

## CANINE PITUITARY DEPENDENT HYPERADRENOCORTICISM SERIES

# Part 3: Current & Investigative Options for Therapy



David Bruyette, DVM, Diplomate ACVIM  
VCA West Los Angeles Animal Hospital, Los Angeles, California, and  
Veterinary Diagnostic Investigation and Consultation, Woodland Hills, California

Canine pituitary dependent hyperadrenocorticism (PDH), also known as **Cushing's disease**, is a common endocrine disorder in older dogs. This disorder is caused by a pituitary adenoma (PA) that secretes inappropriate amounts of adrenocorticotrophic hormone (ACTH), which results in bilateral adrenal hyperplasia and disorderly and excessive production of cortisol by the adrenal gland.

Read the first 2 articles of this series at [tvjournal.com](http://tvjournal.com):

- **Part 1: Comparative Epidemiology & Etiology in Dogs & Humans** (November/December 2015)
- **Part 2: Diagnostic Approach** (January/February 2016).

### THERAPEUTIC APPROACHES

#### Humans

In humans, while pituitary surgery is considered first-line treatment for patients with Cushing's disease,<sup>1</sup> medical therapy now plays a more important role in the armamentarium available to patients if surgery is not successful.<sup>2,3</sup> Repeat surgery, bilateral adrenalectomy, and pituitary radiation are also frequently employed.<sup>1</sup>

#### Dogs

In dogs, medical management is far more common than surgical approaches and generally involves the use of medications directed toward reducing adrenal glucocorticoid production.<sup>4,5</sup> However, recent work on newer medical and surgical therapies and emerging treatments provides the clinician with multiple therapeutic options.

Medical treatments can be classified based on their

mechanism of action and categorized as (**Table 1**):

1. Adrenal-directed steroidogenesis inhibitors or adrenolytics
2. Centrally acting agents
3. Glucocorticoid receptor blockers.

### ADRENAL-DIRECTED THERAPIES

In dogs, o,p'-DDD, also known as mitotane (Lysodren, bms.com), trilostane (Vetoryl, dechra.com), and ketoconazole (in many countries outside of the U.S.), are the most commonly used agents for canine Cushing's disease, although several other agents have been used or are under investigation (**Table 2**, page 33).

#### Mitotane

Mitotane is a potent adrenocorticolytic agent derived from the insecticide dichlorodiphenyltrichloroethane (DDT). The goal of mitotane therapy is to achieve both pre- and post-cortisol measurements in the normal resting range (2–6 mcg/dL).

**Pharmacodynamics.** The drug causes progressive necrosis of the zona fasciculata and zona reticularis of the adrenal gland and, at higher doses, may also cause necrosis of the zona glomerulosa. Other effects of mitotane include fatty degeneration, centrilobular atrophy, and congestion of the liver.

Healthy dogs with and without hyperadrenocorticism (HAC) are usually quite resistant to the effects of the drug, but some may show adverse effects, such as gastric irritation, hypoadrenocorticism, and, very occasionally, neurologic signs.

**Initial Therapy.** Mitotane therapy is begun at a dose of 50 mg/kg, divided, Q 12 H.<sup>6,7</sup> In dogs with significant nonadrenal illness, the dose of mitotane may be reduced by 50% and adjusted upward based

TABLE 1.  
Current & Investigational Treatment of Canine Hyperadrenocorticism

	CURRENT THERAPIES	THERAPIES UNDER INVESTIGATION
<b>Adrenal-Directed Therapy</b>	Mitotane Trilostane Ketoconazole (rarely used)	Aminoglutethimide Metyrapone Etomidate LCI699* COR-003*
<b>Pituitary-Directed Therapy</b>	Selegiline Pituitary surgery	Pasireotide Cabergoline Retinoic acid Gefitinib
<b>Glucocorticoid Receptor Blockade</b>		Mifepristone*

\* Currently no data in dogs with PDH

on clinical and hormonal response. Administering the drug with food improves its gastrointestinal absorption. At induction doses, mitotane is typically administered for 5 to 10 days, until water consumption decreases to less than 100 mL/kg/day. At this point, the dog should be reevaluated and an ACTH stimulation test performed.

