

Canine hyperadrenocorticism: A review and update

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Introduction

Hyperadrenocorticism (HAC; Cushing's syndrome) describes the clinical manifestations of chronic exposure to excessive glucocorticoids. There are three causes of this disorder:

- Iatrogenic
- Excessive secretion of cortisol by an adrenal tumor (AT)
- Excessive secretion of adrenocorticotropic hormone by a pituitary adenoma
 - This is true Cushing's Disease
 - Also referred to as Pituitary-dependent HAC or PDHAC

The clinical signs of HAC include increased thirst and urination, excessive hunger and panting. Additionally, most dogs manifest dermatologic changes, including trunkal alopecia, calcinosis cutis, pyoderma and hyperpigmentation. Some of the physiologic consequences of HAC can be life threatening. Dog with this disease are predisposed to hypertension, chronic infection, glomerular disease and pulmonary thromboembolism.

Establishing a diagnosis of HAC

If the clinical signs and baseline laboratory data (CBC, chemistry panel, urine analysis) suggest HAC, the diagnosis first be confirmed, and then the type of HAC must be determined.

Confirmatory testing: There are several ways to evaluate adrenal function, including a urine cortisol:creatinine ratio (UCCR), adrenocorticotropic hormone (ACTH) stimulation test and the low-dose dexamethasone suppression test (LDDST). The UCCR lacks specificity and is not helpful in dogs with overt signs of HAC. The ACTH stim test and LDDST are both suitable choices, but neither is 100% sensitive or specific. It does appear that the LDDST is less likely to be impacted by non-adrenal disease and may be the confirmatory test of choice in dogs. In addition, the LDDST may provide some useful information about the type of HAC (i.e., PDHAC or AT).

Differentiate the type of HAC: Most clinicians use the LDDST results or abdominal ultrasonography to determine the type of HAC. It is important to perform this step, as surgical removal is the best approach for dogs with an AT (unless the mass is inoperable or metastases are present). If ultrasonography is not available or the findings are inconclusive, measurement of endogenous ACTH concentrations can be used to differentiate PDHAC from AT. High-dose dexamethasone suppression tests were used for many years to differentiate the two forms of HAC, but have been supplanted by safer and more reliable tests.

Therapy for HAC due to AT

Surgical removal is the best management option for dogs with an adrenocortical tumor. Studies have shown that about 50% of these lesions are malignant, and therefore can be quite invasive and metastasize readily. Prompt removal offers the best chance for a permanent cure and will resolve the clinical signs of HAC.

If the mass is inoperable or if other issues preclude surgical intervention, trilostane (Vetoryl[®]) should be considered. It is presently the only drug licensed in the USA for use in dogs with functional adrenocortical tumors. It will not shrink the tumor or prevent metastatic disease, but will control the clinical signs of HAC. The protocol for using trilostane is the same as that for PDHAC (see below).

Therapy for PDHAC

The standard approach for dogs with PDHAC in the USA is medical management. This method does not cure the disease, but instead controls the secretion of cortisol by the adrenal glands. Life-long therapy is necessary to maintain wellness and owners need to commit to close monitoring and diligent follow-up. Although medical therapy for PDHAC has not been shown to improve longevity, most practitioners feel that quality of life for both patient and owner is substantially improved when the disease is successfully managed.

The decision to treat a patient with PDHAC should be made after careful evaluation and discussion. Therapy may be complicated and expensive, and is only warranted in dogs with overt clinical signs or medical problems related to HAC (such as refractory hypertension, persistent / recurrent urinary tract infection or uncontrolled diabetes mellitus).

Several medical therapies have been used for PDHAC in dogs, including mitotane (o,p'-DDD: Lysodren[®]), L-deprenyl (selegiline: Anipryl[®]), and ketoconazole. Of these, only selegiline was approved for use in dogs, but efficacy appeared to be limited. In the last year however, trilostane (Vetoryl[®]) was approved by the FDA for use in dogs with Cushing's syndrome, and is rapidly becoming the treatment of choice.

Understanding trilostane

Trilostane is a synthetic steroid analogue, and is a competitive inhibitor of 3-beta hydroxysteroid dehydrogenase (3- β HSD). This enzyme plays a crucial role in the production of several adrenal cortical hormones; therapeutic concentrations of trilostane dramatically limit the production of cortisol. Although the production pathway for aldosterone is also dependent on 3- β HSD, the zona glomerulosa appears resistant to the effects of trilostane. The effect of trilostane is reversible and dose dependent. In contrast to mitotane, it is not directly toxic to adrenal cortical tissue.

