A Compass for Cushing’s: Demystifying Canine Hyperadrenocorticism

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KEY POINTS

- Absence of laboratory abnormalities does not rule out hyperadrenocorticism. Clinical signs are the most important indicator of the diagnosis.
- Each diagnostic test has strengths and weaknesses. Choosing the appropriate one is an individualized process.
- VETORYL Capsules (trilostane) are FDA-approved for the treatment of hyperadrenocorticism.
- Active listening and then addressing client concerns or comments are key to successful diagnosis and treatment.
- Monitoring needs to be shared by the client and veterinary team.
- Clients will need support and encouragement to accept and comply with treatment recommendations.

Canine hyperadrenocorticism (Cushing’s syndrome) is the constellation of abnormalities resulting from excessive circulating concentrations of glucocorticoid hormones. (See Tables 1 and 2, pages 2 and 3.) Cortisol is the most common secretory product of the adrenal gland in hyperadrenocorticism (HAC), although excessive secretion of other adrenal hormones such as sex hormones and mineralocorticoids has also been documented. Approximately 80% to 85% of cases of spontaneous canine HAC are due to an adrenocorticotropic hormone (ACTH) secreting pituitary tumor (pituitary dependent hyperadrenocorticism; PDH), with the remainder due to autonomous secretion of cortisol by an adrenocortical tumor (AT).

It is important to differentiate spontaneous HAC from iatrogenic HAC, which is caused by exogenous administration of glucocorticoids. Clinical signs of iatrogenic and spontaneous HAC cannot be distinguished so identification of iatrogenic HAC is based on a history of steroid administration and, if necessary, results of an ACTH stimulation test. HAC may interfere with the quality of life of both dog and owner. If left untreated, patients are also more susceptible to potentially life-threatening complications such as urinary tract infection, diabetes mellitus, and systemic hypertension. Although most of the current treatment options for canine HAC do not address the underlying abnormality (a benign pituitary tumor in 85% of spontaneous cases), appropriate treatment can resolve clinical signs and prevent complications.
Diagnosis of HAC relies on the historical and physical examination findings, a laboratory minimum database (CBC, serum chemistry panel, urinalysis), and specific endocrine function tests. Not all dogs respond in the same way to high cortisol concentrations, so making a diagnosis of HAC may be challenging; a myriad of clinical signs may be observed. Although in severe cases the clinical signs are very characteristic, in others they may be more subtle with only one or two being present.

**Signalment & Clinical Signs**

HAC is typically a geriatric disease with a median age of 11 years; it is unlikely in a dog <6 years of age. Owner observations are very important for documenting the clinical signs of HAC because many may not be obvious in the examination room. Neurologic abnormalities from pituitary macrotumor syndrome may be very subtle (Table 1).

**Laboratory Abnormalities**

Although commonly observed (Table 2), absence of laboratory abnormalities does not rule out HAC. Conversely, laboratory abnormalities without clinical signs should not be an indication for testing for Cushing’s syndrome.

**Endocrine Tests**

Measurement of baseline cortisol has no value in diagnosing HAC. Confirmation of HAC is made through endocrine function testing such as the urine cortisol:creatinine ratio (UCCR), the low-dose dexamethasone suppression test (LDDS) test, and the ACTH stimulation test. To distinguish PDH from functional adrenal tumors, the low- and high-dose dexamethasone suppression tests, basal ACTH concentration, and diagnostic imaging are used.

Each of these tests has strengths and weaknesses; the choice depends on the individual case. Because systemic illness can result in false positive results, HAC testing should be postponed until the patient is systemically well.

**UCCR**—The UCCR provides an integrated reflection of cortisol production, thereby adjusting for fluctuations in blood cortisol concentrations. It is a sensitive test for diagnosis of canine hyperadrenocorticism (sensitivity 75%-100%); however, reported specificity varies widely (20%-77%) depending upon the protocol used. The protocol described here raises sensitivity to 99% and specificity to 77%: Two morning urine samples should be collected at home at least 2 days after a veterinary visit. A result well within the reference range makes a diagnosis of HAC unlikely, while 2 urine samples with an increased UCCR from a dog with appropriate clinical signs is consis-

