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Diagnosis and Therapy of Hyperadrenocorticism in the Dog

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KEY POINTS

Dogs chronically exposed to excess cortisol develop a classic combination of dramatic clinical signs and lesions. These common signs include polydipsia, polyuria, polyphagia, abdominal enlargement, alopecia, pyoderma, panting, muscle weakness, and lethargy. It must be remembered, however, that not all dogs with hyperadrenocorticism develop the same signs. From this long list of potential signs (plus others), most dogs exhibit several (but not all) of these problems. Hyperadrenocorticism is a clinical disorder, and animals afflicted with this disease have some of the associated clinical signs or the diagnosis must be questioned. The signs are the sequelae of the combined gluconeogenic, lipolytic, protein catabolic, anti-inflammatory, and immunosuppressive effects of glucocorticoid hormones on various organ systems.

The course of the disease is insidious and slowly progressive. Owners usually report observing some alterations typical of hyperadrenocorticism in their pet for 6 months to as long as 6 years before they seek veterinary attention for their animal, since these changes are quite gradual in onset and are often believed to be a result of simple "aging." It is only when the signs become intolerable to the client or after alterations are specifically pointed out by people who see the pet infrequently that veterinary opinions are sought.

Physical Examination

The physical examination on a typical "Cushing's" dog reveals an animal that is stable, hydrated, has good mucous membrane colour and is not in distress. Veterinarians will usually observe, during the physical examination, many of the signs seen by owners. Among these abnormalities are abdominal enlargement (truncal obesity), panting, bilaterally symmetrical alopecia, skin infections, and comedones. Hyperpigmentation, testicular atrophy, and hepatomegaly are commonly identified on physical examination. Ectopic calcification (calcinosis cutis), clitoral hypertrophy, and easy bruisability are much less common. There is, however, remarkable variation in the number and severity of abnormalities noted. These dogs may have a single dominant sign or 10 signs.

Laboratory Abnormalities

A. Haematology

1. mild haemoconcentration
2. stress leucogram (mature neutrophilia, eosinopaenia, monocytosis, lymphopaenia)

B. Biochemistry Profile

1. increased Alkaline Phosphatase (AP) – steroid induces isoform and hepatic isoform
2. increased Alanine Aminotransferase (ALT) – due to fatty liver
3. hypercholesteraemia
4. mild to severe Hyperglycaemia (sometimes concurrent Diabetes mellitus)
5. electrolytes tend to be within normal limits

C. Urinalysis

1. low specific gravity (hypostenuric or isostenuric)
2. bacteriuria without pyuria
3. proteinuria
4. glucosuria (if concurrent Diabetes mellitus)

D. Abdominal Radiographs

1. hepatomegaly
2. enlarged bladder
3. calcified soft tissue (sometimes also adrenal gland)
4. pendulous abdomen
5. sometimes calcinosis cutis seen

"Screening" Tests

After establishing a presumptive diagnosis of canine hyperadrenocorticism from review of owner observation, physical examination, and laboratory data base, one usually proceeds to attempt confirmation of the diagnosis. When necessary, and if possible, an attempt can also be made to determine whether the dog has pituitary-dependent hyperadrenocorticism (PDH) or an adrenocortical tumour (ACT). Choosing a screening test for Cushing's syndrome is important because that test result may determine whether or not a dog is treated. Routinely used screening tests include ACTH stimulation, low dose dexamethasone, and the urine cortisol: creatinine ratio. The decision to treat a dog for Cushing's syndrome should never be based solely on laboratory information. Cushing's syndrome is a clinical disorder with clinical signs. If a dog has no clinical signs of Cushing's syndrome, we do not recommend treatment. This concept gains importance when it is understood that no screening test is correct all of the time, i.e., sensitivity and specificity is never 100% for any test. Many dogs with nonadrenal disease and many with polyuria/polydipsia syndrome have false-positive screening test results for hyperadrenocorticism. Because false-positive test results have been observed with any commonly used screening test, the definitive diagnosis of Cushing's syndrome should never be solely on screening test results, especially in dogs without classical clinical signs or in those with known nonadrenal disease.

