Overview of Canine Hyperadrenocorticism and Treatment with Trilostane

Sam Trivedi, DVM
Diplomate, ACVIM
Internal Medicine

Providing the best quality care and service for the patient, the client, and the referring veterinarian.

Pathophysiology- Pituitary Dependent (PDH)

Naturally Occurring Canine Hyperadrenocorticism

- Relatively common disorder
  - Middle-aged to older dog
  - 60% female
- Signalment
  - Poodles
  - Dachshunds
  - Can be seen in virtually every breed

Pathophysiology- Adrenal Dependent or Functional Adrenal Tumor (FAT)

Normal

Adrenal Dependent

Naturally Occurring Canine Hyperadrenocorticism

- Relatively common disorder
  - Middle-aged to older dog
  - 60% female
- Signalment
  - Poodles
  - Dachshunds
  - Can be seen in virtually every breed
Clinical Signs

- PU/PD
- Polyphagia
- Muscle Weakness
- Panting
- Bilateral and Symmetrical Alopecia
- Pot Belly, Thin Skin

Physical Exam

- Panting
- Hepatomegaly
- Bilaterally Symmetric Alopecia
- Abdominal Enlargement
- Truncal Obesity
- Hyperpigmentation
- Calcification Cutis
- Skin infections/comedones

Clinicopathologic Abnormalities

- CBC: Stress Leukogram, Thrombocytosis
- Chemistry:
  - Decreases: BUN
  - Increases: ALT, ALP, Cholesterol, Triglycerides, Glucose (mild)
- UA: SG<1.020, Proteinuria, UTIs
- T4: Hypothyroidism due to – feedback at the pituitary and decrease TSH release

Chester 9 YO MC Dachshund

- Referred for further evaluation of elevated ALP
- History
  - Persistently elevated ALP on bloodwork ranging from 200-400 (~2 years), remainder of CBC and Chemistry WNL.
  - Urinalysis revealed USG 1.035, benign sediment
  - No C/S/V/D, otherwise healthy
  - Owner reports that he does go outside frequently throughout the day to urinate, but no nocturia.
Chester 9 YO MC Dachshund

- Physical examination
  - Unremarkable

- Physical examination, bloodwork, and clinical signs not suggestive of Cushing’s. However referring veterinarian and owner concerned about underlying endocrinopathy due to elevated ALP

Screening Tests - UC:CR*

- Urine Cortisol: Creatinine Ratio
  - High sensitivity
  - Negative predictive value
  - If UC:CR is within normal range hyperadrenocorticism is unlikely
  - UC:CR was 7 (RR: 0-34)
  - UC:CR can be affected by stress
    - Very important that urine is collected at home
    - In hospital collection can lead to a false positive secondary to stress


Screening Tests - Low Dose Dexamethasone Suppression*

- Screening test of choice (unless iatrogenic hyperadrenocorticism suspected)
- Premise: Measure cortisol before, then at 4 and 8 hours following administration of 0.013 mg/kg Dex SP
- 8 hour cortisol is the screening portion and tells you if a patient is cushingoid or not
- 4 hour cortisol is the differentiating portion and tells you if there is suppression (indicating PDH)


Jeanie – 12 yo FS Scottish Terrier

- 6 months ago, the owner noticed increased drinking, urination, and appetite.
- She was seen by her rDVM for PU/PD/PP
- CBC: WNL
- CHEM: ALP:1130 and triglycerides:387
- UA: 3+ proteinuria (SG not reported)
- T4 was WNL
Physical Exam

- GEN: QAR T:100.9, P:150, R:40.
- INTEG: Thinning over dorsum.
- MS: BCS:7/9
- CV: No murmurs or arrhythmias ausculted. CRT <2sec.
- RESP: No crackles or wheezes ausculted.
- GU: Moderate bladder palpated.
- LN: Mandibular, pre-scapular, popliteal LN <1cm
- RECTAL: NSF

Initial Diagnostics

- Chemistry: ALP:1136, GGT:8, Chol:332
- Blood Pressure: systolic=188, diastolic= 114, and mean 143
- Urinalysis: SG:1.008, 3+ Protein, pH:6.5, + Bili
- Urine Culture: negative
  - Very important to culture urine in suspected Cushings patients despite absence of pyuria or bacteria
  - Steroid excess will cause dilution of urine (making bacteria less visible), will also cause glucocorticoid-induced inhibition of neutrophil migration into areas of infection (less likely to see pyuria)

Next Test?