It is administered orally, and peak levels occur about 2 hours after ingestion. Absorption appears to be somewhat erratic, but administration with food is recommended. The drug undergoes hepatic metabolism, and is cleared from the circulation within 18 hours.

Starting trilostane

It is essential to take the time to educate owners about HAC before starting trilostane therapy. They need to understand the possible complications associated with the drug. I

recommend providing clients with written information and detailed instructions describing what to expect and when to be concerned.

An adrenocorticotrophic hormone (ACTH) stimulation test does not need to be performed before starting trilostane, but may provide a useful comparison for results when on treatment.

Dosing interval: Although the manufacturers recommend once daily dosing, some clinicians feel that twice daily dosing provides better control. I personally advise caution with the twice daily protocols, as excessive suppression of the adrenal glands may be more likely. I reserve twice daily dosing for dogs with diabetes mellitus or those with clear evidence of 'escape' at the end of the day.

Dosing time: Trilostane should be given in the morning. Follow-up ACTH stim tests must be performed at specific times, and evening dosing confuses this issue.

Starting dose: This is based on body weight, but is influenced by capsule size. If a patient is close to the cut off, I will usually round the dose down. It is safer to start at a low dose and slowly increase as necessary.

The dose range is 2.2 – 6 mg/kg once daily. In my experience, most dogs are acceptably controlled on 3 mg/kg daily, and I would start close to this value.

Body weight	Starting dose
4.5 – 10 kg	30 mg
10 – 20 kg	60 mg
20 – 40 kg	120 mg
> 40 kg	120 – 240 mg

Client instructions: Tell the client to stop the drug if the dog seems unwell at all, and to call you immediately. If the animal vomits or is weak, seek ER assistance if necessary. I routinely send clients home with a small supply of prednisone, to be given at 0.5 – 1 mg/kg if the dog is 'blah'.

Monitoring trilostane

There are two reasons why monitoring is essential

- Avoid overdose
 - Hypocortisolemia
 - Hypoaldosteronemia
- Achieve adequate control of the HAC
 - Minimize clinical signs
 - Prevent morbidity
 - Thromboembolism
 - Hypertension
 - Infection

The first recheck visit should be 10 – 14 days after starting therapy. Many dogs are clinically responding at this time. An ACTH stim test should be performed, and as serum chemistry panel with electrolytes should be obtained.

There is a lot of controversy about the target post ACTH stim cortisol concentration. The manufacturers recommend a result between 1.5 and 9 ug/dl. However, many clinicians feel that a post-stim cortisol over 5.5 ug/dl indicates sub-optimal control.

The following table describes my personal preferences:

POST-ACTH STIM CORTISOL	DOSE ADJUSTMENT
< 0.7 ug/dl	Stop trilostane. Do not restart unless patient shows signs of HAC
0.7 – 1.5 ug/dl	Stop trilostane for 48 hours Restart at 50% of previous dose
1.5 – 5.5 ug/dl	Continue present dose
5.5 – 9.0 ug/dl	Consider a 50% increase in dose if patient shows signs of HAC
> 9.0 ug/dl	Increase the dose by 50 – 100%

Recent studies in Europe have suggested a simpler dosing plan, in which both the pre and post cortisol should be between 2 and 7 ug/dl. I think this idea has some merit, and have used this rule lately in my clinical practice.

Many clinics now have the ability to measure serum cortisol concentrations in-house. If so, you may be able to make some reliable decisions about dose adjustment using just the baseline cortisol concentration, in conjunction with a careful review of the patient's status. This system should only be used if

- The patient is well: eating and drinking and active
- The owner does not report any signs of HAC

RESTING CORTISOL	DOSE ADJUSTMENT
< 1.4 ug/dl	Perform an ACTH stim test
1.4 – 2.9 ug/dl	Continue present dose
2.9 - 5.5 ug/dl	Perform an ACTH stim test
> 5.5	Increase the dose by 50 – 100 %

My recommended monitoring schedule for trilostane is

- 10 – 14 days after starting therapy
- 4 weeks after starting therapy
- 14 days after any dose adjustment
- Every 3-4 months for the first year
- Every 6 months thereafter
- ANY time the patient is unwell (consider just a baseline cortisol first)
- If signs of HAC are noted

Clinical efficacy and studies

Several studies have evaluated trilostane in dogs with PDHAC. The efficacy is equal to that of mitotane, and survival times are comparable. Large numbers of dogs have been

treated with this drug in Europe and Australia, and it has been shown to have a consistent and predictable effect.

