitement au trilostane, médicament de choix dans les cas d'hyperadrénocorticisme hypophyso-dépendant chez le chien, est évalué sur la base de la disparition des symptômes cliniques et des résultats des tests de stimulation à l'ACTH. Le but de la présente étude prospective était de comparer les symptômes cliniques (évalués par les propriétaires) avec les concentrations de cortisol et d'ACTH endogène avant et durant un traitement au trilostane (dose initiale 1–2 mg/kg, 1× par jour). On a utilisé un questionnaire composé de 9 questions relatives aux symptômes cliniques sur la base desquels on a calculé un score clinique total. Dix-huit questionnaires ont été remplis au moment du diagnostic et 97 durant le traitement par les propriétaires de 32 chiens. Un test de stimulation à l'ACTH a été réalisé lors de chaque contrôle. Il existait de faibles corrélations entre le périmètre abdominal, l'appétit et la prise de poids et les taux de cortisol durant le traitement. Le score clinique total n'était toutefois pas corrélé avec les concentrations de cortisol ou d'ACTH. Chez la moitié des chiens, la dose de trilostane a du être répartie en deux prises journalières. Les symptômes cliniques jugés par les propriétaires montraient une mauvaise corrélation avec les taux de cortisol et d'ACTH durant le traitement au trilostane. Si on dose ce médicament de façon faible, il y a souvent lieu d'augmenter la fréquence des prises.

Assenza di relazione tra i sintomi clinici e i valori di laboratorio nei cani affetti da iperadrenocorticismo prima e durante il trattamento con trilostano

Il trattamento con trilostano, il farmaco di prima scelta per il trattamento dell'iperadrenocorticismo ipofisario (PDH) nel cane, è stato valutato via la scomparsa di sintomi clinici e via il risultato del test di stimolazione ACTH. L'obiettivo di questo studio prospettivo era di studiare la conformità dei sintomi clinici (valutati dal proprietario), via la somministrazione di cortisolo e di concentrazioni di ACTH endogeno, prima e durante la terapia con trilostano (dose iniziale 1–2 mg/kg, 1× al giorno). È stato utilizzato un questionario con 9 domande sullo stato clinico del PDH ed è stato calcolato un punteggio totale dello stato clinico come risultato. Sono stati completati dai proprietari di 32 cani diciotto questionari al momento della diagnosi e 97 durante la terapia. Un test di stimulazione con ACTH è stato eseguito ad ogni controllo. Durante la terapia, si sono rilevate poche correlazioni con i valori di cortisolo per quel che riguarda la circonferenza del ventre, l'appetito e l'aumento di peso. Tuttavia, il punteggio totale dello stato clinico non era correlato alle concentrazioni di ACGT e di cortisolo. Durante lo studio, nel 50% dei cani la dose di trilostano è stata modificata da una a due dosi giornaliere. I sintomi clinici valutati dai proprietari hanno evidenziato una scarsa corrispondenza tra le concentrazioni di cortisolo e ACTH durante la terapia con trilostano. Se il trilostano viene somministrato a basso dosaggio, spesso la frequenza deve essere aumentata.

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