In patients that are not demonstrating polydipsia, or those in which water consumption cannot be monitored or polydipsia is due to another underlying disease (eg, diabetes mellitus), mitotane should be administered for a maximum of 5 to 7 days prior to ACTH stimulation testing.

Mitotane should be discontinued immediately if decreased appetite, depression, diarrhea, or vomiting is observed.

**Maintenance Therapy.** Maintenance therapy (50 mg/kg Q 7–10 days or 25 mg/kg Q 3 days) is started once the ACTH stimulation test demonstrates adequate suppression (pre- and post-cortisol measurements of  $\geq 3$  and  $\leq 5$  mcg/dL, respectively) and prednisone therapy (if necessary) has been discontinued (see **Role of Prednisone**). Failure to use maintenance therapy results in regrowth of the adrenal cortex and recurrence of clinical signs.

Efficacy of maintenance therapy is monitored by ACTH stimulation tests 1 month after initiation of maintenance therapy and every 3 to 4 months thereafter. The total weekly dose of mitotane required for long-term maintenance is quite variable (26–330 mg/kg/week), but therapy should always begin with the recommended initial dosage; then titrated to effect based on subsequent ACTH stimulation test results. If clinical signs return in conjunction with elevated cortisol concentrations post ACTH stimulation, the patient can be managed with higher, or more frequent, maintenance doses or a return to

the induction protocol outlined in **Initial Therapy**.

**Role of Prednisone.** Glucocorticoids were typically administered in combination with mitotane therapy for many years, but it is no longer common to administer these drugs concurrently. However, prednisone therapy (0.2–0.5 mg/kg/day) should be initiated in patients with clinical signs of hypocortisolemia until results of the ACTH stimulation test are known.

A small supply of prednisone should be made available to the owner in the event of overdose of mitotane. However, dexamethasone can be used preferentially for emergency situations because it does not interfere with measurement of serum cortisol concentrations.

**Treatment Considerations.** Reasons for mitotane treatment failure include:

- Incorrect diagnosis
- Presence of an adrenal tumor (although some adrenal tumors do respond well)
- Loss of drug potency due to poor storage or compounding of mitotane
- Need for a higher dose or duration of treatment in some dogs.

Note that phenobarbital enhances the metabolism of mitotane, leaving it ineffective. Therefore, patients with Cushing's disease and idiopathic epilepsy should be treated with other anticonvulsant drugs (eg, potassium bromide, levetiracetam).

Median survival time of 200 dogs treated with mitotane was 2.2 years (range, 10 days–8.2 years).<sup>6</sup>

#### Trilostane

Trilostane is a synthetic, hormonally inactive steroid analogue, which is a competitive inhibitor of the 3-beta-hydroxysteroid dehydrogenase system.

**Pharmacodynamics.** Trilostane blocks synthesis of

adrenal steroids, including cortisol and aldosterone.<sup>8-14</sup> It is rapidly absorbed orally (peak concentrations within 1.5 H), although suppression of plasma cortisol concentrations is short lived (< 20 H).

Trilostane is well tolerated in most dogs. Adverse effects are usually mild and self-limiting, and include diarrhea, vomiting, and lethargy in up to 63% of treated dogs.<sup>8,9</sup> However, the percentage of dogs that develop adverse events is much lower when they are treated with current recommended (lower) starting doses. There have been anecdotal reports of acute death shortly after initiating trilostane treatment.

**Initial Therapy.** Current recommendations for trilostane use specify administration of an initial dose of 1 to 2 mg/kg Q 12 to 24 H. This dose is then increased or decreased based on evaluation of ACTH stimulation test results.<sup>15-17</sup> Trilostane should be administered with food, including the days that ACTH stimulation tests are performed, to aid in absorption. Whenever possible the brand name preparation (Vetoryl, dechra.com) should be used to avoid inconsistencies in dose seen when using compounded medications.

ACTH stimulation testing should be performed 10, 30, and 90 days after initiation of treatment; then 30 days after each dose adjustment.<sup>18-21</sup> While samples for testing can be collected either 4 or 6 H after drug administration, it is important that the same sampling time—4 or 6 H—always be maintained for a specific patient.