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**TABLE 1**

**CLINICAL MANIFESTATIONS OF CANINE HAC**

<table>
<thead>
<tr>
<th>Common</th>
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<tr>
<td>Polydipsia/polyuria</td>
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<td>Polyphagia</td>
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<td>Excessive panting</td>
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<td>Abdominal distention</td>
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<td>Endocrine alopecia</td>
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<td>Hepatomegaly</td>
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<td>Muscle weakness/atrophy</td>
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<td>Systemic hypertension</td>
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<td>Lethargy</td>
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<td>Hyperpigmentation of skin</td>
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<td>Comedones</td>
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<td>Thin skin</td>
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<td>Poor hair regrowth</td>
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<td>Urine leakage</td>
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<td>Insulin resistant diabetes mellitus</td>
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<td>Persistent or recurrent UTIs</td>
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<td>Pyoderma</td>
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<table>
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<th>Rare</th>
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<tr>
<td>Thromboembolism</td>
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<td>Ligament rupture</td>
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<td>Facial nerve palsy</td>
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<td>Pseudomyotonia</td>
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<td>Testicular atrophy/persistent anestrus</td>
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<td>Pituitary macrotumor syndrome</td>
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<td>Bruising</td>
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tent with HAC. The author recommends that the diagnosis of HAC should be confirmed by another test such as the LDDS test.

**LDDS**—This test relies on the fact that administration of exogenous glucocorticoids suppresses the production of ACTH from the normal pituitary and therefore cortisol from the normal adrenal gland. Suppression persists in normal dogs for 16 to 24 hours. Since dexamethasone is not detected by the assay for cortisol, cortisol can be measured after administration of exogenous dexamethasone. Dogs with HAC do not exhibit normal suppression after administration of dexamethasone because in PDH, the pituitary gland is less sensitive to glucocorticoid feedback, while adrenal tumors (AT) function independently of ACTH; in addition, dexamethasone is metabolized more quickly in dogs with HAC.

For these reasons, in dogs with either form of HAC, no suppression occurs 8 hours after low-dose dexamethasone administration. The LDDS test has a sensitivity of 85% to 100% and a specificity of 44% to 73%. The LDDS should not be used until iatrogenic HAC has been excluded by the history and if necessary, an ACTH stimulation test. To perform the LDDS test, a blood sample is collected for measuring a baseline cortisol, followed by the administration of dexamethasone (dexamethasone sodium phosphate or dexamethasone in polyethylene glycol) IV at a dose of 0.01 mg/kg. The patient is then left undisturbed in a cage and a second blood sample is collected 8 hours later. In which normal dogs will show suppression of the cortisol concentration typically to < 1.0 µg/mL. Dogs with HAC do not demonstrate this suppression. Additional information may be obtained by measuring a cortisol concentration 4 hours after dexamethasone administration. If suppression occurs at 4 hours but “escape” occurs at 8 hours, PDH is confirmed.

**ACTH stimulation test**—The ACTH stimulation test relies on the assumption that hyperplastic or neoplastic adrenals often have abnormally large reserves of cortisol and therefore over-respond to maximal stimulation by ACTH. In contrast, dogs with iatrogenic HAC usually have a suppressed response to ACTH. A blood sample is collected for measurement of baseline cortisol; synthetic ACTH (cosyntropin, tetracosactrin) is then administered at a dose of 5 µg/kg IV. A second blood sample for measurement of cortisol is collected one hour later. The reported specificity of the ACTH stimulation test for diagnosis of HAC ranges from 59% to 93%. Sensitivity for diagnosis of pituitary dependent HAC ranges from 80% to 84% while sensitivity is only ~ 60% in dogs with functional adrenal tumors. The ACTH stimulation test does not help in distinguishing between AT and PDH. Because of its lower sensitivity compared with the LDDS test, the ACTH stimulation test is not the first test of choice for spontaneous HAC but should be used to differentiate spontaneous from iatrogenic HAC.

**Advantages & Disadvantages of Tests**
The UCCR is an excellent screening test for spontaneous HAC but is usually not used as the only confirmatory test. The LDDS is both very sensitive and specific and can assist in differentiating PDH from AT but will not identify iatrogenic HAC. The ACTH stimulation test is less sensitive but can identify iatrogenic HAC. When clinical signs of HAC are present and there is no history of exogenous corticosteroid administration, the LDDS is the most appropriate initial diagnostic test. If this test is abnormal or borderline, the ACTH stimulation test may be used to confirm or support the diagnosis of HAC and obtain a baseline for monitoring response to treatment. Testing should be repeated in 1 to 3 months if the result is negative but no other cause of the clinical signs is identified. In dogs with obvious clinical signs of HAC and persistent normal cortisol testing, a sex hormone profile may be considered. In animals with suspected iatrogenic HAC, the ACTH stimulation test is the test of choice.