A. Low Dose Dexamethasone Screening Test (LDDST)

1. obtain serum for cortisol at 0, 4 and 8 hours
2. administer 0.01 mg/kg dexamethasone
3. the 8 hour plasma cortisol is used as a screening test for hyperadrenocorticism,
4. test has good sensitivity (95%) but low specificity (70%)
5. the 4 and 8 hour values may be used to discriminating PDH from ACT

B. ACTH Stimulation Test

1. obtain serum for cortisol at 0, 1 hours (if ACTH-gel is used, take second sample at 2 hours)
2. administer ACTH (synthetic ACTH intravenously, ACTH-gel intramuscularly)
3. test has moderate sensitivity (85%) and moderate specificity (85%)
4. test can not discriminate between PDH from ACT (but can diagnose iatrogenic Cushing's)
5. 50% of dogs with ACT have negative test result

C. Urine Corticoid : Creatinine Ratio (UCCR)

1. have owners collect morning urine samples (home collected!) to analyse UCCR
2. test has good sensitivity (98%) but low specificity (65%)
3. test can not discriminate between PDH from ACT

D. Plasma 17-Hydroxyprogesterone (17-HO-P)

1. obtain serum for 17-OH-O at 0, 1 hours
2. administer ACTH (as for ACTH stimulation test)
3. test might diagnose dogs with "atypical Cushings"
4. sensitivity and specificity is less than with ACTH Stimulation test

Discrimination Tests

A. Endogenous ACTH

This test is relatively difficult to perform because the plasma must be handled with care, the test is not routinely available, and it is expensive. However, it is highly specific and sensitive

B. High Dose Dexamethasone Suppression Test (HDDST)

1. obtain serum for cortisol at 0, 4 and 8 hours
2. administer 0.1 mg/kg dexamethasone
3. dogs with ACT have no suppression (but similarly, some dogs with PDH have no suppression),

C. Abdominal Ultrasonography

In dogs suspected as having hyperadrenocorticism, abdominal ultrasonography serves three major functions. First, it is part of the "routine data base" utilized to evaluate the abdomen for any unexpected abnormalities (urinary calculi, masses, etc.). Second, the study is used to evaluate the size and shape of the adrenals. If bilaterally normal-sized or large adrenals are visualized in a dog otherwise diagnosed as having Cushing's, this is considered strong evidence of adrenal hyperplasia due to PDH. If one, large, irregular and/or invasive adrenal is visualized and the opposite is not seen, adrenal tumour must be suspected. Third, if an adrenal tumour is identified, ultrasound is an excellent screening test for hepatic or other organ metastasis, compression of adjacent tissues by a tumour, or tumour invasion into the vena cava or other structures. It must be emphasized that interpretation of abdominal ultrasonography is completely operator dependent. The more experienced and competent the radiologist, the more specific, sensitive and reliable the findings. Adrenal size is best determined

using the width of the left adrenal (7.5 mm represents the upper limit of normal). This parameter had a sensitivity of 81% and a specificity of 100% in detecting adrenal enlargement in dogs with hyperadrenocorticism.

TREATMENT OPTIONS

Pituitary-dependent hyperadrenocorticism

Surgical management

- A. Bilateral adrenalectomy
 1. Technically difficult
 2. Poor surgical/anesthetic risk
 3. Permanently hypoadrenal and require lifelong replacement therapy
- B. Hypophysectomy
 1. Technically very difficult
 2. Lifelong therapy with thyroid hormone and prednisone necessary

Medical therapy

- A. Lysodren (o,p'-DDD)
 1. Selective necrosis of adrenal cortical cells producing cortisol (zona fasciculata and reticularis)
 2. Zona glomerulosa usually spared maintaining aldosterone secretion
 3. Side-effects (35-40%) (Vomiting, Anorexia, Lethargy, Diarrhoea, Neurologic signs, Addison's disease (< 5 %))
 4. two treatment protocols (maintenance and ablation)

