Evaluation of twice-daily, low-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism

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Objective—To evaluate the effects of twice-daily oral administration of a low-dose of trilostane treatment and assess the duration of effects after once-daily trilostane administration in dogs with naturally occurring hyperadrenocorticism (NOH).

Design—Prospective study.

Animals—28 dogs with NOH.

Procedures—22 dogs received 0.5 to 2.5 mg of trilostane/kg (0.23 to 1.14 mg/lb) orally every 12 hours initially. At intervals, dogs were reevaluated; owner assessment of treatment response was recorded. To assess drug effect duration, 16 of the 22 dogs and 6 additional dogs underwent 2 ACTH stimulation tests 3 to 4 hours and 8 to 9 hours after once-daily trilostane administration.

Results—After 1 to 2 weeks, mean trilostane dosage was 1.4 mg/kg (0.64 mg/lb) every 12 hours (n = 22 dogs; good response [resolution of signs], 8; poor response, 14). Four to 8 weeks later, mean dosage was 1.8 mg/kg (0.82 mg/lb) every 12 or 8 hours (n = 21 and 1 dogs, respectively; good response, 15; poor response, 5; 2 dogs were ill). Eight to 16 weeks after the second reevaluation, remaining dogs had good responses (mean dosages, 1.9 mg/kg [0.86 mg/lb], q 12 h [n = 13 dogs] and 1.3 mg/kg [0.59 mg/lb], q 8 h [3]). At 3 to 4 hours and 8 to 9 hours after once-daily dosing, mean post-ACTH stimulation serum cortisol concentrations were 2.60 and 8.09 µg/dL, respectively.

Conclusions and Clinical Relevance—In dogs with NOH, administration of trilostane at low doses every 12 hours was effective, although 2 dogs became ill during treatment. Drug effects diminished within 8 to 9 hours. Because of potential adverse effects, lower doses should be evaluated. (J Am Vet Med Assoc 2008;232:1321–1328)

Naturally occurring hyperadrenocorticism is a well-recognized endocrine disorder in dogs. It is estimated that approximately 85% of dogs with hyperadrenocorticism have PDH and 15% have ATH as a result of a cortisol-secreting adrenocortical adenoma or carcinoma.1–2 In dogs with either PDH or ATH, clinical signs are the result of a chronic excess in circulating cortisol concentration. At present, the most common medical treatment for dogs with NOH is administration of mitotane (o,p’-DDD); its use has been recommended for more than 3 decades.3 Although the effectiveness of mitotane in dogs with ATH is variable, the drug has good efficacy. Clinical signs are controlled in approximately 80% of dogs with PDH that are treated with this drug.1,4–6 Treatment with mitotane is associated with potential adverse effects and disadvantages, such as transient hypoadrenocorticism, permanent mineralocorticoid and glucocorticoid deficiencies, drug intolerance, and relapses.1–6

The most promising new drug for treating dogs with NOH is trilostane.4 Trilostane is a 4α, 5-epoxysteroid competitive inhibitor of the 3β-hydroxysteroid dehy-
in some dogs with either good or poor control of hyperadrenocorticism, the UCCR 24 hours after once-daily trilostane administration is high, suggesting that trilostane does not consistently suppress circulating cortisol concentration for as long as 24 hours.17 In dogs for which there is an inadequate duration of effect, a twice-daily dosing regimen has been recommended.13,15,17 In a review of 7 studies, involving 169 dogs treated once daily with trilostane, 29 (17%) dogs became sufficiently ill to warrant reporting of those adverse effects. Usually, the adverse effects included anorexia, vomiting, diarrhea, and weakness. At least 4 of the 169 (2.4%) dogs were described as having died from the effects of trilostane.13,18-19 In 4 of those previously published reports, the dosages of trilostane administered once daily at the end of the study periods were 5.3 to 50 mg/kg (2.41 to 22.73 mg/lb),13 4.4 to 16 mg/kg (2.0 to 7.27 mg/lb; at 3 months of treatment),14 9.19 to 8.2 mg/kg (0.86 to 3.73 mg/lb),15 and a mean of 3.2 to 11.4 mg/kg (1.45 to 5.18 mg/lb).13 In another study,10 to evaluate twice-daily oral administration of trilostane in dogs, adverse reactions attributable to glucocorticoid or mineralocorticoid deficiencies were detected in 11 of 44 (25%) treated dogs, and the mean dosage at the end of the study period was 3.2 mg/kg, twice daily (total daily dose, 6.4 mg/kg [2.91 mg/lb]).