Low Dose Dexamethasone Test or UCCR

Interpretation

- Q: Do we have a Cushingoid Dog?
  - A: Yes, because the 8 hour cortisol level is above the range of 0.8-1.4 UG/DL
- Q: Can we tell what type of Cushing’s disease we have (PDH or ADH) from these results?
  - A: No, because the 4 hour cortisol level did not suppress below 50% of the baseline level or below the 0.8-1.4 range.
Why did we not use an ACTH stimulation test?

- Sensitivity and Specificity is poor compared to other tests (when screening for Cushings)
- It can be used as a screening test, but it is not able to differentiate
- 3 most practical uses for ACTH stim?*
  - Monitoring therapy for Hyperadrenocorticism
  - Diagnosis of Hypoadrenocorticism
  - Diagnosis of Iatrogenic Hyperadrenocorticism

* Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM consensus statement (small animal).

Back to Jeanie – Next Test?

- Other Differentiating Tests (following LDDS) – 3 options
  - Abdominal Ultrasound
  - Endogenous ACTH*
    - Extremely Labile protein – results can vary if not submitted properly – ACTH rapidly dissolves from fresh whole blood, cannot stand at room temp for even short periods, ACTH adheres to glass
  - High Dose Dexamethasone Test *
    - Still 12% of dogs with PDH will not suppress

* Diagnosis of Spontaneous Canine Hyperadrenocorticism: 2012 ACVIM consensus statement (small animal).

Abdominal Ultrasound

- Mild to moderate hepatomegaly
- Mild splenomegaly
- Small left adrenal gland
- Right adrenal enlarged at caudal pole (~0.9 cm)
  - no invasion of CVC but, phrenicoabdominal vein compressed

Sebastian- 11 YO MC Dachshund

- History
  - PU/PD over the last year that has become significantly worse over the last 3 months
  - Marked polyphagia
- Physical Examination
  - Bilateral truncal alopecia
  - Hepatomegaly
  - Grade III/VI left apical murmur
Diagnostics

- Chemistry panel: WNL
- CBC: HCT 45.1%, Neutrophils 8546, Platelets 615,000
- USG 1.009, Benign sediment
- Urine culture negative

Screening and Differentiating

- Next Diagnostic tests?
- UC: CR 38.3 (RR: 0-34)
- LDDT
  - 0 hr: 1.6 ug/dl
  - 4 hr: 0.4 ug/dl
  - 8 hr: 2.1 ug/dl
- LDDT consistent with?
  - PDH
  - Suppression at 4 hours

Treatment - Trilostane vs Lysodren

- Lysodren
  - Requires loading/induction dose then goes to a maintenance dose
  - Some dogs have to be induced again
- Trilostane
  - Dogs are automatically started on a maintenance dose, administration is usually SID-BID
  - BID dosing shown to be more effective in recent studies*
  - Less likely to lose control


Treatment - Trilostane vs Lysodren

- Trilostane is a competitive inhibitor of 3-beta hydroxysteroid dehydrogenase thereby reducing synthesis of cortisol
- Lysodren (o,p'-DDD) is a chemical derived from insecticide DDT. Causes severe progressive necrosis of zona fasciculata and zona reticularis, can also cause necrosis of zona glomerulosa
Which drug has no risk?