**Differentiation of PDH from Adrenal Tumors**
Endocrine function tests such as the

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**TABLE 2**

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<thead>
<tr>
<th>LABORATORY ABNORMALITIES ASSOCIATED WITH HAC</th>
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<tr>
<td><strong>Test</strong></td>
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<td>CBC</td>
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<td>Serum chemistry panel</td>
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<td>Urinalysis</td>
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EXPLAINING CUSHING’S TESTS TO OWNERS

The interpretation of tests for HAC can be confusing to owners especially when multiple tests are required or when the interpretation of the results is equivocal. It is particularly important for them to understand that the test must be interpreted in the context of the patient’s clinical signs. Some important points to emphasize:

- Testing is usually not recommended if clinical signs of HAC are not present.
- Several different blood and urine tests can be used either singly or together to make a diagnosis of HAC.
- The tests usually require collection of 2 or 3 blood samples in a low-stress environment.
- Tests need to be repeated from time to time to verify that the proper dosage of medication is being used.
- The correct dosage is important in alleviating the clinical signs and returning the pet’s and owner’s life to normal.
- Collecting urine samples may be performed at home; otherwise testing is done in the hospital.
- Sometimes tests are not diagnostic or may give borderline results.
- If the tests are not diagnostic, the recommendation may be to repeat them in 2 to 3 months.
- In some cases additional tests such as radiographs, ultrasound, or measurement of blood pressure may be required.

The ACTH concentration in PDH is not always above the reference range.

high- and low-dose dexamethasone suppression tests, endogenous ACTH concentration, and diagnostic imaging modalities are used to differentiate PDH from AT. Suppression of basal cortisol concentration by > 50% 4 or 8 hours after administration of either a low or high dose of dexamethasone is diagnostic for PDH; if > 50% suppression is seen, HDDS testing is unnecessary. Lack of suppression, however, is not diagnostic for AT and additional testing is required. Measurement of an ACTH concentration is also useful in differentiating PDH from AT. In dogs with a functional adrenal tumor, the ACTH concentration should be low, whereas with PDH the ACTH concentration should be normal or high. Because of episodic secretion of ACTH, the ACTH concentration in PDH is not always above the reference range. If the ACTH concentration is above the laboratory reference range, this confirms PDH, but a low ACTH concentration does not confirm the diagnosis of AT.

Diagnostic Imaging

Approximately 57% of ATs are identified on abdominal radiographs compared to 72% with ultrasonography.4 Other radiographic findings may include hepatomegaly, osteopenia, dystrophic mineralization, and distension of the urinary bladder. Thoracic radiographs may reveal metastasis, pulmonary thromboembolism, or mineralization of the bronchi and pulmonary parenchyma. In dogs with PDH, ultrasound of the adrenal glands typically reveals bilaterally symmetrical enlargement with preservation of normal architecture. The glands may not be identical in size but the smaller gland in dogs with PDH typically has a dorsoventral width > 5 mm.5 The size of the glands may be within normal range in some dogs with PDH.

In dogs with a functional adrenal tumor, there should be unilateral adrenal gland enlargement with abnormal adrenal gland architecture while the contralateral adrenal gland is small (< 5 mm in dorsoventral width). Evidence of a tumor thrombus within the vena cava is detected on ultrasound in 11% of dogs with adrenocortical tumors6 and evidence of distant metastasis to abdominal organs may be present. Bilateral ATs and macronodular hyperplasia of the adrenal gland in dogs with PDH may complicate the interpretation of ultrasound findings. Computed tomography is also useful to evaluate the adrenal glands, especially in dogs with AT. MRI or CT of the brain is helpful in determining pituitary tumor size in PDH. Approximately 70% of dogs with PDH have a detectable pituitary tumor on CT or MRI.7

References

Pinpointing Therapy

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Treatment of canine hyperadrenocorticism (HAC) is directed at resolution of clinical signs, improvement in quality of life for the patient and owner, and reduction of risks associated with uncontrolled disease. These risks include recurrent secondary infections, diabetes mellitus, hypertension, calcinosis cutis, pancreatitis, and clot formation with pulmonary thromboembolism. Treatment should be instituted only in patients showing clinical signs, and even then a discussion should take place with each owner about the pros and cons.

If clinical signs are absent and only blood work values are consistent with Cushing’s disease, treatment is not indicated. Treatment options, protocols, and prognoses also vary depending on the type of HAC.

Adrenal Dependent HAC
Treatment for adrenal dependent HAC includes both surgical and medical options. While excision is the treatment of choice for adrenal tumors (AT) causing HAC, complication rates can be as high as 46% and mortality as high as 21%.

Thus, adrenalectomy should be performed by only an experienced surgeon. If surgery successfully removes all tumor burden, it may be curative, but complications can be severe. When the owner does not want to pursue surgery or the AT is not surgically amenable, medical management is appropriate.