Treatment Protocol for Initiating Lysodren Therapy

1. Owners assess water consumption and appetite at home for 3-5 days.
2. Begin Lysodren at 25 mg/kg PO q12h.
3. When water consumption or appetite starts to decrease or following seven consecutive days of therapy (which ever occurs first) the medication is discontinued and an ACTH response test is performed.
4. If an adequate response to therapy is seen (pre and post cortisol within the resting range) maintenance therapy is begun. If an adequate response has not been seen, daily therapy is continued until clinical signs improve or for an additional 7 days and another ACTH stimulation test is performed.
5. If adverse reactions are noted at any time during therapy (reduction in appetite, anorexia, vomiting, diarrhoea) therapy should be discontinued and the animal brought in as soon as possible for evaluation. Electrolytes, BUN, and an ACTH stimulation test should be performed. If the animal can not be brought in within the next 12-24 hours, replacement doses of steroids (0.25 mg/kg/day of prednisone) are started and the animal is seen at the earliest possible time. Owners should have 5 mg prednisone tablets at home for emergency use.

Maintenance Therapy

1. Lysodren is given at 50 mg/kg once a week or divided twice a week.
2. Watch for clinical signs of returning hyperadrenocorticism.
3. ACTH stimulation test in 4 weeks then every 3-4 months.
4. Electrolytes every 3-4 months. Even though the zona glomerulosa is fairly resistant to the effects of o,p'-DDD, mineralocorticoid deficiency can occur.
5. Therapy is life-long.

Ablation protocol

In this protocol, Lysodren is administered at 100 mg/kg/day divided BID for 30 days. Supplemental cortisone acetate (2 mg/kg divided BID) and fludrocortisone tablets (0.1 mg/10kg BW once a day) are begun beginning on day 3 of Lysodren therapy. The diet is supplemented with 1-5 grams of NaCl per day. One week after the induction phase with o,p'-DDD, the dose of cortisone is reduced to 1 mg/kg/day. Electrolytes and an ACTH stimulation test are performed at the end of the induction period, every six months, and at any time the animal demonstrates signs compatible with either hyperadrenocorticism or hypoadrenocorticism. While this form of therapy may be effective in the management of canine hyperadrenocorticism, it does require close patient monitoring and life-long daily therapy. Close attention must be paid to these animals during times of stress and episodes of non-adrenal illness.

B. Ketoconazole (Nizoral)

1. Inhibits adrenal enzymes responsible for the synthesis of cortisol. Enzymatic inhibition is reversible.
2. No effect on aldosterone
3. Does not destroy adrenal tissue
4. Can be used for both PDH and AT

5. Side-effects (Anorexia, Vomiting, Increased liver enzymes, Lightening of hair coat)
6. Dosage:
 - a. 10-15 mg/kg BID
 - b. Assess response to therapy with ACTH stimulation tests just as with Lysodren
 - c. Daily therapy must be maintained
7. Indications:
 - a. Animals not able to tolerate Lysodren
 - b. Animals non-responsive to therapy with Lysodren
 - c. Pre-operative stabilization prior to adrenalectomy (4-6 weeks)
 - d. Palliative therapy in animals with metastatic adrenal tumors
 - e. Effective in approximately 50% of patients

C. I-Deprenyl

1. I-Deprenyl is not effective in treating dogs with hyperadrenocorticism and can not be recommended

D. Trilostane

Trilostane is a synthetic, orally active steroid analogue. It can act as a competitive inhibitor of the 3 β hydroxysteroid dehydrogenase enzyme system and thereby inhibit the synthesis of several steroids, including cortisol and aldosterone. This blockade is reversible and seems to be dose-related.