- Neither!
- Both drugs can cause hypoadrenocorticism and lead to Addisonian crisis
- Trilostane – In some dogs:
  - May cause idiosyncratic adrenal necrosis
  - May also possibly block mineralocorticoid synthesis
  - 6/22 Dogs in a recent study developed hyponatremia and hyperkalemia and 2 of those dogs died*
  - Survival times of dogs with FAT with trilostane and mitotane did not vary**

*Evaluation of twice-daily, low-dose trilostane treatment administered orally in dogs with naturally occurring hypoadrenocorticism. Vaughan et al. 2008

Recommended manufacturing dose - Vetoryl (Dechra)

- The recommended manufacturing starting dose of trilostane is as follows:
  - 1.7 to 4.5 kg (10 mg PO q 24 hrs)
  - 4.5 to 10 kg (30 mg PO q 24 hrs)
  - 10 to 20 kg (60 mg PO q 24 hrs)
  - 20 to 40 kg (120 mg PO q 24 hrs)
  - Over 40 kg (180 mg PO q 24 hrs)

- Currently, there is no consensus in the veterinary literature for the ideal trilostane protocol (involving starting and maintenance doses)

Trilostane induced idiosyncratic adrenal necrosis

- Rare side effect: Idiosyncratic adrenal necrosis
- No predictable dose, duration of time
  - One study documented necrosis after only 3 doses*
  - Ultrasonographic changes: Small, heteroechoic adrenals*

* Persistent isolated hypocortisolism following brief treatment with trilostane. Ramsey, et al. 2008
^ Persistent isolated hypocortisolism following brief treatment with trilostane. Ramsey, et al. 2008

Trilostane induced idiosyncratic adrenal necrosis

- Histopathology
  - Adrenal cortical necrosis with reactive inflammation and fibrosis*
  - Variable degrees of cortical hemorrhage ^
  - 7 dogs in study found variable adrenal necrosis, 5 with severe changes ^

* Persistent isolated hypocortisolism following brief treatment with trilostane. Ramsey, et al. 2008
^ Persistent isolated hypocortisolism following brief treatment with trilostane. Ramsey, et al. 2008
Recommended dose adjustments and monitoring - Vetoryl (Dechra)

- Manufacturing recommends that if clinical signs are not controlled for the full day, BID dosing may be needed.
- To switch from once to twice daily dosing, increase the total daily dose by 1/3 to ½ and divide the total amount into two doses given 12 hours apart.

What is appropriate dose and frequency of administration?

- Usually administered as BID dosing
- Recent studies showed both SID and BID protocols to be safe and effective at controlling clinical signs*
- Clinical resolution in group with BID dosing varied between 1 week and 1 year (with dose adjustments)
- BID dosing may correlate with better controlled clinical signs
- Due to shorter duration of trilostane, SID dosing likely leads to periods of hypercortisolemia

 Usually administered as BID dosing
Recent studies showed both SID and BID protocols to be safe and effective at controlling clinical signs* (Arenas, et al. JVIM, 2013; 27: 1478-1485)

What is appropriate dose and frequency of administration?

- Dose: 0.5-1.0 mg/kg (starting dose)
  - This was a safe and effective dose, with many dogs responding appropriately*
  - Administration of initial lower doses of trilostane to dogs with natural occurring hyperadrenocorticism is effective**
- Frequency: BID – TID
  - Most dogs showed marked clinical improvement with increased dosing frequency*
  - Effects of Trilostane appear to wane within 9 hours, based on ACTH stim tests taken at different intervals


Trilostane administration in Dogs (< 5kg) with PDH*

- Twice daily administration at 0.8 mg/kg PO BID versus 30 mg/dog SID
- 2/7 dogs on 30 mg/dog SID dosing had clinical signs and abnormal lab findings consistent with hypoadrenocorticism, none of 9 dogs on low dose had adverse effects
- Both groups observed improvement in clinical signs on therapy

*Efficacy of Low- and High-Dose Trilostane Treatment in Dogs (<5kg) with Pituitary Dependent Hyperadrenocorticism. Cho et al. JVIM 2013;27:19-85
Monitoring Therapy

- Clinical signs trump all tests
  - Resolution of clinical signs is consistent with control
- Dosing
  - ACTH Stimulation test 3-5 hours post pill administration with values between 2-5 ug/dl (which is below the reference range)
- Frequency
  - Have owners collect urine in the morning before trilostane administration – evaluate USG and UCCR. If USG < 1.020 and UCCR > 15, and ACTH stim in appropriate range, consider increasing frequency

Jeanie - 12 YO FS Scottish Terrier

- Treat with Trilostane 1 mg/kg PO BID to stabilize clinical signs and repeat ACTH stimulation test 7-10 days after initiating therapy to assess control.

