Results of clinical examinations, laboratory tests, and ultrasonography in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane

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Objective—To determine the efficacy of trilostane, a 3β-hydroxysteroid dehydrogenase inhibitor, in dogs with pituitary-dependent hyperadrenocorticism (PDH).

Animals—11 dogs with PDH.

Procedure—The initial dose of trilostane was 30 mg, PO, q 24 h for dogs that weighed < 5 kg and 60 mg, PO, q 24 h for dogs that weighed ≥ 5 kg. A CBC count, serum biochemical analyses, urinalysis, ACTH stimulation test, and ultrasonographic evaluation of the adrenal glands were performed in each dog 1, 3 to 4, 6 to 7, 12 to 16, and 24 to 28 weeks after initiation of treatment.

Results—All dogs responded well to treatment. All had reductions in polyuria-polydipsia and panting and an increase in activity. Polyphagia decreased in 9 of 10 dogs, and 9 of 11 dogs had improvement of coat quality and skin condition. Concentration of cortisol after ACTH stimulation significantly decreased by 1 week after initiation of treatment. After treatment for 6 months, clinical signs resolved in 9 dogs. In the other 2 dogs, marked clinical improvement was reported for 1 dog, and moderate improvement was reported in the other dog. Ultrasonographically, there was a considerable change in the parenchyma and an increase in size of the adrenal glands. Adverse effects consisted of 1 dog with transient lethargy and 1 dog with anorexia.


The medication of choice for the treatment of dogs with pituitary-dependent hyperadrenocorticism (PDH) has been mitotane.7 Mitotane leads to selective progressive necrosis of the adrenal cortex, which may be partially5 or completely destroyed, depending on the treatment protocol. The efficacy of mitotane is favorable, and > 80% of the dogs with PDH have good to excellent responses to treatment with mitotane.5 Disadvantages for the use of mitotane include potential development of adrenocortical insufficiency, possible drug intolerance, and a relatively high frequency of relapses during treatment.5 During the past few years, numerous substances with central or peripheral action have been investigated to determine their efficacy for treatment of dogs with PDH.7,8,9 With the exception of ketoconazole, which inhibits synthesis of adrenocortical steroids, efficacy of these substances is poor. L-Deprenyl was reported11 to be a safe treatment for dogs with PDH, but it resulted in clinical improvement in only a small proportion of dogs. Results of a recent preliminary study12 indicated that trilostane is a potentially efficacious treatment for dogs with PDH.

Trilostane is an orally administered competitive inhibitor of 3β-hydroxysteroid dehydrogenase. This enzyme system mediates the conversion of pregnenolone to progesterone in the adrenal glands (Fig 1). Cortisol, aldosterone, and androstenedione are produced from progesterone via various biochemical pathways. Trilostane inhibits the production of progesterone and, therefore, the synthesis of its end products.12 Efficacy of trilostane for the treatment of people with hyperadrenocorticism is variable. Although some studies13,14 reported good efficacy of trilostane, others15,16 found inconsistent efficacy, thus indicating that trilostane may not be the drug of choice for use in people.

Ultrasonographically, the adrenal glands of dogs with PDH typically are bilaterally symmetric or bilaterally enlarged with a normal shape.7 Treatment with mitotane results in a substantial decrease in the size of the adrenal cortex because of its adrenocorticolytic effect.15 To our knowledge, there have not been any...
reports for human or veterinary medicine on the response of the adrenal glands to trilostane.

The objective of the study reported here was to evaluate the efficacy of trilostane for the treatment of dogs with PDH. Patients were monitored, using results of physical examination and laboratory tests that included an ACTH stimulation test. Special emphasis was placed on ultrasonographic evaluation of the size and shape of the adrenal glands during treatment.

Materials and Methods

Animals—Eleven dogs that ranged from 6 to 11 years of age (median, 8 years) and that weighed between 4.4 and 15 kg (median, 6.2 kg) were used in the study. There were 3 sexually intact and 3 spayed females as well as 3 sexually intact and 2 castrated males. Breeds represented included Dachshund (n = 4), Poodle (3), Jack Russell Terrier (1), Bolognese (1), Scottish Terrier (1), and Yorkshire Terrier (1). All dogs had PDH.