Pituitary Dependent HAC (PDH)
Treatment options for PDH are also surgery and medical management. At this time, medical management is preferred in the United States. Hypophysectomy is performed at Utrecht University and in limited centers in the United States. Trilostane, mitotane, selegiline, and ketoconazole are all choices for medical management, but trilostane and mitotane are most effective and commonly used. With trilostane or mitotane, dosage adjustments are based on ACTH stimulation testing results as well as the individual patient response to therapy. The author does not consider ketoconazole and selegiline good treatment options for canine hyperadrenocorticism.

Trilostane
Trilostane (VETORYL Capsules) is FDA-approved for the treatment of canine HAC. Median survival time for dogs with adrenal dependent HAC treated with trilostane and mitotane were 353 and 102 days respectively.

Trilostane’s mechanism of action is competitive inhibition of 3β-hydroxysteroid dehydrogenase (3β-HSD). It reduces synthesis of cortisol, aldosterone, and adrenal androgens, and the effects appear to be reversible and dose dependent in most patients. Oral trilostane is rapidly absorbed, and absorption is enhanced when administered with food.

Initial dosage recommendations (2.2 to 6.7 mg/kg once a day) and protocols are the same for PDH and AT. In calculating dosages, round down and start at the lower end of the range. The author starts at an initial total daily dosage of 2-3 mg/kg/day. Once daily administration is recommended on the drug label. However, if clinical signs are not controlled for the full day, twice daily administration may be needed for optimum control. In diabetic patients, always use the twice-daily protocol to provide consistent therapy across a 12-hour interval.

If using a potassium-sparing diuretic or ACE inhibitor, hyperkalemia can develop. Side effects of trilostane are usually mild and can include lethargy, inappetence, and gastrointestinal upset within the first few days of treatment.

A rare life-threatening side effect of trilostane is acute adrenal necrosis with development of Addisonian crisis, which is caused by acute adrenal insufficiency resulting from cortisol deficiency with or without aldosterone deficiency. Dispense dexamethasone tablets (not prednisone,
as it can cross-react with the cortisol assay for the ACTH stimulation test) at a dosage of 0.1 mg/kg for emergency use at home. If Addisonian crisis is suspected (patient is exhibiting vomiting, diarrhea, and collapse), the client should administer dexamethasone and immediately bring the patient to the clinic. An ACTH stimulation test will confirm whether Addisonian crisis has occurred.

Mitotane
Mitotane is an adrenocorticolytic agent. Thus, its effects may not be reversible. There are two consecutive phases of treatment: an initial loading phase and chronic maintenance. In the initial phase, the patient receives ~50 mg/kg/day to be divided and given twice daily with food. Once loading is successfully completed, the patient receives ~50 mg/kg/week, divided over several days.

Monitoring
Mitotane is an older drug whose use is decreasing with time, especially since it is not FDA-approved. Because of the critical nature of the induction phase and the potential serious side effects of therapy, mitotane involves significant monitoring, which is beyond the scope of this article.

With trilostane, the first recheck should be scheduled in 10 to 14 days after starting therapy. Trilostane should be given with food, including on the day of a recheck. The first and every recheck thereafter should include discussions with clients about clinical improvement and any side effects, as well as ACTH stimulation test results and electrolyte levels. The ACTH stimulation test should be performed 4 to 6 hours after dosing. Most dogs will have demonstrated an improvement in clinical signs, such as a reduction in drinking, urinating, and appetite, at the first recheck. Some will not have yet realized the full effects of triostane after two weeks of therapy; it may take a full month. If the ACTH stimulation test results are above the ideal range at the first recheck, an increase in dosage may not be indicated until 30 days after starting therapy. The first recheck can then ideally rule out overdosing. Controlling the hypothalamic/pituitary/adrenal axis is essential. Post-ACTH stimulation test cortisol values should be within the range for well-controlled patients, which varies depending on the reference used. The author uses between 1.5 and about 9 μg/dl. *The key is resolution of clinical signs without excessive cortisol suppression.* If a dosage adjustment is indicated, use a factor of 10% to 15%. Warn owners that it usually takes 2 to 3 dose adjustments to achieve control, and schedule a recheck in 10 to 14 days.

Once a patient is well managed, rechecks with ACTH stimulation and electrolyte testing should occur at 1 and 3 months, and then every 3 to 6 months as long as the disease is clinically well controlled. While there is no perfect schedule, the above schedule is referenced elsewhere. In patients in which once-a-day dosing achieves adequate ACTH stimulation test results but not control of clinical signs, or signs seem controlled during the day but not at night, change to twice-daily dosing, giving half the total daily dose in the morning and evening with meals.