Several years ago, we began to use trilostane to attempt control of NOH in some dogs; dogs were treated with the recommended dose (3 to 6 mg/kg, PO) once daily. Those 22 dogs were reevaluated 57 times during the first 4 to 6 months of treatment. At 23 of those 57 reevaluations, dogs were described by their owners as having resolution of clinical signs. However, at 21 (37%) of the reevaluations, dogs were described by their owners as continuing to have clinical signs, and at 13 (23%) of the reevaluations, dogs were described as ill (any combination of anorexia, vomiting, diarrhea, weakness, and obtundation). Six of 7 ill dogs that were examined by a veterinarian had hyponatremia and hyperkalemia, suggestive of iatrogenic hypoadrenocorticism. Two of those 6 dogs (both with serum electrolyte abnormalities) died before treatment could be implemented. Not including the 2 dogs that died, 7 owners of dogs that had trilostane-associated adverse effects (32% of the 22 dogs) refused to recommence treatment with the drug after their pet's recovery because of the serious nature of their dog's illness or the expense of emergency treatment. Based on the reported incidence of serious adverse effects caused by trilostane,13-19 and the experience gained through our treatment of dogs with trilostane, investigation of a modified dosing regimen seemed warranted. The purpose of the study reported here was to evaluate the effects of twice-daily, low-dose trilostane treatment administered orally in dogs with NOH and to further assess the duration of the drug's effect after once-daily oral administration.

Materials and Methods

Dogs—The study included dogs that were initially evaluated by at least one of the authors at the Veterinary Medical Teaching Hospital of the University of California, Davis, from January 2006 through March 2007. All dogs were enrolled in the study with the informed consent of their owners. The diagnosis of NOH was suspected from review of historical data and physical examination results. Each dog had polyuria as an owner concern, and each had at least 4 of the following 6 clinicopathologic findings: high serum alkaline phosphatase activity, high serum alanine aminotransferase activity, hypercholesterolemia, low BUN concentration or BUN concentration near the lower reference limit (low-normal value), urine specific gravity < 1.020, and microbiological growth on culture of urine. None of the dogs had BUN concentration > 25 mg/dL, and none had received prior treatment for NOH. Each dog underwent abdominal ultrasonography at the hospital.2 For each dog, results of at least 2 of 3 screening tests (ie, ACTH stimulation test, LDDS test, or assessment of UCCR) were consistent with hyperadrenocorticism. The diagnosis of PDH was made if a dog had at least 2 of the following 3 diagnostic test results: an LDDS test result indicative of PDH, ultrasonographic evidence of 2 relatively equal-sized adrenal glands, or plasma concentration of endogenous ACTH > 45 pg/mL.1,12-23 The diagnosis of ATH was made if all of the following were applicable: abnormal LDDS test result, a low or undetectable plasma concentration of endogenous ACTH, ultrasonographic evidence of an adrenal mass, and histologic confirmation of an adrenocortical tumor (adenoma or carcinoma) following examination of adrenal mass tissue removed during celiotomy.1

Treatment and assessments—Initial trilostane dosage for each dog was 0.5 to 2.5 mg/kg (0.23 to 1.14 mg/lb) administered orally every 12 hours. Capsules provided by the manufacturer (30, 60, and 120 mg) were used whenever possible. For several dogs, 10-mg capsules were prepared by a compounding pharmacy. Each owner of a dog enrolled in the study agreed to return the dog for recheck evaluations after 1 to 2 weeks of treatment, and then at 4 to 8 weeks after the first reevaluation and 8 to 16 weeks after the second reevaluation. Alternatively, if a dog was scheduled to undergo surgery for extirpation of an adrenal gland tumor, owners agreed to return the dog for recheck evaluations at the same intervals or until surgery, whichever came first. On the morning of any reevaluation, owners were instructed to obtain a free-catch urine sample from the dog, if possible, for analysis. Owners were asked to feed the dog within an hour after urine sample collection and to administer trilostane at that morning meal (usually between 7 and 9 AM). Dogs were to be brought to the hospital 3 to 4 hours after trilostane administration, at which time an ACTH stimulation test would be completed. Urinalysis and UCCR assessment were performed on the urine sample collected by the owner. If adverse reactions were observed during the first 26 weeks of treatment at times other than planned reevaluations, those problems were assigned to the temporally closest of the 3 planned recheck examinations for purposes of analysis.

