Update on Managing Canine Hyperadrenocorticism

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Sioux City, IA

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Agenda

Pathophysiology
Clinical signs
Diagnostic/differentiation test
Treatment/Monitoring
Clinical trials
Q & A
Dechra Veterinary Products

- International and US presence (US home office Kansas City)
- UK based – 14 European countries
- Licensed Pharmaceuticals
- Companion animal & equine focus
- VETORYL® CAPSULES (5,10,30,60,120 mg), Felimazole™ (2.5, 5.0 mg)
- Zycortal® Suspension (DOCP)
- Dermapet products acquired Oct 2010
- Phycox®
- Otic/Derm/Ophthalmic – (formerly Pharmaderm)
- Equine - irap, Osteokine, Equidone, OsPhos
- Putney acquisition
The Adrenal Glands

Fig. 19.11. The adrenal glands and their arterial blood supply.
The Adrenal Cortex

80-90% of the entire gland and produces

**GLUCOCORTICOIDs**
(cortisol / corticosterone)

**MINERALOCORTICOIDs**
(aldosterone)

**ANDROGENS**
(precurors of sex hormones)
The Adrenal Medulla

10-20% of the entire gland and produces

CATECHOLAMINES
(adrenaline / noradrenaline)
The Normal Hypothalamic-Pituitary-Adrenal Axis

Positive Effect

Negative Feedback
Cortisol has more diverse effects on the body than any other hormone.

Cortisol is released in response to stress. Long term effects...

**Liver**
- Increased gluconeogenesis
- Increased glycogen stores
- Induction of certain enzymes

**Muscle**
- Increased protein catabolism leads to muscle wasting and weakness

**Bone**
- Osteopenia associated with increased protein catabolism and neg. calcium balance

**Skin**
- Increased protein catabolism – thin skin, poor wound healing and poor scar formation
- Possible calcium deposition

**Adipose Tissue**
- Increased lipolysis
- Redistribution of fat deposits

**Blood**
- Decreases in circulating lymphocytes
- Decreases in circulating eosinophils
- Increase in circulating neutrophils

**Immune System**
- Diminished inflammatory response
- Reduced immune response

**Kidney/Urinary**
- Increased GFR and interference with vasopressin release or action (polyuria)
- Increased calcium excretion

**CNS**
- Euphoria, depression, other behavioral changes
Cortisol in perspective

Cortisol is released in response to stress

Therapeutically, corticosteroids are administered in **MASSIVE DOSES** relatively to physiologic levels. With prolonged administration, it can take many months for the HPA Axis to return to normal function after these drugs are stopped – risk of Addisonian crisis
Etiology of HAC — spontaneous or iatrogenic

**Pituitary dependent** (80-85%)
Micro and macro adenomas, (adenocarcinomas)

**Adrenal dependent** (15-20%)
    Functional adrenal adenomas and carcinomas

**Iatrogenic**
    Exogenous corticosteroids

**Ectopic ACTH** — very rare (ACTH production by non-pituitary neoplasia - lung)
Atypical Hyperadrenocorticism

- Clinical signs suggestive of HAC
- Normal ACTH stim, LDDST and UCCR
- Consider measuring other adrenal steroid hormones – may be increased; may be helpful in diagnosis (Univ of Tennessee Endo lab)
- Have responded to treatment for HAC
Failure of Negative feedback

Pituitary-dependent HAC(PDH)

BILATERAL HYPERPLASIA

CRH

Anterior Pituitary

HYPOTHALAMUS

ACTH

CORTISOL

ADRENAL CORTEX
Pituitary dependent HAC (PDH)

Most (>80%) have a pituitary adenoma arising from the pars distalis

Small proportion have a pituitary carcinoma

Most dogs have microadenomas (<1cm)
50% of tumors <3mm

10-20% have macroadenomas (>1cm)

Adrenal-dependent HAC (ADH)

HYPOTHALAMUS

CRH

Anterior Pituitary

ACTH

ACTH

CORTISOL

BILATERAL ATROPHY

ADRENAL CORTEX
Adrenal dependent HAC (ADH)

~50% benign, remainder highly invasive malignancies

In a series of 41 dogs with ADH, 26 (63%) had adrenocortical carcinoma and 15 (37%) had adrenocortical adenoma (Reusch, Feldman 1991)

Difficult to distinguish adrenal adenomas from carcinomas
- clinically
- biochemically
- ultrasonographically

Photo courtesy of Dr Reto Neiger
Hyperadrenocorticism (HAC)

Chronic, progressive; not immediately life-threatening
Quality of life issue for both dog and owner