Serious adverse effects

Based on its pharmacology, irreversible adrenal compromise is not an expected negative effect. However, several dogs have suffered irreversible adrenal gland necrosis whilst on trilostane, and become permanently Addisonian. This is a concern, although awareness and prompt recognition make this a manageable side effect.

Acute adrenal necrosis was first reported in a dog soon after starting the medication. An adrenal gland was removed at surgery and found to be totally necrotic. Other cases have occurred following many stable months of therapy. Several mechanisms have been suggested, but it has been suggested that total suppression of adrenal cortical function is a contributory factor.

Summary

Trilostane is a useful new product for the management of canine HAC. However, treating dogs with HAC requires a thorough understanding of the disease and practitioners have a responsibility to understand how the drug works when prescribing it for their patients.

Managing hyperadrenocorticism (HAC): The Top Ten Questions

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1. Why should I treat a dog with HAC?

Although many dogs with HAC live for long periods without treatment, it seems clear that effective management markedly improves the quality of life for affected animals. Also, potential complications of the disease, such as pyelonephritis, pulmonary thromboembolism and hypertension are mitigated by treatment.

2. What diagnostics do I need to do before I start treating a dog with HAC?

Along with your confirmatory and differentiating tests, you should consider a full CBC, biochemical profile with electrolytes, urine analysis with culture, and blood pressure measurement. These tests will identify pre-existing and concurrent disorders which may need to be addressed.

3. I used the LDDST to confirm and differentiate PDHAC. Do I still need to do an ACTH stim test before starting Vetoryl^R?

An ACTH stimulation test is not essential for the diagnosis of HAC. However, many of us perform an ACTH stim test prior to starting medical therapy as we will use this test to monitor our treatment and make dose adjustments. In some cases, a pre-treatment ACTH stim test is useful for comparison.

4. Should I start my patient on prednisone when I begin Vetoryl^R?

No. With appropriate dosing and monitoring, the risk of hypocortisolemia with Vetoryl^R is small, so routine steroid support is not necessary. Also, we use our physical examination findings and patient clinical signs to assess the therapeutic response; prednisone will cause persistent abnormalities and may limit patient improvement.

5. Does it matter what time of day the Vetoryl^R is given?

Yes. There are two reasons why morning administration is recommended. Firstly, the drug is probably cleared from the body within 24 hours, so optimal control is achieved during the waking hours if the drug is given in the morning. Secondly, the timing of recheck ACTH stim tests is critical, and this is facilitated by morning administration.

6. I have read some reports recommending twice daily Vetoryl^R. Is it better to give this drug once or twice a day?

The drug manufacturer presently recommends starting patients on once daily dosing, and the dosing chart provided is based on this premise. In some circumstances, a switch to twice daily dosing may be appropriate, but this should be done with caution. Bear in mind that the total daily dose for dogs on twice daily medication may be less than for those on a once daily regimen.

7. When should I recheck my patient after starting Vetoryl^R?

Dogs should be rechecked within 10 to 14 days of starting Vetoryl^R. A recheck evaluation should include a history, physical examination and ACTH stim test (initiated 4 hours post morning dosing). If the patient is at all unwell, serum electrolytes should be checked, and many clinicians routinely perform a chemistry panel with electrolytes at every visit.

Additional rechecks should be performed 10 -14 days after dose adjustments and at 30 days and 90 days after the effective dose has been determined. Quarterly checks are recommended for the long term.

8. If my patient is doing well at home, do I really need to do an ACTH stimulation test on the recheck visits?

An ACTH stimulation test is the best way to evaluate adrenal gland function when patients are receiving Vetoryl^R. Regular ACTH stimulation tests let us identify patients who are either over-dosed or under-dosed before problems occur.

9. Why should I check electrolytes if my patient feels unwell?

A rare but serious side effect of Vetoryl^R is complete hypoadrenocorticism (Addison's disease), characterized by a severe deficiency of both cortisol and aldosterone. This is usually reversible, but may be permanent. If a dog is becoming Addisonian, the serum sodium levels will be subnormal and serum potassium concentrations will increase. This requires immediate discontinuation of the drug and aggressive supportive care.

10. I have a patient with HAC and diabetes mellitus. Which disease should I treat first?

You need to address both issues concurrently. Diabetic dogs with HAC are generally very insulin resistant, and need high doses to prevent ketosis. Optimal regulation of these patients is essentially impossible until the HAC is effectively addressed, but exogenous insulin therapy is still life-saving.

