A New Approach to Canine Hyperadrenocorticism

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Pathophysiology

- ACTH-secreting pituitary tumour (PDH)
- Cortisol-secreting adrenal tumour (FAT)
- Result of both is hypercortisolemia

Pituitary tumour (left) and functional adrenal tumor (right).

Increased ALP

- Hyperadrenocorticism
- Idiopathic vacuolar hepatopathy
- Other primary hepatopathy
- Hyperlipidemia
- Other endocrine disease
- Idiopathic (geriatrics)
- Hepatoma
Testing Options

The graph shows cortisol levels in dogs over 8 hours. The blue line represents the normal cortisol levels, decreasing over time. The yellow line indicates the cortisol levels in dogs with an adrenal tumor, which remains relatively stable. The red line labeled PDH shows an intermediate pattern. Normal dogs exhibit a decline in cortisol levels over time.
Urine cortisol:creatinine ratio

- Studies have come to varying conclusions
- Approximately 75% of dogs with non-adrenal illness will have a positive result
- Fairly reliable in ruling out disease
- False negatives are rare but possible
- Most ideal if urine collected prior to arrival at veterinary clinic
Endogenous ACTH

- Only useful for differentiating pituitary-dependent HAC from adrenal-dependent HAC.
- Should be low with adrenal-dependent, and high with pituitary-dependent.
- Problem is that with PDH, the level can be low, normal or high.
- Some problems with stability.
- NOT in glass tubes.
ACTH stimulation test

- Looking for an exaggerated response
- Only the post-stimulation value is of use

**PDH:**
- Clearly abnormal – 30%
- Borderline – 30%
- Normal range – 40%

**FAT:**
- Clearly abnormal – 60%
- Borderline or normal – 40%

- Normal dogs
  - 15% have abnormal stimulation
ACTH stimulation test

If high suspicion of hyperadrenocorticism:
  • Positive result likely has the disease
  • Could still have it with a negative result
  • Diagnostic test
  • Also used for monitoring when receiving medical therapy
ACTH stimulation test

- New protocol for DIAGNOSTIC test and MONITORING test
- Many previous forms of ACTH are unavailable (ie synacthen)
- Cortrosyn available but expensive
- Options available to reduce cost
- Previous backorder issue
1. A cortrosyn vial contains 250 μg / 0.25 mg of synthetic ACTH powder.
2. Reconstitute as directed on vial (add 2.5-ml of sterile saline solution), which results in a concentration of 100 μg/ml (0.1 mg/ml).
3. Aspirate 0.25 ml (25-μg) or 0.5 ml (50-μg) aliquots into plastic syringes. We now make primarily 0.25 ml aliquots (25-μg).

*Please note it is important to use PLASTIC syringes, not glass vials.*
Utilizing cortosyn to reduce $$

5. Label each syringe with the date reconstituted, amount in that syringe, and name Cortrosyn.

6. Freeze the syringes at \(-20^\circ\text{C}\). This is best done in a non frost-free freezer, as they cycle through warmer periods to defrost. Stored in this fashion, the contents can be stored for up to 6 months.

* If you elect to refrigerate the syringes, they can be stored for up to 4 weeks.

http://www.endocrinevet.info/2011/03/how-to-extend-your-supply-of-cortrosyn.html
DIAGNOSTIC ACTH stim test

1. Administer at a dose of 5 μg /kg (round up if needed) either **IM or IV**. Administer **INTRAVENOUSLY** in dehydrated dogs and in all cats.

2. Cortisol levels should be measured prior to injection of Cortrosyn (0 hour), and at 1 hour post administration of Cortrosyn.
MONITORING ACTH stim test

- After a diagnosis in dogs, while receiving trilostane or mitotane.
- Administer at a dose of 1 μg/kg (round up if needed) **INTRAVENOUSLY**.
- Cortisol levels should be measured prior to injection of Cortrosyn (0 hour), and at 1 hour post administration of Cortrosyn.
Low-dose dexamethasone test

- Administration of 0.01 mg/kg dex
- Dexamethasone does not cross-react with cortisol assay (prednisone does)

PDH:
- >99% have increased values at 8 hours
- 35% have increased 4 hour value

FAT:
- >99% have increased values throughout

Normal dogs: >5% to 37-56% abnormal
LDDS test

Adrenal tumour
PDH
Normal dogs
Abdominal ultrasound

- Ultrasonographer must be comfortable in imaging the adrenal glands
- NOT as sole screening test
- PDH:
  - Expect bilaterally enlarged, symmetric glands
- FAT:
  - One adrenal tumour (rare cases have 2)
  - Alternate gland small or not visible
Abdominal ultrasound