The prospective study was performed between June 1999 and July 2001 at our facility. Dogs suspected of having hyperadrenocorticism underwent a thorough clinical examination, and blood samples were collected for a CBC count and serum biochemical analyses. Diagnosis was confirmed on the basis of results of an ACTH stimulation test, low-dose dexamethasone suppression test, and the urine cortisol-to-urine creatinine ratio. In addition, the adrenal glands were examined ultrasonographically. Dogs were included in the study when at least 3 clinical signs of hyperadrenocorticism (polyuria-polydipsia [PUP/D], polyphagia, dermatologic problems, decreased activity, panting, pendulous abdomen) were detected, when at least 2 of the 3 screening tests yielded positive results, when the dog's owner agreed to return the dog to our clinical facility for regularly scheduled reevaluations throughout a 6-month period, and when the dog had not received other treatments (eg, radiation therapy) for the hyperadrenocorticism. Pituitary-dependent hyperadrenocorticism was diagnosed on the basis of a bilateral symmetric appearance or bilateral enlargement of the adrenal glands on ultrasonograms. In 2 dogs, a pituitary mass was detected by use of computed tomography. Informed consent was obtained from the owners of all dogs.

Hematologic, serum biochemical, and endocrinologic analyses—A CBC count and serum biochemical analyses were performed in each dog. Urinalysis of a sample of urine collected by cystocentesis was performed in each dog. The latter consisted of results of a urine test strip, examination of urine sediment, and determination of specific gravity and the urine protein-to-urine creatinine ratio; bacteriologic culture of urine sediment, and determination of specific gravity and the urine protein-to-urine creatinine ratio; bacteriologic culture of urine also was performed during the initial examination of each dog. Proteinuria was defined as a value for the urine protein-to-urine creatinine ratio > 1.0.

An ACTH stimulation test was performed in each dog by collecting blood samples for determination of serum cortisol concentration before and 1 hour after IM injection of 0.25 mg of ACTH. Cortisol concentration was determined by use of a chemiluminescence method. A cortisol concentration of > 20 µg/dl in the sample collected 1 hour after ACTH administration was considered abnormal and consistent with hyperadrenocorticism.

A low-dose dexamethasone suppression test was performed in each dog. It consisted of collection of blood samples before and 4 and 8 hours after injection of dexamethasone (0.01 mg/kg, IV). All injections of dexamethasone were administered between 9 and 11 AM. A cortisol concentration of ≥ 1.4 µg/dl in the sample collected 8 hours after dexamethasone administration was considered to reflect a lack of suppression and was consistent with hyperadrenocorticism. A cortisol concentration at 4 hours after dexamethasone administration that was < 1.4 µg/dl or < 50% of the cortisol concentration prior to dexamethasone administration or a cortisol concentration at 8 hours after dexamethasone administration that was < 50% of the cortisol concentration prior to dexamethasone administration was defined as suppression and considered consistent with PDH. A urine cortisol-to-urine creatinine ratio > 10 × 10^4 was considered abnormal and consistent with hyperadrenocorticism.

Ultrasoundography of adrenal glands—A real-time sector scanner with a 7.5-MHz transducer was used for ultrasonographic examination of the adrenal glands. All ultrasonographic examinations were performed by the same investigator. The maximum length of each gland was measured in the longitudinal plane, and the thickness of each gland, defined as the greatest dorsoventral dimension, was assessed as a single measurement made perpendicular to the long axis. Shape, contour, and acoustic texture of each adrenal gland were subjectively assessed and recorded.

Experimental design—Dogs that weighed < 5 kg received 30 mg of trilostane, PO, q 24 h, and those that weighed ≥ 5 kg received 60 mg of trilostane, PO, q 24 h. Efficacy was assessed by monitoring clinical signs and assessing results of ACTH stimulation testing. The objective was to achieve a serum cortisol concentration of 1.0 to 2.5 µg/dl in samples obtained after ACTH stimulation during subsequent evaluations. In dogs with serum cortisol concentrations < 1.0 or > 2.5 µg/dl after ACTH stimulation, the dose of trilostane was decreased or increased, respectively.