At each reevaluation, owners were questioned about their dog's general well-being, changes in clinical signs, and any adverse effects of treatment. Also, at each evaluation, a physical examination, a urinalysis, and an ACTH stimulation test were completed for each dog. For each dog at each visit, response to treatment was classified by owners as good or poor, or the dog was...
considered ill. A good response was defined as resolution of or marked improvement in clinical signs related to hyperadrenocorticism (ie, absence of polydipsia, polyuria, polyphagia, and panting and increase in muscle strength and activity; hair regrowth was not among the short-term goals of treatment). A poor response was defined as persistence of unacceptable clinical signs of hyperadrenocorticism (eg, polyuria). Dogs were considered ill if signs of anorexia, vomiting, diarrhea, unusual listlessness, or unusual weakness were present. The trilostane dose or administration frequency was altered, as needed, on the basis of owner observations, physical examination findings, or test results. Each dog was monitored by the same clinician throughout the study to help substantiate the owner’s impressions. Whenever there was discrepancy between test results and the owner’s opinion, the latter was given greater weight in determining whether a change in trilostane dose or administration frequency was warranted.

As an aid to resolution of clinical signs (specifically polyuria) without causing illness, treatment was directed, in part, to achieve post-ACTH stimulation serum cortisol concentrations < 5.5 µg/dL at 3 to 4 hours after trilostane administration. If a dog had a post-ACTH stimulation serum cortisol concentration < 1.5 µg/dL and no adverse clinical signs, the trilostane dosage was either unchanged or decreased at the discretion of the veterinarian. No change in trilostane dosage was made if a dog's response to treatment was classified as good and test results supported that determination. If a dog's response to treatment was classified as poor and its post-ACTH stimulation serum cortisol concentration was ≥ 5.5 µg/dL at the first reevaluation, the dosage of trilostane was maintained or increased at the discretion of the veterinarian; if these findings were present at the second or third reevaluation, the dose was increased by 10% to 50%. If a dog's response to treatment was classified as poor and its post-ACTH stimulation serum cortisol concentration was < 5.5 µg/dL, the frequency of trilostane administration was increased (q 8 h) and the dose was unchanged or decreased. If a dog was described by an owner as ill, trilostane administration was discontinued until the dog was considered well (usually 2 to 5 days) and then recommenced after reduction of the dose by 25% to 50%. If possible, a blood sample was collected from ill dogs for hematologic and serum biochemical analyses (including BUN, potassium, and sodium concentrations) and a urine sample was collected for urinalysis. If an owner could not bring an ill dog to the hospital, it was suggested that those assessments should be made by a local veterinarian.

Endocrine tests—For ACTH stimulation testing, blood samples (2 mL each) were collected before and 1 hour after IM administration of synthetic ACTH (0.25 mg) for measurement of serum cortisol concentration. Serum cortisol concentration > 22 µg/dL (607 nmol/L) at 1 hour after administration of ACTH was considered consistent with NOH. For the LDSS test, blood samples (2 mL each) were collected before and 4 and 8 hours after IV administration of dexamethasone (0.01 mg/kg) for determination of serum cortisol concentration. Serum cortisol concentration > 1.4 µg/dL at 8 hours after dexamethasone administration was considered consistent with naturally occurring PDH or ACTH. Serum cortisol concentrations < 1.4 µg/dL at 4 hours or < 50% of basal concentration at 4 or 8 hours after dexamethasone administration were considered consistent with PDH. Values of UCCR ≥ 13.5 × 10⁻⁶ were considered consistent with a diagnosis of hyperadrenocorticism.

Hormone assays—Blood samples obtained for determination of plasma concentrations of endogenous ACTH were collected, stored, and assayed as previously described. Serum and urine cortisol concentrations were measured by use of a commercial cortisol radioimmunoassay that has been validated for use in dogs. The analytical sensitivity of this radioimmunoassay was 0.3 µg/dL (8.3 nmol/L).

Duration of trilostane effect—Inclusion criteria for this investigation were the same as those for the main portion of the study. In addition to completion of 1 ACTH stimulation test 3 to 4 hours after trilostane administration, dogs underwent a second ACTH stimulation test 8 to 9 hours after trilostane administration. Each dog had to have been treated with trilostane for a minimum of 6 weeks but not more than 20 weeks and have a post-ACTH stimulation serum cortisol concentration < 5.5 µg/dL at 3 to 4 hours after trilostane administration. Owners were instructed to obtain a urine sample and to feed and treat their dog in the morning of the testing day (or days), as previously described. Owners whose dogs were receiving trilostane every 8 or 12 hours were instructed to administer the drug once daily beginning 3 days prior to this investigation and on the study day (or days) to duplicate the commonly used once-daily protocol. Owners were instructed not to administer the routine second or third daily doses of trilostane to their dogs until completion of this particular experiment. Arrangements were made for some owners to bring their dog to the hospital 3 to 4 hours after trilostane administration for completion of an ACTH stimulation test, leave, and return the dog to the hospital 8 to 9 hours after trilostane administration that same day for completion of a second test. Arrangements were made for other owners to bring their dog to the hospital 8 to 9 hours after trilostane administration for completion of an ACTH stimulation test, those dogs were returned home, whenupon owners repeated the once-daily treatment protocol the next morning and returned their dog to the hospital 3 to 4 hours after trilostane administration for completion of another ACTH stimulation test. Each dog underwent 2 ACTH stimulation tests in a period of < 20 hours.

