

Tips on Diagnosis and Treatment of Canine Hyperadrenocorticism

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Urine Cortisol to Creatinine Ratio:

Pros: Excellent screening test. A negative result makes the presence of hyperadrenocorticism highly unlikely (98% sensitivity).

Cons: A positive result is suspicious for hyperadrenocorticism (HAC) but frequent false positive results occur (some due to stress). Due to this poor specificity, further testing to substantiate HAC is needed.

Tip: The urine should be obtained by the owner at home, ideally from the first morning urination by free catch. This reduces the likelihood of stress causing a false positive result.

The test is not accurate as a monitor of therapy.

Low Dose Dexamethasone Suppression Testing:

Pros: One of the most sensitive tests for HAC (up to 97% sensitivity). Fewer false negative results. Less expensive than an ACTH stimulation test.

Cons: In 2 studies of dogs with non-adrenal illness that were tested with a LDDST, false positive results were found in 38% and 56% (poor specificity in sick dogs). Multiple samples needed in an 8 hour time period.

Tip: Up to 65% of the time, the LDDST will also differentiate pituitary dependent HAC from an adrenal tumor. If the 8 hour level is above 1.5 ug/dl, the test is positive for HAC. If the 8 hour sample is diagnostic for HAC, a drop of 50% from the baseline level (4 or 8 hours) or a 4 hour level under 1.5 ug/dl is diagnostic for pituitary dependent HAC (PDH).

Avoid any stress during the procedure to reduce false positive results.

High dose dexamethasone suppression test:

Used to differentiate between pituitary dependent disease and adrenal tumors.

Tip: Up to 25% of PDH patients will not suppress. Virtually all adrenal tumors will suppress. With lack of suppression another discriminatory test should be performed (endogenous ACTH level, ultrasound, CT scan).

Atypical Hyperadrenocorticism:

Tip: In patients where clinical signs, physical exam findings and biochemical testing are strongly suspicious for HAC and standard diagnostic testing is negative, consider obtaining pre and post ACTH stimulation testing levels of sex steroid hormones including androstenedione, estradiol, 17-hydroxyprogesterone, and progesterone. These samples can be sent to the University of Tennessee.

If the estradiol level is the only sex steroid that is elevated on the Tennessee hormone panel, consider independently verifying the elevation at another laboratory. We have run a small number of paired samples and found a discrepancy between levels at Tennessee and labs at Cornell and UC Davis. A repeat stimulation test is not required.

Several options are available for conservative treatment of the atypical form if there is symmetrical adrenal size. The endocrinology laboratory at Tennessee typically will suggest treatment with melatonin and flaxseed oil with lignins. Other options include standard lysodren therapy, low dose lysodren therapy and trilostane therapy. The Tennessee lab also suggests that sex steroid levels may actually increase with trilostane treatment, however no specific trials of any of the drugs have been performed. At VSH, we have had several cases that have had a minimal response to melatonin and flaxseed oil but have responded well clinically to trilostane therapy.

Canine Cushing's Syndrome

Syndrome - definition

A group of clinical signs that collectively indicate or characterize a disease or other abnormal condition.

Tip:

Don't treat the diagnosis. Treat the clinical signs. In asymptomatic or mildly symptomatic animals treatment is not a requirement. There is no well established improvement in survival time with or without treatment. In cases where there is a life threatening problem, such as recurrent thromboembolism, recurrent pancreatitis or recurrent infection then treatment should be considered.

Trilostane Therapy (Vetoryl®):

Trilostane is an orally active steroid analogue that is a competitive inhibitor of the 3- β hydroxysteroid dehydrogenase enzyme system. This enzyme mediates the conversion of pregnenolone to progesterone, a precursor of cortisol as well as aldosterone and androstenedione, effectively inhibiting their production. The drug has recently been approved by the FDA and is now easily obtainable.

Pros: Reversible inhibition of steroid synthesis which allows finer control of steroid production with a lower frequency of side effects compared to Lysodren®. Side effects are usually minimal with trilostane, typically with no abnormalities noted. Occasionally there is a slight reduction in activity or lethargy noted during the first week of therapy.

Cons: Requires daily lifelong therapy (sometimes twice and rarely three times daily). Costly, \$1.62 for a 60 mg capsule. The major side effect of iatrogenic hypoadrenocorticism is possible (but rare), and in a small number of cases has been irreversible.

Tips: Some dogs will be controlled based on ACTH stimulation test results (exactly the same control levels targeted with Lysodren®), yet still have persistent clinical signs. In these dogs, consider increasing the dosage interval to BID. Very occasionally TID

dosing may be required. If you are increasing to BID or TID dosing then step back and review the case, making sure you are confident of your diagnosis.

Remember to repeat the ACTH stimulation test 10-14 days after every increase or decrease in dose.

Timing is important, with the ACTH stimulation test performed ideally 4-6 hours post pill. The medication should be given with food to enhance absorption.

Lysodren Therapy (Mitotane®):

Mainstay of therapy for PDH, a toxin selectively targeting the adrenal cortical layer producing sex steroids and corticosteroids, and to a lesser extent mineralocorticoids.

Pros: Less expensive than trilostane over time. Typically only requires once or twice weekly dosing after the initial loading phase.

Cons: High frequency of major and minor complications. In one large study, complications occurred in 25% of 200 cases, with 5% having iatrogenic Addison's disease requiring long term glucocorticoid and mineralocorticoid supplementation. The loading dose is different for each patient and loading can take as little as 3 days or as long as 21 days.

Tips: The most accurate indicator of adequate control during Lysodren loading is the point where water intake normalizes in those patients that are PU/PD. Consider having the owner quantitate water intake before and follow that intake daily during loading. The point where intake normalizes (< 60 ml/kg per day), stop the Lysodren and repeat the ACTH stimulation test. Normalization of appetite (if polyphagia was present) is the second most accurate indicator of control.

Good control is the point where the gland has minimal stimulation. The target cortisol concentration is 1-5 ug/dl of both the pre and post ACTH stimulation test.

Even when good control is attained, repeat ACTH stimulation testing is required as the drug induces its own metabolism over time and dose adjustment is often required.