**Signalment:**
Middle age to older; male/female
Many breeds; poodles, Dachshunds, various Terrier breeds, G. Shepherd, Labrador commonly represented
Boxer and Boston Terrier ↑ risk (Feldman, Nelson 3rd ed. p 265)

**Diagnosis:** HAC is a CLINICAL diagnosis! – need more than lab work
Can be difficult to diagnose – not all have “classic” signs
Owners can confuse some signs with aging
HAC “problems” are not acute, nor do they frighten the owner
Confusing diagnostic test results
Without clinical signs – do not treat for HAC
Clinical Signs- depend on the duration and degree of cortisol excess

- polydipsia (>100 ml/kg/day)
- polyuria (>50 ml/kg/day)
- polyphagia
- lethargy
- panting
- muscle wasting/weakness
- ‘pot bellied’ appearance
Clinical Signs – continued

- bilaterally symmetrical, non-pruritic alopecia
- skin thin, inelastic
- poor wound healing
- poor regrowth of hair
- comedones, calcinosis cutis
- recurrent UTI
- recurrent skin infections
- anestrus/testicular atrophy
- 1\textsuperscript{st} pyoderma in older dog
- Demodex in a older dog
- Ruptured ACL in inactive dog
Calcinosis cutis -

6 yr, male neutered Boston Terrier; on Vetoryl for 4 days
Sometimes develops after treatment has begun.
Clinical Signs - neurologic

Neurological signs with **PDHAC**
- not very common at presentation
- may develop during Tx; probably due to removal of negative feedback inhibition of cortisol on pit/hyp which may allow for rapid enlargement of pituitary tumor = edema and increased intracranial pressure

- dullness, depression, disorientation, loss of learned behavior, anorexia, aimless wandering or pacing, head pressing, circling, ataxia, blindness, seizures, anisocoria

Dogs with MACROADENOMAS may show signs of concurrent CENTRAL DIABETES INSIPIDUS
Clinical Signs - unusual

Myotonia
• persistent active muscle contractions that continue after voluntary/involuntary stimuli
  • rigid limbs & stiff stilted gait
  • may affect all 4 limbs, but signs usually more severe in the hindlimbs
• bizarre high frequency discharges are noted on electromyography
• Clinical response is not predictable - Cause ? – Feldman, Nelson
Cortisol has more **diverse effects** on the body than any other hormone

Cortisol is released in response to **stress**. Long term effects...

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Clinical Signs HAC dogs do NOT have

- Poor appetite
- Vomiting and/or diarrhea
- Coughing, sneezing
- Pain
- Seizures
- Bleeding
- Pancreatitis – VERY RARE!
- Renal failure – VERY UNUSUAL

Feldman, Nelson: Canine and Feline Endocrinology and Reproduction p. 266
Non-specific laboratory findings

stress leukogram
  mature neutrophilia (without left shift)
  monocytosis
  lymphopenia
  eosinopenia (NO EOSINOPHILIA)

hyperglycemia ± glucosuria

hypercholesterolemia/hypertriglyceridemia

steroid induced ↑ALKP

low urine SG (<1.015), proteinuria, UTI
Diagnosing Hyperadrenocorticism

Diagnostic tests - does the dog have Cushing’s?
   Low-dose dexamethasone
   ACTH stimulation test

   *(Urinary cortisol : creatinine ratio (UCCR))*

Differentiation tests – if so, is it PDH or ADH?
   Dexamethasone suppression
      (low / high)
   Endogenous ACTH
   Ultrasound
Effects of exogenous steroids on adrenal tests

Assay cross-reaction

Prednisolone, hydrocortisone cross-react with the measurement antibodies and cause false cortisol results (false high)

Need to discontinue steroids 24hrs to prevent assay interference

No cross-rx with dexamethasone

Physiological effect

Exogenous steroids (even eye, ear, skin) will affect pituitary production of ACTH and cause the adrenals to shrink and less cortisol to be produced

To study the pituitary-adrenal axis free from this effect, should wait 4 weeks

DO YOU HAVE AN IATROGENIC CASE????
ACTH Stimulation Test

- Measure of adrenocortical reserve capacity

**PROTOCOL**

- Baseline sample for cortisol (0 hour)
- Inject synthetic ACTH - Cortrosyn (cosyntropin)
  
  5 µg/kg IV or IM (max dose = 250 ug)

- Second sample for cortisol taken 1 hour later
ACTH Stimulation Test

Interpretation

• Post-ACTH cortisol concentration
  > 22 µg/dl consistent with HAC
  < 15 µg/dl is not consistent with HAC

• False negatives occur
  – 20-30% of dogs with HAC < 22 µg/dl
HAC dogs demonstrate an exaggerated response to ACTH.
ACTH Stimulation Test

[Graph showing cortisol levels before (PRE) and after (POST) stimulation, with normal, PDH or ADH, and iatrogenic responses indicated.