Clinical trials: Besides various abstracts showing short and long term efficacy and safety of trilostane for canine PDH, canine adrenal-dependent HAC and equine Cushing's syndrome, there have been four controlled studies with a total of 180 dogs so far investigating the effect of trilostane in canine PDH (Neiger et al 2002, Ruckstuhl et al 2002, Braddock 2002, Melville-Walker 2002).

Trilostane was found to be effective in resolving the signs of HAC in most dogs. In three studies polyuria/polydipsia resolved over the first six months (mostly within the first 1-2 months) in 116 of 127 dogs (91%) while polyphagia resolved in 68 of 84 dogs (81%). These improvements were maintained as long as the dogs remained on adequate doses of trilostane. None of the 11 dogs was lost during the study period of 6 months by Ruckstuhl et al (2002). In the other 3 studies, lasting between 180 days and a mean of 384 days and 549 days, respectively, three were lost, in six trilostane was withdrawn due to perceived adverse effects and 36 were euthanised or died. The mean survival of all trilostane treated dogs in one long-term study was 661 days.

Trilostane caused a significant reduction in both the mean basal and post-ACTH cortisol concentrations after 10 days of treatment in all four studies. The post ACTH cortisol concentration decreased to less than 250 nmol/l in 81% of dogs within one month and in another 15% at some time whilst on treatment in one study. These improvements were maintained in the study population for the duration of the trial. Well controlled post ACTH cortisol (= 75 nmol/l) or acceptable controlled post ACTH cortisol (= 125 nmol/l) concentration was reached in 7 and 5 of 30 dogs, respectively, after 10 days but could be obtained by increasing the trilostane dose in 20 and 3 of 29 dogs, respectively, after 180 days. In one study with close observation of haematology and biochemistry values, there was significant decreases noted in cholesterol, ALP and ALT but 28 dogs still had ALP levels above the reference range after six months of treatment. A significant decrease in sodium and significant increase in potassium were documented during the study with potassium above the reference range in 34 dogs during the study. The sodium:potassium ratio was less than 24 on 24 occasions. Hyperkalaemia was never treated in any of these incidences.

Trilostane starting dose was in all four studies around a mean of 6 mg/kg. During the first 180 days, over 50% of all dogs had a change in dose, mostly an increase, resulting in a final dose of between 6.1 and 11.4 mg/kg in three studies. With a markedly lower post ACTH cortisol concentration as target, the final trilostane dose was much higher at a mean of 18.1 mg/kg (range 5.3 to 48.7 mg/kg).

Trilostane seems to be well tolerated by most dogs. However, mild, self-limiting side effects such as diarrhoea, vomiting and lethargy were noted by 63% of owners in one study. Acute death was described in two dogs shortly after starting therapy (2 and 4 days) and another two developed signs and biochemical evidence of hypoadrenocorticism. One of these dogs recovered with appropriate therapy. The other died despite withdrawal of trilostane and administration of appropriate therapy. In two dogs on trilostane, an adrenal necrosis was found on histopathology in a subsequent report and anecdotal incidents of acute death shortly after starting trilostane have been seen (Reusch, Neiger, Hörauf, personal communications).

Subsequently it has been demonstrated that the effects of trilostane on basal cortisol concentrations are short lived (less than 20 hours) in most dogs with hyperadrenocorticism. Furthermore there are significant differences between the cortisol responses in ACTH stimulation tests performed at 4 and 24 hours post dosing. Ultrasonographically, there is a significant increase in adrenal gland size in response to therapy. This may be as a result of an increase in endogenous ACTH during therapy.

Current Recommendations For The Use Of Trilostane In Dogs

Many aspects of trilostane use in canine HAC are still under investigation and the following recommendations are therefore likely to change. Veterinarians unfamiliar with the use of the drug should consult manufacturers for up to date information.

Preparations, storage and handling

Trilostane has been available in 60 mg capsules in the UK since late 2001 as Vetoryl® (Arnolds Pharmaceuticals, Crawley, Surrey, UK). It is also available in 60 mg and 120 mg capsules approved for human use as Modrenal® (Wanskerne Ltd, Billingshurst, West Sussex, UK). With very small dogs, capsules might need to be split into smaller gelatine capsules. Trilostane capsules should be stored at room temperature in airtight, light-resistant containers. Pregnant women should wear gloves when handling the drug and all users should wash their hands after handling the capsules.