Putting It All Together
When it comes to uncovering a pet suffering from Cushing’s disease, it is everyone’s job to ask appropriate questions and to actively listen to what the client says. Clients may bring in their older dog for a wellness exam, but when the receptionist asks about changes in the dog’s health or general behavior, they may reveal subtle clues suggesting Cushing’s disease. Often, clients brush these off as simply part of the dog getting older.

Once HAC has been diagnosed, emphasize the goals of management—ie, getting their dog back to normal. Stress how appropriate treatment will improve the clinical signs. Don’t assume clients will not pay for something; if they understand how it will improve quality of life for their dog and themselves, many are willing to do what it takes.

When the disease process is controlled, the patient’s clinical signs will begin to resolve. One of the main goals of treatment is getting life back to normal for both patient and owner. Everyone from the front desk to the exam room can contribute to this goal. Everyone should be listening to the client as he or she describes the dog’s clinical signs, response to therapy, and any complications that may occur. Hearing about the changes, no matter how subtle, is important for evaluating each patient, as an accurate patient evaluation is critical to determining the final dosage of medication for the individual patient. Titration of therapy over time is based on adequate resolution of clinical signs and laboratory testing (ACTH stimulation testing and monitoring of electrolytes).

It is also very important to stress up front that medical management is life-long, requiring rechecks in order to gain and maintain optimum control in the safest manner possible. This will require more checks early on and fewer as good control is achieved: Good client communication is imperative in achieving successful management. Taking time to explain the treatment process at the start will help eliminate owner frustration.

References
Hyperadrenocorticism (also known as Cushing’s disease) is a condition in which the adrenal gland produces too much steroid hormone (cortisol). Common signs of Cushing’s disease include:

- increased drinking and urination
- ravenous appetite
- excessive panting
- distended abdomen (pot-bellied appearance)
- hair loss

Your veterinarian will discuss with you what a diagnosis of Cushing’s disease means for your dog:

- Treatment options include surgery or medical management. Your veterinarian will discuss what option may be best for your dog.
- Many veterinarians choose either trilostane or mitotane as the medication.
- Medications will not cure the disease; rather they are aimed at controlling symptoms.
- Complications of uncontrolled Cushing’s disease include elevated blood pressure, chronic urinary tract infections, skin lesions, and/or diabetes mellitus.
- Close control is required to avoid disease complications.
- Side effects that are usually mild may occur from medications. These might include vomiting, diarrhea, decreased appetite, and reduced energy level.
- If side effects are severe or persistent, they may indicate a more severe adverse event (see right*).
- Cushing’s disease can take several weeks to months to control.
- If your dog is treated with medication, regular physical examinations and lab work such as cortisol checks will be needed to monitor the dose.
- Many dogs respond well to treatment and, over time, owners will see improvement in their dog’s overall well-being.

* An important complication to watch for is an Addisonian crisis, which is life-threatening and reflects a dramatic decrease in cortisol levels. If your pet experiences vomiting, diarrhea, anorexia, lethargy, generalized weakness, or muscle tremors after treatment is started, contact a member of the team immediately.
Moreover, clients may need time on their own—to go home, discuss the situation with family members, and digest the information they have been given. What your clients currently understand is that they have been living with some very troublesome clinical signs and you thankfully have an answer for them.

Gathering Information
Active listening and then responding to voiced concerns are critical to optimal management and client satisfaction. When probing for information that may point to HAC and educating clients about the illness and its management, several factors are important:

- clinical signs of Cushing’s disease
- side effects of medications
- need for routine testing
- client expectations.

The last point is probably the most important. Setting realistic expectations can mean all the difference in a client’s satisfaction with a pet’s care.

Consistent, Positive Message
Communicating about HAC treatment and its chronicity is important and requires a solid team approach, ensuring everyone is on the same page in how we assist clients in making difficult decisions. The treatment options can often be seen as complex and expensive. You will need to stress to clients that this is a chronic illness, but that you will help them throughout the treatment process to make the best decisions for them and their pet.

For a variety of reasons, most practitioners will recommend medical treatment. This is where a team communication approach is most beneficial. From receptionist to technician to veterinarian, everyone needs to provide a consistent, positive message of encouragement and guidance. Receptionists are generally the first point of contact for pet owners and can gather relevant information about how the patient is doing when confirming appointments or checking patients in. Veterinary technicians have a more hands-on role in client communication and can be employed as “translators” between doctor and owner.