- Normal range: 50 to 600 nmol/l
- PDH or ADH: above 600 nmol/l
- Iatrogenic: below 50 nmol/l]
ACTH Stimulation Test

Advantages

Short test (1 hour, \(\Rightarrow\) less stress for animal)

**More specific than LDDST**

(more confidence in a positive test result)

Test of choice in suspect iatrogenic and in monitoring Vetoryl (trilostane) and lysodren

Disadvantages

**Less sensitive than LDDST** (esp. adrenal HAC)

(less confidence in a negative result)

Cannot provide differentiation
Low-dose dexamethasone suppression test

- Measures the resistance of an abnormal pituitary-adrenal axis to suppression by dexamethasone

- Inject 0.01-0.015 mg/kg dexamethasone iv (dexamethasone sodium phosphate or dexamethasone in polyethlene glycol)

- 3 samples for cortisol @ 0, 3-6 and 8 hrs

  8 hr cortisol result > 1.45 µg/dl = POSITIVE
  (> 40 nmol/L )
Low-dose dexamethasone

Normal dog: cortisol secretion inhibited within 2-3 hours and suppression lasts as long as 24–48 hours

HAC dog: variable or transient inhibition of cortisol secretion initially

a) FIRST 8 hr result first: **if 8 hr > 1.45 ug/dl (40 nmol/L) = positive**

b) √ escape from suppression by 8 hours ( if > 50% suppression from base line at 4 or 8 hr – PDHAC.

c) if < 50% or minimal suppression = PDH or ADH
Low-dose dexamethasone

Low dose dexamethasone suppression test

Plasma cortisol (nmol/l)

Time (hours post dexamethasone)

- PDH/ADH
- PDH
- Normal

HYPERADRENOCORTICISM
Low-dose dexamethasone

Advantages

**Highly sensitive**
(Extreme confidence in a negative test result)
(up to 10% of PDH dogs have normal LDDST- D. Bruyette)

May differentiate as well as diagnose (60% of HAC cases)

Disadvantages

Long test (8 hours)

**Poor specificity**
(up to 56% false positives in Non-adrenal illness)

Not appropriate if history of exogenous steroids
Urinary cortisol : creatinine ratio

Collect one (or more) morning urine samples at home in a non-stressed environment. Consult with your laboratory for their normal values.

**ADVANTAGE**
Inexpensive; Convenient for owner

**HIGH SENSITIVITY** (extreme confidence in negative results)

**DISADVANTAGE**
**POOR SPECIFICITY** (positive result not confirmatory – false positives relatively common)
Urinary cortisol : creatinine ratio

DISADVANTAGE

Very poor specificity (some as low as 24%)
Differentiation Test: PDH vs ADH

Low dose dexamethasone
sufficient suppression for differentiation in 60% of positive LDDST

Endogenous ACTH – contact lab or sample handling

Imaging
- **Ultrasound**: bilateral adrenal enlargement in PDH, unilateral in ADH
- **CT/MRI**: adrenal tumour, adrenal hyperplasia or pituitary tumour
  - **Radiography**: adrenal enlargement or mineralisation

High dose dexamethasone
- 0.1 to 1.0 mg/kg iv - sample at 0, 3-6 and 8 hours
- >50% suppression rules out adrenal source
Endogenous ACTH Test

The Normal Hypothalamic-Pituitary-Adrenal Axis

Positive Effect

Negative Feedback
Area of overlap does exist
Meticulous handling important as tube must be kept **frozen**.
Aprotinin tubes can be used without freezing sample – ask reference lab
Contact laboratory for supply of an insulated container.
PDH vs ADH

Why discriminate between PDH & ADH?