Statistical analysis—Data were analyzed by use of a commercially available statistical program. To compare findings between groups, paired Student t tests as well as 1-way ANOVAs were performed as indicated. The Bonferroni method was used for post hoc analysis to adjust for multiple comparisons. A value of P < 0.05 was considered significant. Results are presented as mean ± SD.

Results

Dogs—Overall, 28 dogs with NOH were included in the study. Twenty-two dogs were enrolled for evalu-
Clinical signs and endocrine screening test results—The most common clinical signs initially reported by the owners of the 28 dogs were polyuria (n = 28), polydipsia (25), polyphagia (21), lethargy or weakness (18), panting (14), abdominal distention (12), and dermatologic abnormalities (eg, alopecia, thin skin, or hyperpigmentation; 11). Mean urine specific gravity before treatment was 1.010 (median, 1.011). Among the 28 dogs, 20 had abnormal results of 2 endocrine screening tests and 8 had abnormal results of all 3 endocrine screening tests. Results were abnormal in 12 of 22 ACTH stimulation tests, 25 of 27 assessments of UCCR, and 24 of 25 LDDS tests.

Treatment evaluation—Findings among all dogs and among those in which treatment response was classified as good or poor at each recheck evaluation were assessed (Table 1). Findings from all recheck evaluations were combined and assessed for dogs that had good or poor treatment responses overall (Table 2). At the first reevaluation, treatment response was good in 8 dogs and poor in 14 dogs. Twenty-one dogs underwent an ACTH

Table 1—Summary of trilostane dose and frequency of administration, post-ACTH stimulation test serum cortisol concentration, UCCR values, and urine specific gravity in 22 dogs with NOH at each of 3 recheck evaluations following initiation of treatment. At each visit, response to treatment was classified by owners as good or poor, or the dog was considered ill. Mean values are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reevaluation*</th>
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<tr>
<td></td>
<td>1</td>
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<tr>
<td>All dogs</td>
<td></td>
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<tr>
<td>No. of dogs</td>
<td>22</td>
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<tr>
<td>Mean dose every 12 h (mg/kg)</td>
<td>1.4 ± 0.6</td>
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<tr>
<td>Range of doses every 12 h (mg/kg)</td>
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<td>Mean dose every 8 h (mg/kg)</td>
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<tr>
<td>Range of doses every 12 h (mg/kg)</td>
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<td>Dogs with good response†</td>
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<tr>
<td>No. of dogs</td>
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<tr>
<td>Mean dose every 12 h (mg/kg)</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>Mean dose every 8 h (mg/kg)</td>
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<tr>
<td>No. of dogs with post-ACTH stimulation test serum cortisol concentration &lt; 5.5 µg/dL</td>
<td>7/7</td>
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<tr>
<td>No. of dogs with post-ACTH stimulation test serum cortisol concentration ≥ 5.5 µg/dL</td>
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<tr>
<td>Mean UCCR (× 10⁻⁶) (range)</td>
<td>11.3 ± 2.3</td>
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<td></td>
<td>(9.2–14.2)</td>
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<td>Mean urine specific gravity (range)</td>
<td>1.024 ± 0.009</td>
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<td>(1.012–1.035)</td>
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<td>Dogs with poor response‡</td>
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<td>No. of dogs</td>
<td>14</td>
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<tr>
<td>Mean dose every 12 h (mg/kg)</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>Mean dose every 8 h (mg/kg)</td>
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<tr>
<td>No. of dogs with post-ACTH stimulation test serum cortisol concentration &lt; 5.5 µg/dL</td>
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<tr>
<td>No. of dogs with post-ACTH stimulation test serum cortisol concentration ≥ 5.5 µg/dL</td>
<td>11</td>
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<tr>
<td>Mean UCCR (× 10⁻⁶) (range)</td>
<td>44.2 ± 47.9</td>
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<td>(15.8–153.6)</td>
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<tr>
<td>Mean urine specific gravity (range)</td>
<td>1.011 ± 0.005</td>
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<td>(1.003–1.019)</td>
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<td>Ill dogs§</td>
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<tr>
<td>No. of dogs</td>
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<tr>
<td>Doses every 12 h (mg/kg)</td>
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<tr>
<td>No. of dogs with post-ACTH stimulation test serum cortisol concentration &lt; 5.5 µg/dL</td>
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†Recheck examinations were completed 1 to 2 weeks after initiating trilostane treatment (first reevaluation), 4 to 8 weeks after the first reevaluation (second reevaluation), and 8 to 16 weeks after the second reevaluation (third reevaluation). Urine was obtained 1 hour prior to the morning trilostane administration. The ACTH stimulation tests were completed 3 to 4 hours after trilostane administration. 1A good response to treatment was defined as resolution of or marked improvement in clinical signs related to hyperadrenocorticism (ie, absence of polydipsia, polyuria, polyphagia, panting, and increase in muscle strength and activity; hair regrowth was not among the short-term goals of treatment). 1A poor response to treatment was defined as persistence of unacceptable clinical signs of hyperadrenocorticism (eg, polyurial). Dogs were considered ill if signs of anorexia, vomiting, diarrhea, unusual listlessness, or unusual weakness were present. Pretreatment mean urine specific gravity was 1.010 (median, 1.011).
stimulation test at the first reevaluation; samples collected from 1 dog were lost. For 7 dogs with a good response and 3 dogs with a poor response, serum cortisol concentrations after ACTH stimulation were < 5.5 µg/dL; post-ACTH stimulation serum cortisol concentrations ≥ 5.5 and < 12.5 µg/dL were detected in the remaining 11 dogs that underwent testing. In dogs with a good treatment response, the mean UCCR was lower and the mean urine specific gravity was higher than the respective values in dogs with a poor treatment response. The twice-daily, low-dose trilostane treatment was not changed in all 8 dogs with a good response and 4 of the 14 dogs with a poor response. The trilostane dose or administration frequency was changed in 10 of the 14 dogs with a poor treatment response: in 9 dogs, the dose was increased, and in 1 dog, the dose was unchanged but frequency of administration was increased to every 8 hours.