It is easy for us, exposed to this illness regularly, to underestimate the impact on pet owners of the uncontrollable appetite, accidents in the house, and change in appearance of their dog. These issues can take a toll on pet owners and the dog/owner bond. Our job as veterinary team members is to prevent this from happening. As a veterinary professional, you can involve your team by having them explain medication administration, monitoring, and possible side effects, including those that could indicate an Addisonian crisis. Adverse effects can be minimized by ensuring the medication is administered correctly, with a full meal. Side effects of trilostane and mitotane may also mimic those of Addisonian crisis. If they persist, new ones develop, or are immediately concerning, clients should be instructed to come in for an ACTH stimulation test immediately.

Monitoring
Clients should be prepared for the fact that it may take some time and repeated ACTH stimulation testing to determine optimum dosages. Explaining why we take a slow and steady approach to medication administration will offer clients peace of mind that their money is being spent in the best way possible and that we are always mindful of the patient’s well-being. **Emphasize the success stories.** It is not uncommon for clients to report their dog is acting like a goofy puppy again.
Diagnosis, Treatment and Monitoring of Hyperadrenocorticism

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. As with all drugs, side effects may occur. In field studies and post-approval experience, the most common side effects reported were: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without elevated sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, and renal insufficiency. In some cases, death has been reported as an outcome of these adverse events. VETORYL Capsules are not for use in dogs with primary hepatic or renal disease, or in pregnant dogs. Refer to the prescribing information for complete details or visit www.Dechra-US.com.
Confirming the diagnosis of hyperadrenocorticism (HAC)

No test for HAC has 100% diagnostic accuracy. The diagnostic value of all endocrine tests will be significantly enhanced by performing them only when clinical signs consistent with HAC are present in the patient. Three endocrine diagnostic tests are available, all with particular advantages and disadvantages:

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<tr>
<th>Test</th>
<th>Sensitivity &amp; Specificity</th>
<th>Additional info</th>
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<tr>
<td>Urinary Cortisol to Creatinine Ratio (UCCR)</td>
<td>• Highest sensitivity of all three tests makes it a great screening test&lt;br&gt;• Highest confidence in a negative test result&lt;br&gt;• Lacks specificity&lt;br&gt;• False negatives are relatively common</td>
<td>• To avoid false-positive results, urine samples should be collected at home at least two days after a visit to a veterinary clinic&lt;br&gt;• Collect first urine sample from patient in the morning&lt;br&gt;• Specificity and sensitivity can be increased when urine from 2-3 days is pooled and collectively tested and when the test is performed on dogs showing symptoms consistent with HAC</td>
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<tr>
<td>Low-Dose Dexamethasone Suppression</td>
<td>• High sensitivity&lt;br&gt;• High confidence in a negative test result&lt;br&gt;• Moderate specificity&lt;br&gt;• False positives can occur</td>
<td>• Long test (8 hours)&lt;br&gt;• In some cases may differentiate between PDH and ADH&lt;br&gt;• Considered the screening test of choice unlessiatrogenic HAC is suspected</td>
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<tr>
<td>ACTH Stimulation</td>
<td>• Highest specificity of all three tests&lt;br&gt;• Highest confidence in a positive test result&lt;br&gt;• Lacks sensitivity&lt;br&gt;• False negatives are relatively common</td>
<td>• Relatively short test (1 hour)&lt;br&gt;• Test of choice if there is a history of exogenous steroid therapy</td>
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For detailed information on performing and interpreting these tests, please contact Dechra Veterinary Technical Services at (866) 933-2472 or your reference laboratory consult line.

Differentiating between types

It is necessary to differentiate between Pituitary Dependent Hyperadrenocorticism (PDH) and Adrenal Dependent Hyperadrenocorticism (ADH) to provide a more accurate prognosis and enable the full range of possible treatments to be discussed with the dog’s owner.

Discriminatory tests available to differentiate between PDH and ADH include the low- and high-dose dexamethasone suppression tests, ultrasonography, and advanced imaging such as MRI and CT and measurement of endogenous ACTH.

Diagnostic summary

A confident diagnosis requires consistent endocrine confirmatory test results in a dog with clinical signs compatible with hyperadrenocorticism.
**Treatment and Monitoring of Hyperadrenocorticism**

**DAY 1**
Start VETORYL® Capsules at approximately 1 mg/lb (2.2 mg/kg) once daily as per prescribing information
Give daily by mouth with food in the morning.