It is important to realize that the insulin dose may need to be rapidly reduced as the HAC is managed. Insulin resistance will diminish, putting the patient at risk of hypoglycemia. Careful patient monitoring and effective client education are essential in these cases.

Diagnosing hyperadrenocorticism (HAC): The Top Ten Questions

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1. When should I test a dog for HAC?

Most veterinarians with an interest in HAC only pursue this diagnosis if one of these three criteria is satisfied:

- The client presents the pet with a complaint related to HAC
 - e.g. excessive thirst, urinary accidents, ravenous appetite, panting, skin disease.
- There is a strongly clinical index of suspicion for HAC, based on
 - Physical examination findings
 - Patient history
 - Laboratory abnormalities
 - Concurrent medical disorders
 - Recurrent or persistent urinary tract infection
 - Refractory hypertension
 - Insulin-resistant diabetes mellitus
 - Thromboembolic disease

2. What laboratory abnormalities are expected in dogs with HAC?

The CBC should demonstrate a stress leukogram, with a mature neutrophilia and monocytosis. The red cell count is expected to be normal or slightly increased. An increase in platelet numbers is commonly noted.

The chemistry panel usually indicates an increase in ALP activity and hypercholesterolemia. Modest increases in alanine amino transferase (ALT) activity may be noted in some patients, but the value rarely exceeds twice the upper limit of the normal range. Blood urea nitrogen may be slightly decreased.

Most dogs with HAC have dilute urine, and hyposthenuria (specific gravity <1.008) is commonly noted.

3. Should I test for HAC if a dog has an elevated alkaline phosphatase (ALP) activity but no other abnormalities?

No. Many older dogs have elevated ALP activity but are still clinically normal. There are several reasons for increased serum ALP, including drug-induced, breed-related, idiopathic vacuolar hepatopathy and hepatobiliary disease.

4. What is the best way to diagnose HAC?

Unfortunately, we do not have a single definitive test for HAC in dogs. All the current confirmatory tests (e.g. ACTH stimulation test, low-dose dexamethasone suppression test, urine cortisol:creatinine ratio) have limitations and do not have perfect sensitivity and specificity. If you feel strongly that a patient has HAC, you may need to perform more than one test to confirm the diagnosis.

The current consensus suggests that the LDDST may be the most appropriate confirmatory test in both dogs and cats. However, both false positive and false negative results are possible.

5. When should I perform a urine cortisol :creatinine ratio?

This is a screening test for HAC with a very high negative predictive value. This means that a normal ratio essentially excludes the diagnosis. A positive result supports HAC but a more specific test, such as the LDDST, is needed to establish the diagnosis. This test is a good choice if you have a low index of suspicion for the disease.

As stress of any kind will increase urine cortisol concentrations, it is best to run this test on a urine sample collected at home.

6. If my ACTH stim test or LDDST indicates HAC, do I need to do anything else before starting treatment?

Yes. There are two kinds of HAC: most dogs (85%) have pituitary-dependent disease (PDH), but some dogs have a functional adrenocortical tumor (AT). It is essential to differentiate between these two kinds of HAC, as management options are different. The LDDST sometimes indicates PDHAC, but the ACTH stimulation test does not differentiate between the two kinds.

Consequently, a differentiating test is usually needed. Generally, the best options are abdominal ultrasonography or measurement of endogenous ACTH concentrations. Alternatively, a high-dose dexamethasone suppression test may distinguish between the two types. However, some dogs with PDH fail to suppress on a HDDST and further testing may be needed to establish a definitive diagnosis.

7. Do any medications affect adrenal function tests?

Yes. Many synthetic steroids will cross react with commercial cortisol assays. Consequently, cortisol levels may be falsely elevated. Prednisone, prednisolone,

methylprednisone, prednisone sodium succinate and hydrocortisone are all measured by serum cortisol assays. Dexamethasone does not cross react. It is always advisable to withhold all exogenous steroids (including topical products) for at least 24 hours before trying to evaluate the pituitary-adrenal axis and adrenal gland function.

8. Do I have to perform an abdominal ultrasound examination as part of the diagnostic work-up for HAC?

An abdominal ultrasound scan, performed by a competent individual on an up-to-date machine can provide very useful information about adrenal gland shape, size and symmetry. If your differentiating test confirms PDHAC, a scan may not be necessary. However, if an AT is suspected, an ultrasound scan is highly advisable.