Dosage and administration

The optimal dose rate and frequency interval for the treatment of canine HAC are not yet known. The current suggested starting dose rate for dogs with PDH is 5-10 mg/kg once daily. This needs to be adjusted according to clinical signs and serum cortisol values. Doses up to 40-50 mg/kg (divided twice daily) have been given with no unwanted side effects. In some dogs twice daily dosing may be necessary. The drug is given with food.

Cautions and drug interactions

In dogs only minor side effects are commonly seen such as mild lethargy and decreased appetite 2-4 days from start of therapy (potentially due to steroid withdrawal syndrome) and mild electrolyte abnormalities. Overt hypoadrenocorticism seems to be a rare event despite the marked decrease in serum cortisol values found shortly after trilostane dosing.

As trilostane can cause hyperkalemia through its aldosterone inhibiting effect it is advised to use caution if given together with a potassium-sparing diuretic. No unwanted drug interactions have been seen in dogs on trilostane together with several non-steroidal anti-inflammatory drugs, various antibiotics, insulin and levothyroxine.

Monitoring

It is important to monitor the clinical and biochemical effects of therapy and to adjust the trilostane dose to achieve optimal control. Dogs are re-examined and an ACTH stimulation test is performed at 10 to 14 days, 30 days and 90 days after starting therapy. It is important that all ACTH stimulation tests are performed 4 to 6 hours after trilostane administration and interpreted in the light of the history and the findings of a thorough physical examination. If the post ACTH cortisol concentration is less than 20 nmol/l then trilostane is stopped for 48 hours and re-introduced at a lower dose. If the post ACTH cortisol concentration is more than 200 nmol/l then the dose of trilostane is increased. If the post ACTH cortisol concentration is between these two values and the patient appears to be clinically well controlled then the dose is unaltered. If however the post ACTH cortisol concentration is between these two values and the patient appears not to be clinically well controlled then the trilostane may need to be given twice daily.

Once the clinical condition of the animal and the dose rate has been stabilised then dogs should be examined and an ACTH stimulation test performed every 3 to 6 months. Serum biochemistry (especially electrolytes) should be performed periodically to check for hyperkalaemia.

Radiation therapy

A. Used to treat pituitary macroadenomas

B. Good results in reducing tumour size and decreasing neurologic signs, but frequently poor results on controlling excess tumour secretion of ACTH so medical therapy is still needed.

Adrenal dependent hyperadrenocorticism

1. Adrenalectomy

a. Treatment of choice. Unfortunately, adrenal tumours, even benign ones, can be very large, highly vascular, and locally invasive (vena cava, aorta, kidney). If you are considering surgical therapy consider referral to someone who does these often and who has the ability to determine extent of disease prior to surgery (CT, ultrasound, angiography). Always remember the goal of therapy is to alleviate clinical signs.

b. Submit all tissue for histopathology and prognosis. 50% of adrenal tumours are malignant and carry a poor prognosis.

- c. Intra and post-operative care is critical to survival!!
 - d. Begin supraphysiologic doses of glucocorticoids during surgery and for the first few days after recovery. The dose is gradually tapered over 4-6 weeks.
2. Lysodren
- a. Responses can be achieved albeit at higher dosages than normally considered for PDH
 - b. Induction protocol is the same as for PDH
 - c. May require 100-200 mg/kg/day to obtain remission. Maintenance therapy is then started using the effective daily induction dosage given once or twice a week.
 - d. When used in this fashion you are using Lysodren as a chemotherapeutic drug and the goal is to wipe out all adrenal tissue thereby inducing both glucocorticoid and mineralocorticoid insufficiency
3. Trilostane
- a. use in exactly same way as in PDH (with excellent success).

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