**Maintenance Therapy.** Hormonal end points are post cortisol concentrations less than 6 to 9 mcg/dL, in conjunction with remission of clinical signs. In patients that fail to reach clinical remission with continued elevations in post ACTH cortisol concentrations, the dose of trilostane should be increased by 25% and the pet retested in 7 to 10 days. If post ACTH cortisol concentrations demonstrate adequate hormonal control but clinical signs persist, twice daily dosing may be indicated. If you are switching from once daily to twice daily dosing, the once daily dose should be split in half and administered Q 12 H. For example, if the patient was initially on 60 mg Q 24 H, the dose would be changed to 30 mg Q 12 H.

Compared with higher doses administered Q 24 H, twice daily therapy, at a starting dose of 1 to 3 mg/kg, may:

- Result in good control of clinical signs, with less risk of adverse effects
- Be more effective at consistently controlling hypercortisolemia throughout the day

- Be appropriate as a starting dose in dogs with diabetes and other related complications of Cushing's disease.<sup>22-26</sup>

**Treatment Considerations.** Occasionally, dogs receiving trilostane have developed hypoadrenocorticism, which is generally glucocorticoid deficient only, although dogs with evidence of mineralocorticoid deficiency have been reported. Trilostane-induced hypoadrenocorticism is generally reversible but, in rare cases, this may take several months, most likely due to adrenocortical necrosis. See **Consider This Case**, page 35, for a case example of trilostane therapy in a dog with PDH.

### Mitotane Versus Trilostane for Canine Cushing's Disease

Studies have compared trilostane and mitotane therapy in dogs with PDH or adrenal tumors.<sup>27-31</sup> In a retrospective study of dogs treated with either mitotane ( $n = 25$ ) or trilostane ( $n = 123$ ), long-term survival was not statistically different between the groups. Median survival in the mitotane group was 708 days (range, 33–1399) and, in the trilostane group, 662 days (range, 8–1971). Of the dogs that died in this study, 11% died due to causes attributed to the underlying PDH, and a further 17% died of causes that may have been related to underlying PDH. In 38% of cases, cause of death could not be directly attributed to PDH and, in 34%, the cause of death was unknown.<sup>31</sup>

### Ketoconazole

While ketoconazole was used more frequently in the past,<sup>32,33</sup> its use now is generally in countries where mitotane and trilostane are not available, or when these agents have failed to correct hypercortisolism or resulted in adverse reactions. Its systemic use has recently been restricted or banned in several countries due to potential of significant hepatotoxicity in humans.

**Pharmacodynamics.** Specifically, ketoconazole has been shown to inhibit cholesterol side-chain cleavage enzyme, which converts cholesterol to pregnenolone, 17- $\alpha$ -hydroxylase, and 17,20-lyase—which convert pregnenolone into androgens—and 11- $\beta$ -hydroxylase, which converts 11-deoxycortisol to cortisol.

**Efficacy.** One study examined the safety and efficacy of ketoconazole in 48 dogs with PDH.<sup>34</sup> Data collected from each record included signalment,

clinical signs, results of ACTH stimulation tests before and after treatment with ketoconazole (10 mg/kg PO Q 12 H), serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activities, dosage of ketoconazole, clinical response, and survival time.

Forty-three of 48 dogs (90%) had evidence of clinical improvement during the treatment period. In all dogs, treatment with ketoconazole resulted in significantly lower serum cortisol concentrations before and after ACTH stimulation testing; 69% (33/48) of serum cortisol concentrations measured after ACTH stimulation were within the basal resting range. Serum ALP and ALT activities significantly decreased after treatment with ketoconazole.

**Prognosis.** Survival time after diagnosis of PDH ranged from 2 to 61 months (mean, 26.9 months; median, 25 months).<sup>34</sup> Another study evaluating ketoconazole found that after diagnosis, 50% of the dogs died approximately 1.8 to 2 years (range, 0.6–3) after starting therapy.<sup>35</sup>

### Additional Therapeutic Options

Several other adrenal steroidogenesis inhibitors have been used in humans and, at times, in dogs (**Table 2**).<sup>36,37</sup>

### PITUITARY-DIRECTED THERAPIES

Recent work on somatostatin and dopaminergic receptor changes in humans and dogs with Cushing's disease has opened the door to targeted therapy of pituitary tumors. Such therapies not only result in decreased ACTH production but a reduction in tumor size. Several agents have been studied or are in clinical trials (**Table 3**, page 34).

