Diagnosis and Treatment of Hyperadrenocorticism in Dogs
David Bruyette, DVM, DACVIM

1. Introduction

A. Cushing's syndrome refers to all causes of hyperadrenocorticism with overproduction of cortisol.

1. ACTH-dependent

A. Cushing's disease: Pituitary hypersecretion of ACTH which results in bilateral adrenal hyperplasia (90% of cases)

B. Ectopic ACTH production: Non-pituitary tumors secreting ACTH resulting in bilateral adrenal hyperplasia. Has not been completely documented in dogs or cats.

2. ACTH independent

A. Adrenocortical adenoma or carcinoma: Hypersecretion of cortisol with atrophy of normal adrenal and suppressed ACTH concentrations (10% of cases).

3. Iatrogenic

A. Excessive or prolonged administration of glucocorticoids. Clinically indistinguishable from natural disease. Results in adrenal atrophy and suppressed ACTH levels.

2. Signalment

A. Poodles, Dachshunds, Schnauzers, Boston Terriers, Boxers.

B. Middle to old age. Average 12 years; range 6 months to 17 years.

C. No sex predilection.

D. Rare in cats. Usually seen with insulin resistant diabetes mellitus and/or cats with severe dermal atrophy/ulceration.

3. Clinical Signs

A. PU / PD

B. Pendulous, "pot-bellied abdomen": Due to muscle catabolism by glucocorticoids and hepatomegaly.

C. Bilaterally symmetric alopecia: Head and extremities spared.

D. Thin skin

E. Muscle weakness and muscle atrophy; cruciate ruptures

F. Mineralization of skin (calcinosis cutis)

G. Hyperpigmentation: ACTH similar to MSH, co-existing hypothyroidism, chronic skin irritation.

H. Reproductive abnormalities

1. Anestrus

2. Clitoral hypertrophy

3. Testicular atrophy

4. Perianal adenomas in females and neutered males.

I. Respiratory signs

1. Panting: Pulmonary hypertension and decreased compliance, primary CNS disturbance, pulmonary mineralization.

2. Dyspnea: Rare; seen with pulmonary thromboembolism and concurrent congestive heart failure.

J. Central nervous system

1. Seen with large pituitary tumors (macroadenomas). Present at time of diagnosis or following therapy for Cushing's disease as microscopic pituitary tumors enlarge into macroadenomas.

2. Signs due to compression/invasion of pituitary and/or hypothalamus:

A. Seizures

B. Pacing

C. Lethargy

D. Inappetence

E. Behavior change

F. Head pressing

G. Circling

4. Diagnosis of Hyperadrenocorticism

A. History and clinical signs

B. R/O iatrogenic disease with questions concerning current or past medications. These medications can include oral, ophthalmic, otic, and topical medications. Make sure the owner tells you about everything and anything that went on or in their pet.

C. Laboratory data

1. Hemogram

A. Polycythemia (PCV 45-55%)

B. Stress leukogram

1. Lymphopenia

2. Eosinopenia

3. Neutrophilia (mature)

2. Biochemistry profile

A. Elevations in:

1. Serum alkaline phosphatase (SAP)

2. Cholesterol

3. Serum alanine aminotransferase (ALT)

4. Fasting blood glucose: Diabetes in 5-10%.

3. Thyroid function tests

A. T3 and T4 basal levels are generally decreased.

B. Response to TSH parallels normal.

C. Secondary to negative feedback of cortisol on pituitary.

D. 80% have a normal fT4ED

D. Does not require thyroid supplementation.

4. Blood pressure: 50 – 80% are hypertensive, cause unknown.

A. Recent study demonstrated normal or decreased levels of atrial natriuretic factor (ANF) in dogs with hyperadrenocorticism. Argues against hypervolemia as the etiology of the hypertension.

5. Urinalysis

A. Decreased urine specific gravity.

B. Proteinuria

D. Radiographic abnormalities

1. Thoracic films

A. Bronchial calcification

B. Metastases from adrenal adenocarcinoma

2. Abdominal films

A. Hepatomegaly

B. Osteopenia

C. 50% of adrenal tumors are visualized as soft tissue or calcified masses.

D. Subcutaneous calcification

E. Adrenal function tests

1. Three tests used to diagnose hyperadrenocorticism. They do not differentiate between PDH or AT.

A. ACTH stimulation test

1. Look for exaggerated cortisol response in response to ACTH.

2. See protocols at the end of this discussion.

3. Diagnostic in 85% of pituitary-dependent cases (PDH)

4. Diagnostic in 70% of adrenal tumors (AT)

5. Overall accuracy 80-85 %

6. A suppressed response to ACTH in animals with clinical signs of hyperadrenocorticism suggests iatrogenic disease.

B. Low-dose dexamethasone suppression test

1. Low doses of dexamethasone inhibit ACTH release from the pituitary via negative feedback and decrease plasma cortisol concentrations in normal dogs.