**DAY 10-14**
History, physical examination, serum biochemistry, with electrolytes
Perform ACTH stimulation test 4-6 hours after morning capsule
Ensure morning capsule was given with food

Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well
Stop VETORYL Capsules for approximately 7 days
RETURN TO DAY 1 and administer a LOWER DOSE
Repeat ACTH stimulation test in 10-14 days after restarting lower dose

≥30 DAYS FROM INITIATION OF TREATMENT
History, physical examination, serum biochemistry, with electrolytes
ACTH stimulation test 4-6 hours after morning capsule given with food
Assess degree of clinical improvement

**SIGNIFICANT IMPROVEMENT**
Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well
Stop VETORYL Capsules for 7 days depending on the severity of the clinical signs and then
RETURN TO DAY 1 AT LOWER DOSE
Continue monitoring history, physical examination, electrolytes and ACTH stimulation test every 90 days.
If dose is altered always recheck ACTH stimulation again 10-14 days later

Post-ACTH serum cortisol >1.45 µg/dL (>40 nmol/L) and clinically well
Continue treatment at current dose
It is not recommended to increase dose yet, even if cortisol is >9.1 µg/dL

≥30 DAYS FROM INITIATION OF TREATMENT
Post-ACTH serum cortisol >1.45 µg/dL (>40 nmol/L) and clinically well
Continue treatment at current dose
It is not recommended to increase dose yet, even if cortisol is >9.1 µg/dL

Showing clinical signs consistent with:
1. Corticosteroid withdrawal syndrome ("relative" cortisol deficiency characterized by weakness, lethargy, stiff gait, anorexia, fever during first 10 days of therapy)
2. Hypoadrenocorticism (e.g., anorexia, lethargy/ depression, weakness, shaking/shivering, vomiting, diarrhea, bradycardia, collapse)

STOP VETORYL TREATMENT
Confirm whether clinical signs are due to hypoadrenocorticism with ACTH stimulation test and analysis of serum electrolytes (in particular Na+ and K+)
Treat symptomatically as required, e.g.
• dexamethasone to treat hypocortisolemia
• IV 0.9% NaCl to resolve hyperkalemia

**CLINICAL SIGNS NOT FULLY CONTROLLED**
If clinical signs are not controlled for a full 24 hour period, twice daily dosing or a dosage increase may be indicated
To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.
If Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L), total daily dose can be slowly increased and split into two doses
Continue to monitor as per approved label recommendations
Perform ACTH stimulation test 4-6 hours post morning capsule

If you have questions at any point during patient management, contact Dechra Veterinary Technical Services at (866) 933-2472

Rule out concurrent illness
If Post-ACTH serum cortisol >5.4 µg/dL (>150 nmol/L)
Increase dose
RETURN TO DAY 1

To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.
VETORYL® Capsules (trilostane)

Adrenocortical suppressant for oral use in dogs only.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: VETORYL Capsules are available in 5 sizes (5, 10, 30, 60 and 120 mg) for oral administration to dogs (≤ 15 kg). Each VETORYL Capsule contains 5 mg, 10 mg, 30 mg, 60 mg or 120 mg of trilostane, a 17β-hydroxy-5α-steroid-3α-carbonitrile that is an orally active synthetic androgenic antagonist that selectively inhibits the actions of androgens on the adrenal cortex, thereby inhibiting the conversion of progesterone to androgens. This inhibition blocks production of glucocorticoids and to a lesser extent, mineralocorticoids and sex hormones while steroid precursor levels increase.

The structural formula is:

INDICATIONS: VETORYL Capsules are indicated for the treatment of pituitary-dependent hyperadrenocorticism in dogs.

DOSAGE AND ADMINISTRATION: Always provide the Client Information Sheet with prescription (see INFORMATION FOR DOG OWNERS).

1. Starting dose. The starting dose for the treatment of hyperadrenocorticism in dogs is 1-3 mg/kg (2.2-6.7 mg/kg) once a day. Start therapy based on body weight and available combinations of capsule sizes. VETORYL Capsules should be administered with food.

2. Action in 10-14 day evaluation (Table 2). After approximately 10-14 days at this dose, re-examine the dog and conduct a 4-6 hour post-ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function). If physical examination is acceptable, take action according to Table 1.

3. Individual dose adjustments and dose monitoring are essential. Re-examine and conduct an ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function) 10-14 days after every dose alteration. Care must be taken during dose increases to monitor the dog's clinical signs.

The post-ACTH serum cortisol concentration obtained after 4 weeks of treatment is an important reference point. If the post-ACTH serum cortisol concentration obtained at this time is ≤ 0.3 µg/dL then maintenance at this dose is recommended.

4. Long term monitoring. Once an optimum dose of VETORYL Capsules has been reached, re-examine the dog 30 days, 90 days and every 3 months thereafter. At a minimum, this monitoring should include:

• A thorough history and physical examination.
• ACTH stimulation test (normal ACTH stimulated cortisol release is ≥ 14.5 µg/dL in a 4-6 hour post-ACTH stimulation test and serum biochemical tests (with particular attention to electrolytes, and renal and hepatic function).