Normal dogs

PDH

Adrenal tumour
MRI / CT scan

- Useful for evaluating pituitary gland, can include adrenals if necessary
- ~50% pituitary tumours not visible
Treatment Options

**Medical**
- Trilostane
- Mitotane

**Surgical**
- Primarily adrenal tumours

**Radiation therapy**
- Primarily pituitary tumours
Trilostane

- Steroid analogue
- No innate hormonal activity
- Competitive inhibitor
  - $\rightarrow$ 3$\beta$-hydroxysteroid dehydrogenase

- ↓ Glucocorticoid and sex hormones
- Aldosterone production generally spared
Dosing

- Based on body weight categories
  - Starting dose range was 5-10 mg/kg/d
  - Starting dose from current manufacturer recommendation is 2.2 – 6.7 mg/kg/d
  - One talk suggested starting at 1 mg/kg/d (Feldman ACVIM Forum 2007)
  - Recent study indicates that 89% of dogs need < 3mg/kg/d (Feldman JVIM 2012)
  - Variable GI absorption
Dosing

- Evidence that the amount of trilostane needed to control clinical signs and hypercortisolemia decreases as the dog’s weight increases (JVIM 2012)
Dosing

- Short duration of action
  - Suppressed cortisol hypersecretion < 24 hrs
  - Once vs. twice daily dosing is controversial
    - 80% of dogs need only once daily (Braddock 2003)
    - Very few differences noted in once vs twice daily dosing (Augusto 2012)
    - Low dose twice daily dosing is effective and potentially safer (Feldman 2013)
    - Similar control with once vs twice daily, small % of dogs may have better clinical control with twice daily (Arenas 2013)
Dosing – Bottom Line

- It is reasonable to start with either once or twice daily, however client compliance may be increased with once daily.

- Most important is to start with a low dose (we use 1 mg/kg once daily) to avoid serious side effects, however control may take longer.

- If you are having trouble getting control, consider twice daily dosing.
Response to Therapy

- Reduced PU/PD, polyphagia
  - ~ 5-12 days
- Decreased lethargy & pendulous abdomen
  - ~ 1 month
- Dermatological changes
  - Several months to resolve

- Clinical response in >80% dogs with PDH
  (Neiger et al., 2002)
Monitoring Response

- ACTH stimulation test
  - Test 4-6 hours after medication administration (0, 1 hr)
  - Clinical remission
    - Post-ACTH cortisol < 250 nmol/L
  - Better control post-cortisol 27-69 nmol/L
  - My goal is 80-120 nmol/L
  - Recheck ACTH stims @ 1,3,6,13 weeks, then q 6 mos

- Abdominal ultrasound
  - *Increased* adrenal gland size

(Mantis et al., 2003)
Monitoring Response

- **Sources of guidance**
  - Vetoryl package insert
  - Call for assistance
    - Dechra Canada
    - MOVEH internal medicine service
    - Laboratory internal medicine consultation line
Monitoring Response

• Study (ACVIM 2017) looked at using only cortisol levels to monitor trilostane therapy
• Looked at pre-pill and 3 hour post pill cortisol levels for trilostane (PDH and FAT)
• Encouraging preliminary results that the pre-pill level, along with clinical signs, can be used to monitor trilostane dose
• ONLY for use in dogs that are not sick
Dechra UK Recommendations

Suitable dogs
- Once- or twice-daily Vetoryl dosing
- PDH or FAT
- Clinically well dogs (can have signs of HAC)
- Calm dogs

Unsuitable dogs
- Aggressive or stressed dogs
- Unwell dogs
Dechra UK Recommendations

Monitoring Appointment

• Have Vetoryl given at a convenient time from at least the day before (e.g. 9 am), then NOT that day

• Make sure that nothing stressful has happened that morning (e.g. vomiting, injury)

• Ensure the owner has completed a Quality of Life Questionnaire

• Take history and examine the dog, checking for signs of HAC
Dechra UK Recommendations

Assessing pre-cortisol level – No clinical signs of HAC

- **<40 nmol/L**
  - Re-evaluate case, lower dose and retest in 10d?