Each dog was monitored during a period of ≥ 6 months. Dogs were reevaluated 5 times (1, 3 to 4, 6 to 7, 12 to 16, and 24 to 28 weeks) during the initial 6 months after initiation of treatment with trilostane. Reevaluation consisted of assessment of the clinical history, using a prepared questionnaire, physical examination, hematologic and serum biochemical analyses, urinalysis, ultrasonographic examination of the adrenal glands, and an ACTH stimulation test. These ACTH stimulation tests were performed 2 to 6 hours after administration of the daily dose of trilostane.

At each reevaluation, all dogs underwent a physical examination. Results were compared with those of the previous evaluations. At each reevaluation, a questionnaire was completed by each owner regarding their dog's general demeanor, behavior, activity, water intake, frequency of urination, appetite, panting, and sleep behavior. Each owner was asked to compare the current condition of their dog with that of their dog at the preceding evaluation and to decide whether there was improvement, deterioration, or no change in their dog's condition.

Statistical analysis—Results were analyzed by means of nonparametric statistical methods. Ranges and median values were reported. Differences were tested, using the Wilcoxon matched-pairs signed-rank test. Differences were considered significant at values of P < 0.05.

In some situations, box-and-whisker plots were used to graphically summarize the distribution of the data. These plots provided information about the range, median, and 25th to 75th percentiles of the data.

Results

Clinical signs—All dogs had dermatologic problems. Dermatologic problems consisted of alopecia (9 dogs), hyperpigmentation (4), thin skin (4), hypertrichosis (1), and scaly skin (1). Other conditions included PU-PD (10 dogs), polyphagia (10), decreased amount of activity (6), hepatomegaly (6), pendulous abdomen (6), panting (4), and anestrus (3).

All dogs had a decrease in PU-PD within a short time
after initiation of treatment (range, 1 to 7 weeks; median, 1 week), and owners reported an increase in the amount of activity in all dogs (range, 1 to 10 weeks; median, 3 weeks). Panting decreased in all 4 dogs (range, 1 to 7 weeks; median, 4.5 weeks). Polyphagia decreased in 9 of 10 dogs (range, 1 to 25 weeks; median, 6 weeks) but remained unchanged throughout the study in the other dog. Abdominal muscular tone improved in 5 of 6 dogs (range, 3 to 16 weeks; median, 10.5 weeks) but became worse in the other dog. Estrous cycles resumed during treatment in 2 of 3 anestrous bitches. Coat and skin condition improved in 9 of 11 dogs (range, 1 to 56 weeks; median, 7 weeks). One dog did not have noticeable improvement in coat and skin condition after treatment for 6 months; however, there was a marked improvement in this dog after treatment for 1 year. In the other dog, the coat and skin condition became worse, and the dog developed severe hypertrichosis dorsally and alopecia ventrally. In addition, the abdomen of that dog became more pendulous.

Owners reported complete resolution of PU-PD in 9 dogs (median, 11 weeks). Resolution of polyphagia (median, 12 weeks), resumption of typical activity (median, 12 weeks), and resolution of panting (median, 10.5 weeks) was reported for 8, 6, and 2 dogs, respectively. Resolution of skin conditions and regrowth of hair was reported for 9 of 11 dogs.

By 6 months after initiation of trilostane, 9 of 11 owners were pleased with the results of treatment. Two owners were pleased that there was a decrease in PU-PD, polyphagia, and panting, but they were dissatisfied with the lack of improvement in coat and skin conditions of their dogs. One of these 2 owners also was dissatisfied with the lack of improvement in their dog’s pendulous abdomen.