### Selegiline

The monoamine oxidase B inhibitor selegiline (L-deprenyl), which raises concentrations of dopamine in the brain, has been used to treat hyperadrenocorticism in dogs.<sup>43</sup> The medication appears effective in 20% to 30% of patients with pars

TABLE 2.  
Investigated Medications for Adrenal-Directed Therapy

MEDICATION	PHARMACODYNAMICS	NOTES
<b>Aminoglutethimide</b> Cytadren, novartis.com	Blocks conversion of cholesterol to pregnenolone by inhibiting P450 <sub>11β</sub> ; consequently decreases synthesis of hormonally active steroids	<ul style="list-style-type: none"> <li>• Use in dogs limited.</li> <li>• Efficacy lower than that of mitotane, trilostane, and ketoconazole.</li> <li>• Adverse effects (eg, toxicity, elevated liver enzymes) limit its use in dogs.<sup>38</sup></li> </ul>
<b>Metyrapone</b> Metopirone, novartis.com	Primarily inhibits 11-beta-hydroxylase and, to a lesser extent, 17-alpha-hydroxylase, 18-hydroxylase, and 19-hydroxylase	<ul style="list-style-type: none"> <li>• Used in humans for diagnosis of adrenal insufficiency and, occasionally, treatment of Cushing's disease.</li> <li>• Used in dogs with Cushing's disease in attempt to distinguish PDH from functional adrenal tumor.<sup>39</sup></li> <li>• Availability varies by country.</li> </ul>
<b>Etomidate</b> Amidate, hospira.com	Short-acting IV hypnotic nonbarbiturate anesthetic agent used for general anesthesia; suppresses steroidogenesis by dose-dependent inhibition of 11-beta-hydroxylase and desmolase	<ul style="list-style-type: none"> <li>• Has role in humans with significant biochemical disturbances, sepsis, and other serious complications (ie, severe psychosis) and in those with acute contraindications to surgery or that cannot tolerate oral medications.<sup>36,37</sup></li> <li>• Use in canine surgical patients revealed adrenal suppression for 2 to 6 H following single bolus injection of 1.5 to 3 mg/kg.<sup>40,41</sup></li> <li>• Its use as constant rate infusion for management of Cushing's syndrome has not been reported.</li> </ul>
<b>LCI699</b> novartis.com	Potent inhibitor of aldosterone synthase and 11-beta-hydroxylase	<ul style="list-style-type: none"> <li>• Mechanism of action similar to that of metyrapone; however, it is more potent and has longer plasma half-life (approximately 4 H versus 2 H), which allows twice daily dosing.</li> <li>• Currently under investigation in phase III prospective safety and efficacy study in human patients with Cushing's disease<sup>42</sup>; no information regarding its use in dogs available.</li> </ul>
<b>COR-003</b> NormoCort, strongbridgebio.com	Single 2S, 4R enantiomer of ketoconazole	<ul style="list-style-type: none"> <li>• Expected to be more potent inhibitor of key enzymes in cortisol synthesis pathway and less potent inhibitor of metabolic enzyme, cholesterol 7-alpha-hydroxylase.</li> <li>• Presently in phase III studies in humans; no information regarding its use in dogs available.<sup>36,37</sup></li> </ul>