Jeanie - 12 YO FS Scottish Terrier

- Jeanie doing incredibly well at home with complete resolution of clinical signs
- Pre Cortisol 1.5UG/DL (0-6)
- Post ACTH Stim Cortisol 4.9UG/DL (6-15)
- USG 1.035, UCCR 12
- Blood Pressure
  - Systolic: 163 (down from 188)
  - Diastolic: 94
- Mean: 128
- Repeat Chemistry WNL

Why not go straight to surgery?

- High cortisol levels lead to poor healing post surgically
- Hypertension increases anesthetic complications
- Increased risk of PTE
- Control secondary hypothyroidism
- Adrenalectomy performed 4 weeks after initiation of trilostane therapy and was without complication, trilostane discontinued day prior to surgery
Sebastian - 11 YO MC Dachshund

- Started on Trilostane 1 mg/kg PO BID
- Recheck exam 2 weeks later
  - Still PU/PD – improved but still has to be let out during the night
  - USG 1.015, UCCR 44.2
  - ACTH stim (4 hours post pill administration)
    - Pre Cortisol 4.2 UG/DL (0-6)
    - Post ACTH Stim Cortisol 7.5 UG/DL (6-15)

Dose was increased 2 mg/kg PO BID
- Recheck exam 2 weeks later
  - Clinically doing very well. PU/PD resolved. Does not need to be let out in the middle of the night
  - USG 1.022, UCCR 30.2
  - ACTH stim (4 hours post pill administration)
    - Pre Cortisol 2.9 UG/DL (0-6)
    - Post ACTH Stim Cortisol 4.6 UG/DL (6-15)

Sebastian - 11 YO MC Dachshund

- Despite decreased USG and elevated UCCR, Sebastian was kept on this dose as clinical signs were resolved, ACTH was WNL, and owner was happy with treatment
- Treat signs and the owner with Trilostane not the numbers

Henry Haas – 14 yo MC Cockapoo

- Previous History
  - Diagnosed with PDH via LDDS
  - Acute onset blindness, SARDS diagnosed via flatline ERG
  - Trilostane therapy initiated, PU/PD resolved
  - Previously diagnosed with hypothyroidism
  - Historical IMPA
Current History

- Recent lethargy ~ 4 days
- Recurrent PU/PD
- No V/D/S/C
- No recent travel history
- Current medications – Trilostane 10 mg (1 mg/kg) PO q 24 hrs, Soloxine PO BID, tobramycin ophthalmic OU BID, cyclosporine OU BID, artificial tears OU BID, and glucosamine PRN

RDVM Diagnostics & Treatment

- In house CBC: WBC 19.87 (H)
- In house Chemistry: ALKP 264 (H), AMY 1378 (H), BUN 27 (H), CREAT 1.5 (H), K+ 6.6 (H), GLOB 5.7 (H)
- ACTH Stim: <1.0 (L) (Pre and Post)
- Treatment: 2.2 mg/kg DOCP IM once, 1.36 mg (0.15 mg/kg) dexamethasone SP IV once
- Transferred to ASEC for further care

Physical Exam

- Wt 9 kg T 101.7 P 90 R 30
- Gen: BAR, BCS 4/9
- Eyes: Nuclear sclerosis OU
- Integument: “Rat tail” appearance, IVC in R cephalic
- GI: Mild hepatomegaly and discomfort on cranial abdominal palpation

Initial Diagnostics

- ISTAT: BUN 31 (H), K+ 5.6 (H), Cl 130 (H), TCO2 10 (L)
- Urine dipstick: Negative for glucose, pH 6.0
- UA, culture MIC: No growth on final culture
Initial Imaging (Abdominal Ultrasound)

- Bilateral adrenomegaly with hyperechoic mesentery is likely due to inflammation or adrenal necrosis (possible trilostane reaction), however a neoplastic process cannot be ruled out.
- Hyperechoic liver is consistent with vacuolar degeneration or hepatopathy; neoplasia or inflammatory process are considered less likely.
- Splenic focus is likely hematopoiesis, although neoplasia or inflammation cannot be ruled out.
- Gallbladder debris may represent forming mucocele.