If you do not have easy access to quality ultrasonography, a lateral abdominal radiograph should be considered. About 50% of adrenal tumors become calcified, and can be identified on a plain radiograph.

9. I have a patient who looks Cushingoid, but my ACTH stim test was subnormal, with a post cortisol < 5.0 ug/dl. Does this dog have Addison's disease?

No. In a patient who appears to have HAC, a 'flat-line' ACTH stim test is most consistent with adrenal gland atrophy due to exogenous steroid administration. Question the client carefully about any recent medication use, including topical products.

10. I have a patient how looks Cushingoid, but all my routine pituitary-adrenal function tests are unremarkable. What should I do next?

This patient may have atypical Cushing's syndrome. This is a disorder in which the adrenal glands secrete excessive amounts of a precursor to cortisol. An extended adrenal panel, looking at pre and post ACTH concentrations of the precursor and sex hormones may help you establish this diagnosis.

Trouble-shooting hyperadrenocorticism (HAC): The Top Ten Questions

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1. My client forgot to give Vetoryl^R this morning. What should she do?

If it is more than 6 hours after the dose was missed, simply wait until the next morning and get back on the regular schedule. If it has been less than 6 hours, go ahead and give the missed dose immediately and continue as usual tomorrow.

2. My client accidentally gave a double dose of Vetoryl^R. What should she do?

A single small overdose is unlikely to cause major problems, but the dog may show signs of hypocortisolemia, namely lethargy, anorexia and GI upset. Administration of oral prednisone (0.1 mg/kg daily) for 2 days should prevent any clinical signs. Vetoryl^R can then be re-started at the usual dose.

3. My client accidentally gave a dose of Vetoryl^R to the other dog in the household. What should she do?

Based on laboratory toxicity studies, a single dose of up to 6.7 mg/kg should be safely tolerated by a healthy dog.

4. Can I give Vetoryl^R to a dog with liver or kidney disease?

The manufacturers do not recommend using this product in dogs with liver or kidney disease. In addition, it should not be used in dogs receiving potassium sparing diuretics (e.g., spironolactone) and should be used cautiously in dogs receiving angiotensin converting enzyme inhibitors (e.g., Enalapril).

5. I want to switch a patient from mitotane to Vetoryl^R. How should I do this?

The product insert recommends a one month break from mitotane before starting Vetoryl^R and an ACTH-stimulated cortisol > 9.0 ug/dl. However, many dogs show clinical signs of Cushing's syndrome shortly after discontinuing mitotane, and an ACTH stimulation test may be performed sooner if this occurs.

6. I have a patient with PDHAC and neurologic signs. Will Vetoryl^R control problems arising from an enlarging pituitary mass?

No. Vetoryl^R works at the level of the adrenal gland to limit cortisol production. It does not limit ACTH release by the pituitary tumor and not will not prevent or mitigate neurologic problems in dogs with macroadenomas. Adjunctive radiation therapy may be an appropriate choice for this patient.

7. I have a patient with an adrenal tumor. If I give Vetoryl^R prior to surgery, will the mass get smaller?

No. Vetoryl^R has not cytotoxic effects on adrenal tumors. It will not shrink the mass or prevent metastatic spread. However, Vetoryl^R does effectively control the clinical signs of HAC in these patients, and is licensed for use in dogs with adrenal tumors. Surgery is the optimal approach in these cases, but Vetoryl^R should be considered if the mass is inoperable or if other factors make surgery a poor choice.

8. Can I break open the Vetoryl^R capsule and mix it with food?

No. Capsules should not be opened or emptied. Intact capsules should be given with food.

9. I recently rechecked a dog on Vetoryl^R. The post ACTH stim cortisol concentration was lower than the pre value. What does this mean?

There are several explanations for discordant results, i.e., those in which the baseline cortisol is greater than the post-ACTH value. These include laboratory error, mislabeling of samples in the clinic, interference by exogenous steroids, and use of an ineffective ACTH product.

If the patient is clinically well and both results are between 2 - 5.4 ug/dl, it is appropriate to continue Vetoryl^R at the present dose and recheck as usual. If both values are below 2 ug/dl or above 7.5 ug/dl, or if the dog is not clinically normal, the test should be repeated as a dose adjustment may be necessary.

10. Can I use Vetoryl^R in a cat with HAC?

Vetoryl^R is not licensed for use in cats. As feline HAC is an uncommon and complicated disorder, consultation with a specialist (e.g., Dip ACVIM) is warranted.