**TABLE 3.**  
**Investigated Medications for Pituitary-Directed Therapy**

MEDICATION	PHARMACODYNAMICS	NOTES
<b>Pasireotide</b> (SOM230) Signifor, novartis.com	Somatostatin receptor (SSR) ligand, with high binding affinity for multiple receptor isoforms (SST1–3 and SST5). SST5 and SST2 are highly expressed in ACTH pituitary adenomas; while SST5 is most commonly over expressed in humans, SST2 appears to be most common in dogs	<ul style="list-style-type: none"> <li>Recently approved for treatment of human patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.</li> <li>Animal studies documented that SSR mediates inhibition of cyclic adenosine monophosphate and regulation of ACTH secretion.</li> <li>Tested in dogs with Cushing's disease (dose, 0.03 mg/kg SC Q 12 H); results, including decreased ACTH, UCCR, and adenoma size, indicated potential therapeutic usefulness in these dogs.<sup>48</sup></li> <li>While dogs seem to overexpress SST2 receptors, a recent paper showed no decrease in cortisol concentrations in dogs treated with octreotide, a selective SST2 receptor antagonist.<sup>49</sup></li> </ul>
<b>Cabergoline</b> Dostinex, pfizer.com	Dopamine D2 receptor agonist with higher affinity and longer half-life than bromocriptine	<ul style="list-style-type: none"> <li>In humans, its effectiveness and tolerance in treatment of prolactinomas and growth-hormone secreting adenomas have been demonstrated.<sup>50</sup></li> <li>In addition, its antineoplastic effects have been reported as effective for treatment of nonfunctional corticotroph cell tumors.<sup>51</sup></li> <li>Of 40 dogs with PDH, 42.5% responded to treatment with cabergoline (0.07 mg/kg/week), with significant decrease in ACTH, alpha-melanocyte stimulating hormone (a-MSH), UCCR, and tumor size.<sup>35</sup></li> <li>Cabergoline may be useful as a treatment for canine PDH, especially if a pars intermedia tumor is documented or suspected.<sup>35</sup></li> </ul>
<b>Retinoic Acid</b>	Inhibits proliferation, invasion, and tumor growth <i>in vivo</i> ; induces differentiation and apoptosis in different cell types; mediates factors essential in control of the ACTH and a-MSH precursor, proopiomelanocortin (POMC) <sup>52</sup>	<ul style="list-style-type: none"> <li>Recently shown to inhibit ACTH secretion both <i>in vitro</i> and <i>in vivo</i> through action on POMC gene transcription and also inhibit corticotrophinoma development and proliferation.<sup>53</sup></li> <li>Recent study compared treatment with 9-cis retinoic acid (2 mg/kg Q 24 H) versus ketoconazole in dogs with Cushing's disease; retinoic acid controlled ACTH and cortisol over-secretion and tumor size (in dogs with ACTH-secreting tumors), resolving clinical signs.<sup>54</sup></li> <li>This study highlighted possibility of retinoic acid as novel therapy for treatment of ACTH-secreting tumors in humans with Cushing's disease.<sup>53</sup></li> </ul>
<b>Gefitinib</b> (EGFR Antagonist)	Suppresses expression of POMC; thus, inhibiting ACTH secretion; decreases tumor size and corticosterone levels; reverses signs of hypercortisolemia	<ul style="list-style-type: none"> <li>Pharmacodynamics indicate that inhibiting epidermal growth factor receptor (EGFR) signaling may be a novel strategy for treating Cushing's disease.</li> <li>Studies in dogs and humans are underway.<sup>55</sup></li> </ul>

intermedia disease, with few side effects.<sup>44</sup> Currently, it is used in PDH patients in which the cost of monitoring ACTH stimulation tests and electrolytes prohibits treatment with adrenal enzyme blockers or adrenolytics.

#### Pituitary Surgery

Several groups have described the successful use and complications associated with administration of transsphenoidal hypophysectomy (TSH) in dogs with PDH.<sup>45-47</sup>

Recently, Mamelak and colleagues described a

technique for transsphenoidal removal of pituitary adenomas in 26 dogs with PDH using a high definition video telescope.<sup>47</sup> Pituitary tumors were removed using a modified transoral transsphenoidal approach, and localization of the sella was performed by drilling pilot holes in the basisphenoid bone, followed by computed tomography. Sustained tumor control and hormonal remission based on normalized ACTH and urine cortisol creatinine ratio (UCCR) measurements were observed in 20/21 (95%) of dogs one year post surgery.



**Tumor Size.** In the study by Mamelak and colleagues,<sup>47</sup> all dogs had tumors with pituitary height/brain area (P/B) ratios greater than 0.32 and a median P/B ratio of 0.73. Median tumor volume was 820 mm<sup>3</sup>, which is 9 times larger than the median volume of 89 mm<sup>3</sup> reported by Hanson and colleagues, whose study reported mean tumor height of 6 mm, mean width of 6.2 mm, and mean height of 5.4 mm, with a median P/B ratio of 0.3. Forty-three percent of the dogs had a normal P/B ratio.<sup>45</sup>

Interestingly, Hanson and colleagues concluded that pituitary size (height) was the most significant predictor of postoperative survival and mortality.<sup>45</sup> In those studies, initial remission of PDH occurred in 85% of dogs, with relapse in 28% by 3 years. Similarly, Hara and colleagues evaluated outcomes in 25 dogs that underwent TSH using the protocol of Meij and colleagues.<sup>46</sup> Median P/B ratio was 0.38 (range, 0.24–0.71), and 24% of dogs had a normal P/B ratio.