PDH & ADH are treated the same way medically

However; adrenalectomy, bilateral adrenalectomy are possible depending on patient, client, etc
(hypophysectomy- very rarely done)
If appropriate, Important to give clients the option of surgery
Adrenalectomy

- Indicated if:
- No evidence of metastases/invasion of abdominal vessels
- Dog in good enough shape to have surgery
- Surgeon who can do the surgery
- Owner will to pay.
- Strong recommendation: Vetoryl for 4-8 weeks prior to reverse metabolic derangements of hyperadrenocorticism
ADHAC - adrenalectomy

- Consider: VETORYL Capsule therapy for 3-4 weeks before surgery
- Decreased perioperative mortality
  (R. Nelson – Midwest Vet Conference 2010)
- Adrenocortical tumors are quite sensitive to trilostane – treat prior to adrenalectomy – 9/9 dogs underwent successful adrenalectomy after 8-10 weeks trilostane therapy
  (E. Feldman – JAVMA June 1, 2011)
Additional medical concerns with HAC

Hypertension
- has been clearly associated with HAC (>50% untreated HAC dogs)
- cause unknown
- doesn’t resolve with control of excess glucocorticoid

Hypercoagulable State
- HAC has been associated with pulmonary thromboembolism, aortic thrombosis & iliac thrombosis
- cause incompletely understood; probably multifactorial including: obesity, hypertension, ↑ hematocrit, sepsis, prolonged periods of recumbency, ↑ procoagulation factors, ↓ decreased antithrombin)

Adrenal tumours can sometimes rupture
IMPORTANT CONSIDERATIONS

Reconsider diagnosis /treatment if:

- Anorectic
- Eosinophilia
- Normal UCCR
- No clinical signs consistent with HAC

- Most sensitive and specific diagnostics tests are history and clinical examination
- Without clinical signs present, treatment is not warranted
- Dechra does not recommend trial therapy
Medical options for PDH & ADH

**VETORYL CAPSULES** (trilostane) - approved by FDA for

PDH and ADH, short acting enzyme inhibitor, reversible

Mitotane - not approved, cytotoxic effect

Ketoconazole - not approved, steroid synthesis inhibition, expensive

Anipryl (selegiline hydrochloride) – approved for PDH; increase dopamine concentration, decrease ACTH; poor efficacy
Vetoryl is now in 5 sizes
Vetoryl® (trilostane) reversibly inhibits 3β-hydroxysteroid dehydrogenase, blocking the production of cortisol and corticosterone.
VETORYL® CAPSULE (trilostane) activity – cortisol levels

![Graph showing the mean serum cortisol levels over time after administration of VETORYL® CAPSULE. The x-axis represents hours post-pill, and the y-axis represents mean serum cortisol levels (nmol/L). The graph shows a sharp decline in cortisol levels within 4 hours post-pill, reaching a minimum, and then a gradual increase over the next 20 hours.]
VETORYL® CAPSULE (trilostane) activity

Peak plasma trilostane concentrations at 0.5 – 1.5 hr; ketotrilostane 1-1.5 hr (active metabolite)
Rapidly absorbed from the gastrointestinal tract
Dosing with food significantly ↑ rate & extent of absorption (area under curve significantly larger with fed)
SID versus BID

- **Basis for SID**
  - All dogs in US FDA clinical trial started on SID treatment
  - 86% completed trial on SID
  - **Majority** of dogs without concurrent diabetes do well SID
  - There is a real **minority** of dogs without diabetes who do better on BID

- **Basis for BID**
  - Pharmacokinetic curve of trilostane, ketotrilostane and cortisol
  - After approximately 18 hr +/- drug is out of system
  - If concurrent diabetes, dose BID
VETORYL® CAPSULE - How can SID work?
How might SID fail?
VETORYL® CAPSULES (trilostane)

Dose rate **1-3 mg/lb** (2.2 – 6.7 mg/kg) (see data sheet)

Ideally start at LOWER end – near 1 mg/lb; round DOWN

Start SID (BID if needed) - Dose in morning if SID

There is NO induction period

(10 mg, 30 mg, 60 mg, 120 mg)

Blister packs of 30
Monitoring

Biochemistry (including electrolytes) & ACTH stimulation test (monitoring test of choice; 4-6 hours post dosing !!!);

TARGET RANGE = 1.45 ug/dl – 9.1 ug/dl (50-250 nmol/L)

1) 10 -14 days (Key re-check !), 4 weeks, 12 weeks after beginning Vetoryl therapy - quite common for cortisol levels to continue to drop from 1st to 2nd ACTH stim.

2) thereafter every 3 months

3) dose adjustment- do ACTH stim 10-14 days after starting new dose

ASSESSMENT OF CLINICAL SIGNS AT EACH RECHECK !!!!!
Controlling cost of ACTH Stimulation Test

- Determine correct dose for patient – 5 µg/kg IV or IM
- Determine how many tests can be done per vial (each vial contains 250 µg)- ex. 5 tests for 10 kg dog.
- Draw appropriate dose into individual plastic syringes for future testing in that patient.