**Hematologic analysis and urinalysis**—At the start of the study, lymphopenia, eosinopenia, monocytosis, and neutrophilia were evident in 6, 4, 5, and 1 dogs, respectively (Table 1). By the time of the fifth reevaluation, these hematologic conditions were evident in 6, 0, 5, and 2 dogs, respectively; the number of dogs with eosinopenia had decreased significantly. **Serum alkaline phosphatase** (ALP) activity was increased in 8 dogs at the start of the study but only in 4 dogs at the end of the study. Compared with initial ALP values, serum activity of ALP was significantly decreased at the third and fifth reevaluations. Hypercholesterolemia was detected in 6 dogs at the start of the study but in only 2 dogs at the first reevaluation and only 1 dog at the fifth reevaluation. There was a significant decrease in mean cholesterol concentration at the third reevaluation. At the start of the study, high concentrations of sodium and potassium and low concentrations of phosphorus and potassium were detected in 8, 3, 1, and 1 dogs, respectively. At the fifth reevaluation, high concentrations of sodium and potassium were detected in 2 and 6 dogs, respectively, and none of the dogs had

<table>
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<th>Variable</th>
<th>Time of analysis</th>
<th>Range</th>
<th>Median</th>
<th>No. of dogs with values &gt; reference range</th>
<th>No. of dogs with values &lt; reference range</th>
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*Urine-specific gravity = 1.020. †Urine specific gravity < 1.020.

UP:UC = Urine protein-to-urine creatinine ratio. — Not applicable.
 substantial bacteriuria (and 2 dogs (neither of which had proteinuria) had sub-

ACTH stimulation ranged from 2.0 to 10.5 µg/dl after ACTH injection. Cortisol concentration before

study, 8 of 10 dogs tested had a positive result for the

ACTH stimulation test. Cortisol concentration before

administration of antibiotics.

Specific gravity of urine samples at the start of the study ranged from 1.005 to 1.029 (median, 1.011). Urine specific gravity of 8 dogs was < 1.020. At the fifth reevaluation, values varied from 1.010 to 1.043 (median, 1.024), and urine specific gravity of 4 dogs was < 1.020. Urine specific gravity increased significantly between the start of the study and the fifth reevaluation (Fig 2; Table 1).

Endocrinologic analyses—At the start of the study, 8 of 10 dogs tested had a positive result for the ACTH stimulation test. Cortisol concentration before ACTH stimulation ranged from 2.0 to 10.5 µg/dl (median, 6.25 µg/dl), whereas concentrations after ACTH stimulation ranged from 10.8 to 47.3 µg/dl (median 32.7 µg/dl). At the first reevaluation, values after ACTH stimulation ranged from 0.2 to 17.0 µg/dl (median, 2.9 µg/dl). This median decrease of cortisol concentration after ACTH stimulation was 54%; the values differed significantly. At each of the reevaluations, the cortisol concentration was significantly lower, compared with the concentration at the start of the study. For the first through fifth reevaluations, 2, 1,
of dogs with hyperadrenocorticism.5,6 The efficacy of mitotane has been the drug of choice for the treatment of dogs with PDH. Until recently, indicates that trilostane is a safe and efficacious drug for the treatment of PDH. However, the high frequency of adverse effects, which are the result of adrenocortical insufficiency attributable to overdosage or poor tolerance of the drug, led to the discontinuation of mitotane in some cases.

Discussion

Analysis of the results of the study reported here indicates that trilostane is a safe and efficacious drug for the treatment of dogs with PDH. Until recently, mitotane has been the drug of choice for the treatment of dogs with hyperadrenocorticism.5,6 The efficacy of mitotane is good, and 66 to 86% of dogs with hyperadrenocorticism have good to excellent responses with rapid improvement in clinical condition after administration of mitotane. However, the most obvious and rapid changes are a reduction in appetite, water intake, and urine output that are evident during the first 5 to 9 days after initiation of treatment. On the other hand, clinical improvement in skin changes requires weeks to months.7 Disadvantages of mitotane include a relatively high frequency of adverse effects, which are the result of adrenocortical insufficiency attributable to overdosage or poor tolerance of the drug. Because of this, a safer drug for the treatment of dogs with PDH has been pursued for some time. In the study reported here, 9 of 11 (82%) dogs with PDH had a good response to trilostane. After treatment for 6 months, appearance of these 9 dogs and their water intake were considered to be normal. In the other 2 dogs, there was a decrease in PU-PD, polyphagia, and panting, but owners did not report improvement in coat and skin conditions.