At the second reevaluation, 15 of 22 owners classified the treatment response of their dog as good, whereas 5 owners classified the response as poor; 2 owners described their dog as ill. Fourteen of 15 dogs with a good response and both dogs that were ill had post-ACTH stimulation serum cortisol concentrations < 5.5 µg/dL. In 1 ill dog, pre- and post-ACTH stimulation serum cortisol concentrations were 0.7 and 1.3 µg/dL, respectively; the values in the other dog were 1.3 and 4.5 µg/dL, respectively. In 1 dog with a good treatment response and all 5 dogs with a poor treatment response, post-ACTH stimulation serum cortisol concentrations were ≥ 5.5 µg/dL but < 18.6 µg/dL. In dogs with a good treatment response, the mean UCCR was lower and the mean urine specific gravity was higher than the respective values in dogs with a poor treatment response. Among the 8 dogs in which the treatment response was classified as good at the first reevaluation, 7 had a good response and 1 was described as ill at the second reevaluation. Among the 14 dogs in which the treatment response was classified as poor at the first reevaluation, 8 had a good response, 5 continued to have a poor response, and 1 was described as ill at the second reevaluation. Both dogs that were considered ill had anorexia, vomiting, and weakness. One of the 2 dogs had diarrhea. Both ill dogs were examined by veterinarians, were hyponatremic and hyperkalemic, required fluid therapy, and recovered within 4 days. Owners of both dogs refused to recommence trilostane administration. Four dogs in which the response to treatment was classified as good at the second reevaluation underwent surgery. Each of the 4 dogs had an adrenocortical tumor successfully extirpated (1 adrenocortical adenoma and 3 adrenocortical carcinomas) and for each dog, trilostane was permanently discontinued following surgery. For the 11 dogs with a good treatment response at the second reevaluation that did not undergo surgery and that continued to receive treatment with trilostane, the drug dosage was not changed. For the 5 dogs in which the response to treatment was classified as poor, the dose of trilostane was increased and the frequency of administration (q 12 h) remained unchanged for 2 dogs, the dose of trilostane was not changed but the frequency of administration was increased to 3 times/d for 2 dogs, and the dose of trilostane was increased and the frequency of administration (q 8 h) was maintained for 1 dog.