Confirming a Diagnosis

- Resting cortisol
  - Value > 2.0 rules OUT Addisons
- ACTH Stimulation
  - Post < 2.0
  - Pre and post typically < 1.0
- ** NOTE: Na/K ratio
  - Debate about ratio being diagnostic if < 23, but cannot use this to rule in or out!
Initial Treatment (Henry Haas)

- IV fluids 0.9% NaCl at 42ml/hr (1.5 x)
- Famotidine 4.5 mg (0.5 mg/kg) IV BID
- Anzemet 5.4 mg (0.6 mg/kg) IV SID
- Baytril 90 mg IV (10 mg/kg) SID
- Buprenex 0.09 mg (0.01 mg/kg) IV QID
- Sodium Bicarbonate CRI 5ml/hr (30mEq Sodium bicarbonate + 30ml NaCl 0.9%)

11/7/13- Continued Diagnostics & Treatment

- Repeat ISTAT (4 pm): BUN 29 (H), HCT 32% (L)
  - Electrolytes WNL (Na+ 149, K+ 3.6)
  - Acidosis corrected (TCO2 18)
- Changes to therapy
  - Discontinued bicarbonate supplementation, buprenorphine
  - IVF reduced to 0.9% NaCl at 22 mls/hr
  - Initiated tramadol 25 mg PO TID, prednisone 5 mg PO BID and famotidine 5 mg PO BID

11/8/13- Continued Treatment & Discharge

- Decreased tramadol to 12.5 mg PO BID
- Discontinued baytril (urine culture negative)
- Discharged on
  - prednisone 5 mg (0.55 mg/kg) PO BID
  - famotidine 5 mg PO BID
  - Tramadol 12.5 mg PO BID
  - DOCP injections q 25 days
- Recheck
  - 10 days for recheck electrolyte panel
  - Second DOCP injection due 12/1/2013

Conclusions Regarding Idiosyncratic Adrenal Necrosis

- ALWAYS warn owners that Trilostane is not a benign drug
- Idiosyncratic adrenal necrosis can occur anytime
- No predictable doses or numbers of administration
- Life long therapy
- BUT very treatable with excellent prognosis!
Conclusions Regarding Diagnosis

- Low Dose Dexamethasone Suppression Test is best test we have for screening (as chance at differentiating also)
- Abdominal Ultrasound recommended as best differentiating test (user dependent)
- High Dose Dexamethasone Suppression will only show suppression in 10-12% more than LDDS
- No test is 100% perfect
- UC:CR good for ruling OUT, but not diagnosing
- ACTH Stimulation used for diagnosis of iatrogenic hyperadrenocorticism, hypoadrenocorticism, as well as monitoring of therapy

Conclusions Regarding Treatment

- Trilostane administration can be initiated with a maintenance dose whereas lysodren requires a induction dose, personal preference is trilostane
- With trilostane monitor clinical signs to assess therapy, rather than specific values; be sure to watch for signs of anorexia, or GI upset as can indicate overdose
- Starting trilostane therapy with lower doses and/or an increased frequency will result in fewer dogs becoming ill
- Idiosyncratic adrenal necrosis can happen at ANY dose!
- Post ACTH cortisol, UCCR and USG are useful means of assessing response to therapy
- Dose changes should be made based on clinical signs not on numbers alone!

Thank you, Colleagues!

- Thank you to all of our colleagues for taking time out of your busy schedules to spend the day with us. We appreciate your time!