The time required for a noticeable response to trilostane was similar to that for mitotane treatment, with rapid improvement in PU-PD, polyphagia, and activity and a delay until improvement was evident in coat and skin conditions and abdominal musculature. The reason for the differing response patterns is that PU-PD, polyphagia, and reduced activity are direct effects of increased cortisol concentrations, whereas changes in coat and skin are attributable to a long-term excess concentration of cortisol that causes atrophy of hair follicles and sebaceous glands, calcium deposition, and pigmentation. Similarly, development of a pendulous abdomen is a prolonged process that involves centripetal deposition of fat and atrophy of muscles. Thus, a decrease in the cortisol concentration results in a more rapid resolution of those symptoms that are directly caused by increased amounts of cortisol.

Similar to observations in dogs treated with mitotane, some dogs treated with trilostane had transient worsening of the dermatologic problem. Thus, the coat and skin conditions were judged to have deteriorated before clinical improvement became apparent.

A drawback of the study reported here was that we did not include control groups. We did not include an untreated control group because of ethical considerations. A control group consisting of dogs treated with mitotane was not added because of the fact that the...
effects of mitotane have already been studied, and its efficacy is known.

Data were collected as objectively as possible via the use of standardized questionnaires for the owners and thorough examinations performed in accordance with a detailed protocol at the start of the study and each reevaluation. Assessment of a number of variables was subjective and based solely on owner observations; thus, possible over- or underestimation of response to treatment cannot be ruled out. However, after treatment for 6 months, there was good agreement between the opinions of the owners and veterinarians; both groups reported noticeable improvement in 9 dogs, moderate improvement in 1 dog, and slight improvement in 1 dog.

In the study reported here, the number of dogs with lymphocytopenia and monocytosis was unchanged, and the serum ALP activity was still increased in some dogs. This can be explained by the short duration of trilostane activity. It is known that the action of trilostane begins shortly after administration, but it lasts for only a few hours. With once-daily administration, we would expect the cortisol concentration to increase during the day. However, the short period of suppression is sufficient to lead to an improvement in clinical condition but will not always result in hematologic and biochemical improvements.

Trilostane inhibits the 3β-hydroxysteroid dehydrogenase enzyme system, which results in decreased synthesis of cortisol by the zona fasciculata, aldosterone by the zona glomerulosa, and androstenedione by the zona reticularis. Coincident with this inhibition of steroidogenesis is an accumulation of steroid precursors in the pathway prior to the site of the induced enzymatic blockade. The ACTH stimulation test determines adrenal reserve and, thus, appeared to be suitable for evaluating the extent of enzyme inhibition during treatment, determining excessive or insufficient administration, and calculating dosage adjustments. In our study, testing was limited to the measurement of cortisol concentration before and after ACTH administration. Despite the short half-life of trilostane, the owners were instructed to administer the drug only once daily to ensure optimal compliance. The ACTH stimulation test was performed 2 to 6 hours after administration of trilostane, and results documented that this drug was efficacious. It is likely that cortisol concentrations after ACTH administration would have been higher if blood samples had been collected at a greater interval after drug administration. Therefore, it is most important for investigators who are evaluating results of the ACTH stimulation test to know the time at which trilostane was administered. However, on the basis of results of our study, it appears that once-daily administration is sufficient to achieve excellent clinical results.

Trilostane also affects the synthesis of aldosterone. In the study reported here, we did not measure aldosterone concentrations directly. Possible aldosterone deficiency was identified by measuring electrolyte concentrations during each reevaluation.