At the third reevaluation, 16 dogs remained in the portion of the study to evaluate twice-daily, low-dose trilostane treatment. The response to treatment was classified by owners as good in all 16 dogs; 11 of these 16 dogs had also had a good response at the second reevaluation. Among the 16 dogs with a good treatment response, 14 had post-ACTH stimulation serum cortisol concentration < 5.5 µg/dL and 2 had post-ACTH stimulation serum cortisol concentration ≥ 5.5 µg/dL (5.9 and 7.4 µg/dL, respectively).

Duration of trilostane action—Twenty-two dogs met the inclusion criteria for this portion of the study; 16 dogs had been included in the evaluation of the twice-daily, low-dose trilostane treatment. Twelve dogs (group A) were brought by their owners to the hospital approximately 4 hours after collection of a urine sample and approximately
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3 hours after feeding and administration of trilostane. For each of these dogs, an ACTH stimulation test was completed. Dogs were then allowed to leave the hospital with their owners; approximately 5 hours later (9 hours after administration of trilostane), owners returned their dogs to the hospital for a second ACTH stimulation test. Ten other dogs (group B) were brought by their owners to the hospital approximately 10 hours after collection of a urine sample and approximately 9 hours after feeding and administration of trilostane. For each of these dogs, an ACTH stimulation test was completed. Dogs were then allowed to leave the hospital with their owners. The following day, these 10 dogs were brought by their owners to the hospital approximately 3 hours after feeding and administration of trilostane; a second ACTH stimulation test was completed.

Mean pre- and post-ACTH stimulation serum cortisol concentrations (determined before and 1 hour after ACTH stimulation, respectively) at 3 and 9 hours after trilostane administration for groups A and B were compared. For group A, the 3-hour pre-ACTH stimulation serum cortisol concentration was 2.38 ± 1.56 μg/dL and the 3-hour post-ACTH stimulation value was 2.47 ± 1.26 μg/dL; the 9-hour pre-ACTH stimulation serum cortisol concentration was 3.62 ± 1.74 μg/dL, and the 9-hour post-ACTH stimulation value was 7.78 ± 3.79 μg/dL. For group B, the 3-hour pre-ACTH stimulation serum cortisol concentration was 2.37 ± 1.64 μg/dL, and the 3-hour post-ACTH stimulation value was 2.77 ± 1.50 μg/dL; the 9-hour pre-ACTH stimulation serum cortisol concentration was 3.53 ± 1.32 μg/dL, and the 9-hour post-ACTH stimulation value was 8.44 ± 3.01 μg/dL. There was no significant difference (lowest value of P = 0.51) in any of the 4 sets of data between these 2 groups; thus, the results from all 22 dogs were combined. At 3 hours after trilostane administration, mean ± SD pre-ACTH stimulation serum cortisol concentration (2.37 ± 1.56 μg/dL) among the 22 dogs was not significantly (P = 0.22) different from the mean post-ACTH stimulation value (2.60 ± 1.31 μg/dL). The mean pre-ACTH stimulation serum cortisol concentration (3.58 ± 1.53 μg/dL) at 9 hours after trilostane administration was not significantly (P = 0.13) different from either the 3-hour pre- or post-ACTH stimulation value. However, at 9 hours after trilostane administration, mean post-ACTH stimulation serum cortisol concentration (8.09 ± 3.39 μg/dL) was significantly (P < 0.001) higher than the pre-ACTH stimulation value. The mean post-ACTH stimulation serum cortisol concentration at 9 hours after trilostane administration was also significantly (P < 0.001) higher than either the 3-hour pre- or post-ACTH stimulation values.

Three hours after trilostane administration, post-ACTH stimulation serum cortisol concentration was < 5.5 μg/dL in all 22 dogs. Nine hours after trilostane administration, post-ACTH stimulation serum cortisol concentration was < 5.5 μg/dL in 3 of the 22 dogs; values were ≥ 5.5 μg/dL in 19 dogs. Post-ACTH stimulation serum cortisol concentrations at 9 hours after trilostane administration were higher than values at 3 hours after trilostane administration in 21 of the 22 dogs.