**Survival.** Surgical experience is likely an important variable in dogs undergoing TSH. In the study by Hanson and colleagues, survival at 1, 2, 3, and 4 years were 86%, 83%, 80%, and 79% in 181 patients, respectively.<sup>45</sup> Disease free intervals (DFIs) were 90%, 77%, 72%, and 68%, respectively.

In the study by Hara and colleagues, initial remission was attained in 84% of dogs, with 12% relapsing within 4 years. Survival rates at 1, 2, 3, and 4 years was 92%, 81%, 81%, and 81%, respectively.<sup>46</sup> No data on DFIs were reported.

In the study by Mamelak and colleagues, 1-year survival was 81%, with all 5 deaths occurring within the first 5 days, with 100% of the surviving dogs in remission at 3 months and 95% in remission at 1 year. To date, 7 dogs have survived greater than 2 years and 1 dog greater than 3 years.<sup>47</sup>

**Further Investigation.** Continued experience with surgery to remove pituitary tumors in both dogs and cats is important to not only improve survival and DFIs but also facilitate continued collection of tumor tissue, allowing for additional studies on pathogenesis of this disease and novel therapies for both humans and pets.

## IN SUMMARY

The most commonly used treatments in the management of PDH are mitotane and trilostane. Most clinicians prefer the use of trilostane, given similar efficacy and fewer side effects when compared with mitotane, especially at the lower dosages currently being recommended. In the future,

A 10-year-old castrated male cocker spaniel was referred for evaluation of severe polyuria and polydipsia (PU/PD) of 3 months duration.

## DIAGNOSIS

### Physical Examination

On physical examination no significant abnormalities were detected, with the exception of mild hepatomegaly. The skin and hair coat appeared to be normal.

### History

Previous laboratory analysis, including a complete blood count and serum biochemical profile, was unremarkable, with the exception of a urine specific gravity (USG) of 1.010 and positive urine culture for *Escherichia coli*. The pet was treated with enrofloxacin (5 mg/kg Q 24 H) for 10 days; however, no change in the PU/PD was observed.

An ACTH stimulation test was performed, with a resting cortisol and 1-hour post cortisol results of 2.7 and 14.8 mcg/dL, respectively. These results were considered normal for the laboratory.

### Differential Diagnosis

HAC was still considered to be the most likely differential cause for the PU/PD, despite the previously normal ACTH stimulation test, given the signalment, history, and clinical signs.

### Diagnostics

A low-dose dexamethasone suppression test (LDDS) was performed following IV administration of 0.01 mg/kg of dexamethasone. The resting cortisol, 4-hour post LDDS, and 8-hour post LDDS results were 5.1 (reference range, 1.4–5 mcg/dL), 1.2, and 4.6 mcg/dL, respectively.

The elevated 8-hour cortisol (reference range, < 1.4 mcg/dL), in combination with greater than 50% suppression in cortisol concentrations seen at 4 hours, was diagnostic of PDH.

## TREATMENT PLAN

Treatment options were discussed with the referring veterinarian and treatment with trilostane (Vetoryl) was recommended, starting with 2 mg/kg PO Q 24 H in the morning.

## Consider This Case



## Consider This Case (continued)

The owner was instructed to:

- ▶ Administer the medication with food to enhance gastrointestinal absorption
- ▶ Monitor the animal's water consumption, urination, appetite, and activity level
- ▶ Observe for any adverse reactions, such as vomiting and diarrhea.

A recheck examination consisting of a physical examination and ACTH stimulation test with monitoring of electrolytes was scheduled 10 days following the start of medication.

### FOLLOW-UP

#### Ten-Day Recheck

At the time of the recheck examination, the owners reported a marked reduction in the PU/PD.

An ACTH stimulation test was performed 4 hours post administration of trilostane, with pre and post ACTH cortisol concentrations 2.2 and 5.4 mcg/dL, respectively, indicating adequate adrenal suppression. Determination of electrolytes with an in-house chemistry analyzer was performed and sodium and potassium concentrations were within normal limits.