Control is indicated by favorable clinical signs as well as post-ACTH serum cortisol of 14.5-91.0 µg/dL (40-250 nmol/L).

If the ACTH stimulation test is ≤ 1.4 µg/dL (<40 nmol/L) and/or if electrolyte imbalances characteristic of hyperadrenocorticism resolve, decrease the dose to the next lower size over the next 1-2 weeks and continue the decrease until the required dose is reached. If the post-ACTH serum cortisol concentration is still ≤ 0.3 µg/dL after the dose reduction, decrease the dose again by 25-50%.

CONTRAINdications: The use of VETORYL Capsules is contraindicated in dogs that have demonstrated hyperprolactinemia to trilostane. Do not use VETORYL Capsules in animals with primary hepatic disease or renal insufficiency (See WARNINGS AND PRECAUTIONS).

DO NOT use in pregnant dogs. Studies conducted with trilostane in laboratory animals have shown teratogenic effects and early postnatal loss.

WARNINGS: Hyperadrenocorticism can develop at any dose of VETORYL Capsules. In some cases, it may take months for adrenal function to return and some dogs never regain adequate adrenal function.

All dogs should undergo a thorough history and physical examination before initiation of therapy with VETORYL Capsules. Other conditions, such as primary hepatic and/or renal disease should be considered when the patient is exhibiting signs of illness in addition to signs of hyperadrenocorticism (e.g. vomiting, diarrhea, poor/reduced appetite, weight loss, and hypertension). Pre-treatment biochemical tests are essential. If the post-ACTH serum cortisol concentration obtained at the initiation of therapy is ≤ 0.3 µg/dL (post-ACTH serum cortisol ≥ 14.5 µg/dL), it should be explained to the owner that control of hyperadrenocorticism may be more difficult.


Practitioners should be informed that control of hyperadrenocorticism should result in resolution of polyphagia, polyuria and polydipsia. Owners should be informed of the importance of periodic follow-up for all dogs administered VETORYL Capsules.

CLINICAL PHARMACOLOGY: Trilostane is absorbed by administration with food. In healthy dogs, maximal plasma levels of trilostane and its metabolites are observed within 5 hours, with mean values of 14-21 mg/L (368-525 µg/dL). Accumulation of trilostane or its metabolites over time.

In a laboratory study, VETORYL Capsules were administered to 8 healthy 6 month old Beagles per group at 0X (empty capsule, control), 3X (receiving 16.5 mg/kg twice daily), 5X (receiving 27.5 mg/kg twice daily). At the end of 28 days, the dogs in the 0X group had a body weight gain of 20.1 mg/kg twice daily) and five animals in the 5X group (receiving 33.5 mg/kg twice daily) died between Days 23 and 46. They showed weight loss, decreased activity, decreased appetite, vomiting, diarrhea, tremors, diarrhea, lateral recumbency, and staggering gait. Bloodwork showed hyponatremia, hyperkalemia, and azotemia, consistent with a hyperadrenocortical crisis, Post-mortem findings included epithelial necrosis and cytoplasmic degeneration of mucosal crypts, mucosal ulceration, chronic inflammatory foci, and infiltration of the lungs. ACTH stimulated cortisol release was reduced in all dogs treated with VETORYL Capsules. The dogs in the 3X and 5X groups decreased activity. The 5X group had less weight gain than the other groups. The 3X and 5X dogs had lower sodium, albumin, bilirubin, protein, and globulin compared to the control dogs. The 3X and 5X dogs had lower mean corpuscular volume than the controls.

The dogs in the 3X and 5X groups had lower mean corpuscular volume than the controls. There was a dose dependent increase in amylase. Post-mortem findings included dose dependent adrenal cortical hypertrophy.

STORAGE INFORMATION: Store at controlled-room temperature 25°C (77°F) with excursions between 15°C-30°C (59°F-86°F) permitted.

HOW SUPPLIED: VETORYL Capsules are available in 5, 10, 30, 60 and 120 mg strengths, packaged in 50 flakelike blister packs of 10 capsules, with 3 capsules per carat.

VETORYL Capsules 5 mg NDC 17033-105-30
VETORYL Capsules 10 mg NDC 17033-140-30
VETORYL Capsules 30 mg NDC 17033-130-30
VETORYL Capsules 60 mg NDC 17033-160-30
VETORYL Capsules 120 mg NDC 17033-190-30

TAKING VETORYL® Capsules:

NADA 141-291. Approved by FDA.

Distributed by:

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