Discussion

With rare exception, NOH in dogs is neither a rapidly progressive nor a life-threatening condition that requires rapid response to treatment. Typically, hyperadrenocorticism is a chronic progressive disease that ultimately causes unacceptably bothersome clinical signs (eg, polyuria, weakness, and panting) in affected dogs. A primary goal of treatment of dogs with NOH is to achieve resolution of signs of the condition, as perceived by the owners. Most owners of dogs with NOH are willing to administer treatment for a considerable period and to allow sufficient time to elapse to achieve resolution of clinical signs. However, treatments may cause adverse effects that are more worrisome than signs of the disease, including severe illness or death. If their pet recovers from such adverse effects, some owners may permanently discontinue treatment because of their concerns that adverse effects could recur, perhaps with more serious consequences. If possible, treatment of hyperadrenocorticism should be benign with respect to associated adverse effects yet effective within a reasonable time period in minimizing or resolving clinical signs. This concept becomes logical when it is appreciated that treatment for NOH in dogs is elective.

Trilostane, given once daily to dogs, effectively blocks the 3β-hydroxysteroid dehydrogenase-isomerase enzyme system and inhibits synthesis of cortisol that occurs autonomously within an adrenocortical tumor or in response to ACTH stimulation. Regardless, by decreasing serum cortisol concentrations in affected dogs, clinical signs of hyperadrenocorticism are diminished or eliminated. Most published reports13,14,19 on the use of trilostane state that some dogs require trilostane administration more frequently than once per day to resolve clinical signs. There is also a percentage of treated dogs that become ill or die, regardless of frequency of trilostane administration, suggesting that apparent overdose or development of adrenal gland necrosis could be associated with factors other than dose or administration frequency.20 The incidence of worrisome adverse effects in our early experiences of trilostane treatment of dogs with NOH, together with other reported episodes of trilostane-induced illness, suggested to us that the recommended dose and frequency of administration were not safe.13-19,29,d It appears possible that, in some dogs, trilostane may more effectively block the synthesis of mineralocorticoids than glucocorticoids. This would explain how severe clinical signs (dehydration, weakness, hypotension, and hyperkalemia) could develop in a dog, such as in 1 of the 2 dogs of the present study that became ill during trilostane treatment, that had pre- and post-ACTH stimulation serum cortisol concentrations (1.3 and 4.5 μg/dL, respectively) that were not as low as the values in most overdosed dogs.30

The decision to evaluate twice-daily, low-dose trilostane treatment in dogs with NOH was an attempt to determine whether resolution of clinical signs could be achieved while decreasing or eliminating the incidence of adverse reactions. Among the 22 dogs that were treated according to the modified protocol, 20 (90%) responded well and 2 (9%) developed worrisome adverse effects. The latter represented 2 episodes of illness in a total of 59 recheck evaluations; this incidence of treatment-induced illness (3.4%) in the present study is less than that reported for other studies13-18,d of dogs treated with trilostane (17%).
For each of the 22 dogs in the present study, the initial dose of trilostane (0.7 to 2.4 mg/kg [0.32 to 1.09 mg/lb], q 12 h; 1.4 to 4.8 mg/kg/d [0.64 to 2.18 mg/lb/d]) was less than the once-daily dose of 3 to 6 mg/kg recommended by the manufacturer. The mean dose of 1.4 mg/kg twice per day (2.8 mg/kg [1.27 kg/lb]) daily was less than the lowest recommended initial once-daily dose. Further, the pharmacologic action of a total daily dose that is administered in portions throughout the day may be quite different from that of the same total daily dose that is administered once daily. At the first reevaluation, 8 of the 22 dogs in the present study had markedly improved or resolution of clinical signs; at the second reevaluation, the number of dogs for which the response to treatment was considered good had increased to 15 dogs. This number of dogs that achieved the desired treatment response could be considered a positive result. However, because 2 dogs were extremely ill at the approximate time of second reevaluation, one must question whether the trilostane treatment protocol used in our study might still be too aggressive. The 2 dogs that became ill were receiving trilostane at doses of 1.9 and 2.3 mg/kg (0.86 to 1.05 mg/lb) every 12 hours, respectively. Although the individual doses were less than those recommended by the manufacturer or in published reports, the total daily doses were within the recommended range. However, the doses given to these 2 dogs exceeded the mean total daily dose that was administered to the 22 dogs enrolled in the present study. Had the initial dose for all the dogs been even lower, perhaps fewer would have had a good treatment response at the first and second reevaluations but the episodes of illness might not have occurred or, perhaps, they would have been less severe.