2. Dogs with Cushing's are more resistant to steroid suppression. Therefore, lack of suppression following dexamethasone = hyperadrenocorticism.

3. Diagnostic in 95% of PDH

4. Diagnostic in 100% of AT

5. Overall 90-95%

6. May also be used to distinguish PDH from AT (see below)

7. See protocols

C. Urine cortisol/creatinine ratio

1. Assessment of cortisol production and excretion rate.

2. Sensitivity of this test is greater than that of the LDDS (some animals with clinical signs of hyperadrenocorticism may have normal LDDS response tests but elevated urine cortisol to creatinine ratios). Used as a screening test.

3. Test is easy to perform.

4. As with all adrenal function tests, elevated results may occur in animals with non-adrenal disease.

5. Positive tests confirmed with a LDDS.

6. Must be performed on urine obtained at home, preferably in the AM

2. Tests to differentiate PDH from AT (performed after confirming diagnosis of hyperadrenocorticism).

A. High-dose dexamethasone suppression test

1. With PDH, a high dose of dexamethasone results in a decrease in ACTH release from the pituitary and a decrease in plasma cortisol.

2. With AT, the tumor secretes cortisol autonomously thereby suppressing ACTH production. With low ACTH concentrations already present, dexamethasone has no effect on plasma cortisol.

3. 70% of patients with PDH suppress plasma cortisol to less than 50% of the pre-treatment value.

4. 100% of patients with AT do not suppress.

5. Therefore: Suppression = PDH; Lack of suppression = Inconclusive

6. See protocol

B. Endogenous ACTH concentration

1. PDH: Levels normal or high

2. AT: Levels low to undetectable

3. Contact lab regarding sample handling and collection. Use of the preservative (Aprotinin) allows for greater utilization of this test.

4. Excellent method to differentiate PDH from AT.

Testing Protocols

These are suggested protocols that are used in the evaluation of patients with hyperadrenocorticism. You must use the protocol and normal values from the laboratory to whom you are submitting samples to properly evaluate endocrine tests.

1. ACTH Stimulation Test

    A. Synthetic ACTH (Cortrosyn) 5 ug/kg IV or IM; collect serum at 0 and 1 hour, or

    B. ACTH gel (Acthar) 2.2 U/kg IM; collect serum at 0 and 2 hours.

    C. Hyperadrenocorticism if post-cortisol > 20 ug/dl (530 nmol/L)

2. Low-Dose Dexamethasone Suppression Test

    A. 8 A.m: Baseline serum cortisol. Administer 0.01 mg/kg dexamethasone sodium phosphate (0.015 mg/kg dexamethasone) IV.

    B. 12 p.m: Collect 4 hour post-dexamethasone cortisol.

    C. 4 p.m: Collect 8 hour post-dexamethasone cortisol.

    D. In normal animals cortisol suppresses to less than 1.0 ug/dl (27.5 mmol/L) at 8 hours.

    E. 50% or greater suppression at either 4 or 8 hours together with lack of suppresion at 8 hours is diagnostic for PDH and additional tests are not necessary.

3. Urine Cortisol/Creatinine Ratio

    A. First morning urine sample is preferred. Sample should be obtained at home. Requires 1 – 2 mls.

    B. Stable at room temperature or refrigerated for 3 days.

    C. Normal range 2.8 - 4.8. A normal result effectively rules-out hyperadrenocorticism, an abnormal result should be confirmed with a LDDS or ACTH stimulation test.

Differentiating PDH From AT

    1. Low-Dose Dexamethasone Suppression Test

A. See above.

2. High-Dose Dexamethasone Suppression Test

A. 8 a.m: Obtain serum cortisol. Administer 0.1 mg/kg dexamethasone sodium phosphate (0.15 mg/kg dexamethasone) IV.

B. 4 p.m: Collect post-dexamethasone cortisol.

C. Suppression defined as greater than a 50% reduction of cortisol.

D. Suppression = PDH, non-suppression = Inconclusive

3. Endogenous ACTH Concentration

A. Check with lab on sample collection and handling.

B. Normal: 20-100 pg/ml (4.4-22.0 pmol/L)

C. PDH: 40-500 pg /ml (8.8-110 pmol/L)

D. AT: < 20 pg/ml (<4.4 pmol/L)

Treatment Options

A. Pituitary-dependent hyperadrenocorticism

1. Surgical management

A. Bilateral adrenalectomy

1. Technically difficult

2. Poor surgical/anesthetic risk

3. Permanently hypoadrenal and require lifelong replacement therapy

B. Hypophysectomy

1. See discussion at the end of this section

2. Lifelong therapy with thyroid hormone and prednisone necessary.

2. Medical therapy

Prognosis: Most dogs with PDH live normal lives (average 2.2 years, but remember most are geriatric to begin with.)