After treatment for 1 week, the cortisol concentration after ACTH stimulation in all dogs was significantly lower than that at the start of the study. Our target for the cortisol concentration after ACTH administration was between 2 and 4 µg/dl, which was derived from our experience with mitotane, using a treatment regimen that was designed to partially destroy the adrenal cortex. However, we subsequently found that better control of clinical signs was achieved when the cortisol concentration after ACTH administration was between 1.0 and 2.5 µg/dl. We assume that the need for the low target range is attributable to the relatively short duration of action for trilostane. Interestingly, dogs that had cortisol concentrations < 1.0 µg/dl after ACTH administration did not have clinical signs of adrenal insufficiency. This is in contrast to treatment with mitotane in which cortisol concentrations < 1.0 µg/dl after ACTH administration that caused lysis of the adrenal cortex frequently is associated with lethargy, anorexia, and vomiting. We speculate that in dogs treated with trilostane, steroid precursors that have accumulated as a result of enzyme inhibition have certain glucocorticoid-like effects. Although the cortisol concentration is low, signs of hypocortisolism may be prevented by the precursors. Throughout the entire study reported here, signs possibly related to adrenal gland insufficiency were observed only once in each of 2 dogs. Unfortunately, confirmation by measurement of serum electrolyte concentrations and ACTH stimulation testing could not be performed. The clinical signs resolved rapidly once treatment was temporarily discontinued or the dosage reduced.

The initial dosage of trilostane used was the same as that reported by Hurley et al. However, frequent adjustments in dosage were required, particularly during the first few weeks of treatment. It was apparent that the effective dosage of trilostane differed markedly among dogs with PDH. According to Komanicky et al, this is possibly attributable to substantial variation among individuals in 3β-hydroxysteroid dehydrogenase activity in the adrenal glands. However, it appears that stabilization of the response to treatment occurs over a period, after which adjustments in dosage are seldom necessary.

In 1 dog, the condition of the coat and skin deteriorated, and centripetal obesity developed during treatment. Although treatment led to a decrease in cortisol concentration after administration of ACTH, compared with that same value at the start of the study, they remained between 2.5 and 5.2 µg/dl despite continuous increases in the dosage of trilostane. In humans, a variable or poor response to trilostane has been reported. It was hypothesized that blocking of adrenal gland activity is not attributable to trilostane itself but to a trilostane metabolite. Thus, failure to respond to treatment could have been the result of an inactive metabolite rather than to resistance of the adrenal glands to trilostane. Whether this was the reason for the poor response in the 1 dog in the study reported here or whether the dose was too low remains unknown. It was, however, remarkable that the clinical condition worsened even when the cortisol concentrations after ACTH administration were close to the target range of 1.0 to 2.5 µg/ml. In that dog, frequency of administration was increased to twice daily (ie, q 12 h); however, we did not detect any changes. In addition to the aforementioned reason, it also was possible that a massive accumulation of steroid precursors led to the clinical signs of PDH.
Changes in the ultrasonographic appearance of the adrenal glands during the study were distinct. In most dogs, there was a noticeable increase in thickness and echogenicity of the outer zone, which was assumed to be the adrenal cortex. Possibly, the increase in thickness of the cortex reflected increased synthesis of precursors attributable to increased secretion of ACTH, which was a result of abolishing the negative feedback normally exerted by cortisol. Such an increase in ACTH secretion was detected in 14 of 15 dogs after mitotane treatment. A concomitant enhancement of precursors during trilostane treatment has been documented in guinea pigs and humans.6,22,23,24

In some dogs that had been treated with trilostane for more than 1 year, the adrenal glands had assumed an irregular shape with a nodular appearance, and the normal echogenic pattern changed to a pattern of heteroechogenicity throughout the entire gland. Both adrenal glands were similarly affected in each dog. To our knowledge, such changes have not been reported, and because postmortem examinations have not been performed on these dogs, the exact nature of the changes remains unknown. However, it appears likely that these changes reflect nodular hyperplasia. In humans, bilateral nodular hyperplasia has been identified as a morphologic consequence of several pathophysiologic disorders such as long-standing hypersecretion of ACTH.25 The changes observed in the adrenal glands were sufficiently striking to warrant further investigation; it cannot be ruled out that these changes may result in neoplasia.

The study reported here was deliberately limited to dogs with PDH, because in our clinic, dogs with functional adrenocortical tumors undergo surgical removal or treatment with mitotane with the goal of complete destruction of the adrenal glands.2,6 However, according to other investigators, trilostane is also efficacious in dogs with functional adrenocortical tumors.

References