Results of the present study indicate that trilostane is both potent and effective in dogs at doses less than those recommended by the manufacturer and reported in the veterinary medical literature. At the first reevaluation, 10 of the 22 dogs had post-ACTH stimulation serum cortisol concentrations < 5.5 µg/dL. Perhaps the safety of the twice-daily, low-dose trilostane treatment would have been improved if, at the first reevaluation, none of the dogs had a post-ACTH serum cortisol concentration < 5.5 µg/dL, none of the dogs had a good response to treatment, and the dosage needed by each dog to achieve resolution of clinical signs was determined over a period of 1 to 2 months by slowly adjusting the dose and frequency of administration to achieve effect. Such a slow-adjustment protocol could result in treatment of most dogs with a dose just above an established threshold that achieves the response desired, thereby reducing risk of drug overdose. The increase in time needed to achieve such a response would be balanced by a decrease in the incidence of adverse effects. This raises the question of whether owners would object to a prolonged treatment period before an appropriate trilostane dosage could be established for their dog. In the present study, not only did none of the owners withdraw their dog from the study because of continuing clinical signs, but also none of the owners objected to administration of the drug every 8 or 12 hours. Several owners did comment that administration of multiple treatments each day was much easier to accept than the severe polyuria that caused their pet to become incontinent, urinate indoors, or wake family members several times each night to be allowed out to urinate.

Results of the investigation of the duration of trilostane-induced effects in the study of this report provided additional support for the recommendation that trilostane be administered to dogs every 8 or 12 hours. All 22 dogs in our study were given trilostane at doses adequate to achieve post-ACTH serum cortisol concentrations < 5.5 µg/dL, at about 3 hours postadministration. However, at 9 to 10 hours after administration (ie, in the evening), post-ACTH serum cortisol concentrations were significantly greater than either set of mean basal values and significantly greater than the 3- to 4-hour (morning) post-ACTH mean serum cortisol concentration. Further, the 9- to 10-hour (evening) post-ACTH stimulation serum cortisol value in 21 of the 22 dogs was greater than the morning value, suggesting that in those dogs, the effect of trilostane was waning within < 9 hours.

Some dogs with NOH that are treated initially with the recommended dosage of 3 to 6 mg of trilostane/kg once daily have a good response and some have a poor response to treatment at early recheck examinations. Experience suggests that most of the poor responders are being given adequate or excessive doses of trilostane. The explanation for the persistence of clinical signs is, in most dogs, inadequate duration of trilostane effect. Inadequate duration of effect is suggested by the fact that some dogs that responded poorly to treatment had a post-ACTH stimulation serum cortisol concentration < 5.5 µg/dL, indicating that the drug is effective in the first few hours after administration. However, many poor-responder dogs had low urine specific gravity and high UCCR, which suggests that the effectiveness of the drug was diminished by the time that urine was collected the following morning. In contrast, for dogs receiving low-dose trilostane treatment every 8 or 12 hours with a poor response, their poor response is most likely the result of doses that are insufficient or that are given too infrequently. This concept of underdosing in the group of dogs with poor treatment response in the present study is supported by the fact that most poorly controlled dogs had a post-ACTH stimulation serum cortisol concentration ≥ 5.5 µg/dL. In dogs with a good treatment response in our study, the UCCR was significantly lower and urine specific gravity was significantly higher than corresponding values in dogs with a poor treatment response. Among poor responders, increases in the trilostane dose or frequency of administration resulted in an increase in the number of dogs that subsequently had a good treatment response, decreases in their UCCR values, and increases in their urine specific gravity values. It is reasonable to suggest that free-catch pretreatment urine samples collected in the morning at home by owners should be evaluated for specific gravity and UCCR as a means of assessing treatment responses. Data from the present study suggested that findings of urine specific gravity less than an arbitrary value (1.020) and UCCR greater than an arbitrary value (15) might indicate the need for increasing the frequency of trilostane administration when the post-ACTH stimulation serum cortisol concentration is.
less than an arbitrary but safe value such as < 7.5 µg/dL, and also indicate the need for increasing the dose (not the frequency of administration) of trilostane when the post-ACTH stimulation serum cortisol concentration is ≥ 7.5 µg/dL.


e. HDI 5000, ATL Ultrasound, Philips Medical Systems Co Inc, Bothell, Wash.


g. Endocrinology Laboratory, University of California, Davis, Calif.

h. Coat-a-Count cortisol assay, Diagnostic Products Corp, Los Angeles, Calif.

i. SPSS, version 13.0 for Windows, SPSS Inc, Chicago, Ill.

References


Appendix

Recommended starting doses for once-daily oral administration of trilostane* in dogs as provided by the manufacturer (April 2005).

Body weight* of dog (kg) | Dose (mg)
---|---
≥ 3 and < 10 | 30
≥ 10 and < 20 | 60
≥ 20 and < 40 | 120
≥ 40 | 120–240

*To convert to pounds, multiply by a factor of 2.2.