1. Complications

    A. Recurrence of disease.

    B. CNS signs.

    C. Pulmonary thromboembolism.

    D. Infections.

    E. Hypertension.

    F. Congestive heart failure.

2. Adrenal tumors:

    1. Adenomas: Good if no evidence of local invasion.

    2. Carcinomas: Guarded to grave with metastases.

Trilostane Therapy Of Canine Hyperadrenocorticism

The efficacy and safety of trilostane in the treatment of canine PDH were evaluated in a multicentre study at the Royal Veterinary College in London, the Veterinary Teaching Hospital in Dublin and Small Animal Hospital in Glasgow. Seventy-eight dogs with confirmed PDH were treated with trilostane for up to 3 years. The starting dose varied from 1.8 to 20 mg/kg (mean = 5.9 mg/kg).

Trilostane appeared to be well tolerated by almost all dogs with only 2 dogs developing 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. A further two dogs died within one week of starting trilostane but in neither case could a direct link with the trilostane therapy be established. The low prevalence of side effects compared favourably to those reported with mitotane.

Trilostane was found to be nearly as effective as mitotane in resolving the signs of hyperadrenocorticsm. Polyuria, polydipsia and polyphagia had dissipated in 40 dogs within 3 weeks after starting trilostane. Within 2 months, a further 20 dogs showed

decreases in their water and food consumption. These improvements were maintained as long as the dogs remained on adequate doses of trilostane. Skin changes resolved in 24 out of 39 (62%) of dogs that initially presented with dermatological signs. All of these improvements were maintained as long as the dogs remained on adequate doses of trilostane. Only 8 dogs that were treated with trilostane for more than 2 months showed poor control of clinical signs. In contrast, mitotane is effective in about 80% of cases of pituitary dependent hyperadrenocorticism (PDH).

Trilostane caused a significant ($p<0.001$) reduction in both the mean basal and post-ACTH stimulation cortisol concentrations after 10 days of treatment. The post ACTH cortisol concentration decreased to less than 250 nmol/l (9 µg/dl) in 81% of dogs within one month and in another 15% at some time whilst on treatment. These improvements were also maintained in the study population for the duration of the trial.

Thirty-five dogs had at least one dose adjustment over the treatment period. The dose was increased in 23 dogs up to four times the starting dose. In one dog the dose was increased nine fold over a period of six months. The dose was decreased in nine dogs to as low as a quarter of the starting dose.

The mean survival of all trilostane treated dogs was 661 days. Direct comparison with mitotane was difficult as 65% of the dogs were still alive at the time of censor and therefore the mean survival may still increase.By comparison, the mean survival of mitotane treated dogs has been reported to be 810 to 900 days.

Dosage and administration

The current suggested initial starting dose range for dogs with PDH is 1-2 mg/kg once daily. This needs to be adjusted according to clinical signs and serum cortisol values (see below). 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.

TRANSSPHENOIDAL HYPOPHYSECTOMY

A variety of treatments are available for PDH. Medical treatment options include drugs that chemically destroy the adrenals (lysodren or op-DDD) inhibit enzymes in the adrenal leading to the synthesis of cortisol (ketoconazole, trilostane) or inhibit the release of ACTH from the pituitary gland (Anipryl or selegiline). While these treatments can improve the clinical signs in 40-80% of patients they need to be chronically administered, necessitate frequent monitoring and do not cure or address the primary cause of the disease (the pituitary tumor). In humans, surgery to remove the tumor is the most successful long-term therapy. The most common approach used is the

transsphenoidal method, in which a passage way is made in the sphenoid sinus, an air space behind the back of the nose, which is just below the pituitary gland. Surgical cure rates for PDH are reported to be in the range of 65-85%, although more recent long-term follow up data suggest that the recurrence rate is as high as 25 % within 5 years. When no discrete adenoma can be identified, remission of hypercortisolism is observed in only about 40%. Surgery has also been used to treat PDH in dogs. Several groups, most notably in the Netherlands have performed these surgeries with success rates paralleling those reported for humans. However, these surgeries have generally not been performed in the US. Veterinarians at VCAWLAAH, in collaboration with human neurosurgeons that regularly perform transsphenoidal surgery in humans have developed the methods to perform these surgeries in the US and are conducting a research study to determine how effectively these surgeries can be performed.

Given the survival times and the ability to cure the disease by removing the pituitary tumor we are conducting ongoing studies to evaluate the role of transsphenoidal hypophysectomy in the treatment of canine PDH. We will also be looking at the tumor tissue to investigate the pathogenesis of Cushing's disease and evaluate novel medical therapies.