Due to the laboratory results, along with the observed improvement in clinical signs, the current dose of trilostane was continued and the pet scheduled for a recheck examination in 4 weeks.

#### Four-Week Recheck

During the subsequent recheck examination, the owners reported that the pet was more active, with normal water consumption and urination.

A morning urine sample collected by the owner demonstrated a USG of 1.028. Electrolytes were within normal limits. The pre and post cortisol concentrations were 1.4 and 4.8 mcg/dL, respectively, indicating continued adequate adrenal suppression.

The dose of trilostane was maintained and the pet scheduled for a recheck examination in 3 months.

#### Three- and 6-Month Rechecks

Three and 6 months later the pet was clinically normal. One episode of vomiting and diarrhea had occurred at 4.5 months, but the patient responded to the use of a bland diet, and clinical signs resolved in 24 hours, with no adjustments made to the treatment protocol.

At the 3- and 6-month recheck examinations, electrolyte concentrations were within normal

limits and post ACTH cortisol concentrations were less than 4.2 and 5 mcg/dL, respectively. The dose of trilostane was maintained and the pet scheduled for a recheck examination in 3 to 4 months.

### DISCUSSION

This case illustrates several important points regarding Cushing's disease and its treatment with trilostane.

The referring veterinarian had 3 questions regarding this patient's presentation and diagnostic results:

1. The lack of clinical signs of Cushing's disease other than PU/PD
2. The normal initial ACTH stimulation test
3. The finding of normal serum ALP on the initial laboratory evaluation.

#### Clinical Signs

PU/PD may be the only clinical sign of HAC. Dermatologic abnormalities, such as bilateral symmetric endocrine alopecia and pyoderma, need not be present.

#### ACTH Stimulation Test

Up to 15% to 20% of dogs with HAC have a normal ACTH stimulation test upon initial evaluation of the pituitary–adrenal axis. When faced with a patient that has clinical signs indicative of HAC but a normal ACTH stimulation test, consider LDDS to establish a diagnosis or rule out HAC. Conversely, up to 10% of dogs have an initially normal LDDS; therefore, if LDDS is used as the initial screening test and a normal test result is obtained, consider an ACTH stimulation test.

#### Serum ALP Results

Up to 20% of dogs do not have an elevated ALP in response to either exogenous or endogenous steroid excess, likely due to lack of the gene encoding for the steroid inducible isoenzyme.

#### Treatment Evaluation

The target hormonal goal for the ACTH stimulation test is considered a post ACTH cortisol of less than 9.1 mcg/dL. Together with improvement in clinical signs, this level of adrenal suppression indicates appropriate dosing with trilostane. In our hands, up to 80% of patients obtain clinical and hormonal improvement with once daily dosing.

expanded use of TSH and medications that are pituitary—rather than adrenal—directed should help increase survival and improve the quality of life of patients diagnosed with PDH.

ACTH = adrenocorticotrophic hormone; ALP = alkaline phosphatase; ALT = alanine aminotransferase; a-MSH = alpha-melanocyte stimulating hormone; DDT = dichlorodiphenyltrichloroethane; DFI = disease free interval; EGFR = epidermal growth factor receptor; HAC = hyperadrenocorticism; LDDS = low-dose dexamethasone suppression; PA = pituitary adenoma; P/B = pituitary height/brain area; PDH = pituitary dependent hyperadrenocorticism; POMC = proopiomelanocortin; PU/PD = polyuria/polydipsia; SSR = somatostatin receptor; TSH = transsphenoidal hypophysectomy; UCCR = urine cortisol creatinine ratio; USG = urine specific gravity

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## DAVID BRUYETTE

David Bruyette, DVM, Diplomate ACVIM, is the medical director at VCA West Los Angeles Animal Hospital and President and CEO of Veterinary Diagnostic Investigation and Consultation. He was an assistant professor and head of internal medicine at Kansas State University and director of its Analytical Chemistry Laboratory. Dr. Bruyette received his DVM from University of Missouri and completed an internship at Purdue University and residency in internal medicine at University of California–Davis. He then became a staff internist at West Los Angeles Veterinary Medical Group and member of the Department of Comparative Medicine at Stanford University.





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