- **40-138 nmol/L**
  - Continue current dose, recheck in 3 months

- **>138 nmol/L**
  - Re-evaluate case
  - Divide twice daily and retest in 10d?
  - Slightly higher dose and retest in 10d?
Dechra UK Recommendations

Assessing pre-cortisol level – Clinical signs of HAC present

- <40 nmol/L
  - Re-evaluate case, contact Dechra if needed

- >40 nmol/L
  - Increase to twice daily and retest in 10d OR
  - Higher dose and retest in 10d
Obtaining Trilostane

- Can obtain Vetoryl in 5, 10, 30, 60 and 120 mg sizes
- Can obtain any other size from Compounding Pharmacies
- Historically this would allow slight increases or decreases in dosing, however more options now with Vetoryl
Obtaining Trilostane

- Should you use Vetoryl or compounded trilostane?
- Most ideal to use a veterinary licensed product if possible.
- Backing of company if there are concerns with the product.
- Quality of compounded trilostane?
Quality of Trilostane

- Study using trilostane capsules obtained from 8 US compounding pharmacies
- Compared to Vetoryl capsules and placebo
- 96 compounded batches and 16 control batches were tested

Cook et al 2012 JAAHA
Quality of Trilostane

- Batches included 10 randomly selected capsules of each strength from 120 capsules that had been ordered over a 6 week period.
- Acceptance range was 90-105% of label claim.

Cook et al 2012 JAAHA
Figure 1: Average percent label claim (\% LC) for control (n=12) and compounded (n=96) batches of trilostane.

Cook et al 2012 JAAHA

Control
96.1 - 99.6 %

Compounded
39 - 152.6 %
% of Label Claim

Using an acceptance criterion of 90–105% LC, 36/96 (38%) of the compounded batches failed to meet the target content

Control
96.1 - 99.6 %

Compounded
39 - 152.6 %
% of Impurities

**FIGURE 2** Average percent (% weight/weight [w/w]) impurities/related substances for control (n=12) and compounded (n=96) batches of trilostane.

Cook et al 2012 JAAHA
% of Impurities

Only 1 batch of compounded trilostane considered unacceptable

- Control: 0.392%
- Compounded: 0.624%

Cook et al 2012 JAAHA
% Dissolution

Control
0% failed >70%
at 75 mins

Compounded
20% failed >70%
at 75 mins

Cook et al 2012 JAAHA
Bottom Line

- Consider using Vetoryl if possible
  
  OR

- Use a compounding pharmacy that you trust
Bottom line - Trilostane

- Considered by most as the standard of medical treatment for PDH
- Can be used for FAT as well
- Many different sizes to allow for specific doses
- Requires long-term monitoring to determine dose
- Occasional side effects
Mitotane (o,p’-DDD)

- Chemical related to insecticide DDT

- Adrenocorticolytic
  - Binds covalently to adrenal proteins
  - Converted to reactive metabolite

- Drug intolerance
  - Anorexia, vomiting, diarrhea, weakness, ataxia
  - Hypoadrenocortical crisis
Mitotane (o,p’-DDD)

- Two protocols:
  - Partial adrenocortical destruction
    - Induction phase, monitor clinical signs closely
    - Maintenance phase long-term
  - Complete adrenocortical destruction
    - Require glucocorticoid and mineralocorticoid replacement therapy for life

- Long-term monitoring
  - ACTH stimulation tests, initially every 1-3 months
Bottom line - Mitotane

- Previous standard of medical treatment
- Still occasionally used, esp for FAT
- More common and serious side effects
- Occasional practitioners who are more comfortable with mitotane
- Many practitioners these days have not used mitotane
APPROX COST – 10 kg dog

Vetoryl: $47 per month

Compounded: $34 per month

Lysodren: $40-50 per month
FAT - Surgery

- Best treatment is surgical excision if possible
- Technically challenging, esp on right side
- Poorer prognosis if mass > 5 cm, vascular invasion, vein thrombosis, metastasis present or adenocarcinoma
- Some are inoperable or metastatic
- 15% develop intraoperative complications
- 50% develop postoperative complications
- Perioperative mortality rate 22-29%
Client Education

- Key component in diagnosis and treatment
- Diagnosis may require several tests
- Treatment may require lengthy period of dose adjustments
- Response of some symptoms may take weeks to months
- Important to set expectations and understanding early in process
Take home messages

- Diagnostic testing is not always straightforward
- Client education through entire process is very important
- Abdominal ultrasound can be quite helpful
- Monitoring protocols are changing
- Treatment options need consideration
- Use specialty/referral options for advice or referral when needed
Questions?