Remaining Cortrosyn can be aliquoted into 1.0 mL plastic syringes. Store syringes frozen (-20°C) for up to 6 months; thaw to room temp before use
  - No preservative to inhibit bacterial growth

ACTH Stimulation Test

MONITORING TEST OF CHOICE ONCE THERAPY WITH VETORYL BEGINS!!

- TARGET RANGE 1.45-9.1 ug/dl
- (50-250 nmol/L)
- Critical Point - MUST be done in the 4-6 hour period post dosing with Vetoryl!
- If done too early or late – possibility to inappropriately raise the dose !!
- Galac, S, et al. UCCR cannot be used as an alternative to monitor trilostane dosage
- Proceedings ECVIM 2008
Timing of ACTH stimulation samples
4-6 hr post dosing
How to evaluate clinical progress

POSITIVE response to therapy =

1) **IMPROVEMENT IN CLINICAL SIGNS** – consider noting the time it takes the dog to eat; awareness of signs of over suppression (anorexia, lethargy)

2) **Post-ACTH cortisol 1.45 – 9.1 µg/dl** (50-250 nmol/L) tested 4-6 hrs after dosing – some prefer max of 4.5 – 5.0 µg/dl

Check monitoring flow chart
Optimizing VETORYL® CAPSULE treatment

Increase in ONCE daily dose required if:

Clinical signs **not** controlled **AND**
Post-ACTH cortisol > 9.1 µg/dl (250 nmol/l)
(performed 4-6 hrs after dosing)
(most dogs with post-cortisol values between 5.0-9.1 ug/dl respond well – if still symptomatic, increase dose)
Optimizing VETORYL® CAPSULE treatment

TWICE daily dosing may be required if

Clinical signs **not** controlled **BUT**
- Post-ACTH cortisol < 9.1 µg/dl (< 250 nmol/L )
  (performed 4-6 hours after dosing) –
  - **If owners do not note clinical signs apparent in evening** – then consider increasing SID dosing.
  - **If owners DO note clinical signs are apparent in evening or during night, but controlled during day,** then consider changing to BID dosing.
Change from SID to BID dosing
Use combination of capsule to slowly increase the dose and divide

Ex: 60 mg SID to 30 mg BID
or 60 mg am, 10 mg pm

Ex: patient on 30 mg SID – options
a) 30 mg am, 10 mg pm
b) 20 mg am, 20 mg pm

Importance of Monitoring
When to consider BID dosing

- Concurrent diabetes mellitus
- Dog dosed in morning, symptoms controlled during the day, but symptoms become apparent in evening.
- Dog still symptomatic, but ACTH stimulation results are within the target zone (1.45 – 9.1 ug/dl)
- Vet/owner not satisfied with progress
- Difficulty in managing concurrent hypertension with SID Vetoryl and/or anti-hypertensive medications
Corticosteroid deficiencies

Glucocorticoid deficiency
‘cortisol withdrawal syndrome’ – small % of dogs may develop these signs within 7-10 days of starting treatment

- abdominal “cramping”, hypoglycemia, weakness, lethargy, vomiting, anorexia, weight loss, poor response to stress

Tx: stop Vetoryl for ~ 7 days; restart lower dose

Mineralocorticoid deficiency

- weakness, lethargy, anorexia, v+/d+, collapse, shock, hypothermia, hyponatremia, hyperkalemia, Na+:K+ <27

Tx: stop Vetoryl; symptomatic therapy needed – IV fluids (0.9% NaCl), glucocorticoid, mineralocorticoid if needed
– IV fluids may be enough

Wait until clinical signs return – restart lower dose

IMPORTANT TO DIFFERENTIATE !! – clinical signs maybe similar - perform electrolytes and ACTH stimulation
Clinic Aids

Treatment and Monitoring Brochure (great flowchart)

• Ideal for posting in pharmacy/lab
• Quick reference for vets and techs
Treatment and Monitoring of Hyperadrenocorticism

**Day 1**
- Start VETORYL® capsules at approximately 1mg/kg (2.2mg/lb) once daily as per prescribing information.
- Give daily by mouth, with food, in the morning.

**Day 1-14**
- History, physical examination, serum biochemistry, with electrolytes.
- Perform ACTH skin test 4-6 hours after morning capsule.
- Ensure morning capsule was given with food.

**High ACTH serum cortisol (1400-1800 ng/dl) and/or clinical signs**
- Post-ACTH serum cortisol <48 µg/dl (4.0-5.0 µg/dl) after 24 hours, and clinically well.
- Continue treatment at current dose.
- If clinical signs are not controlled for at least 24 hours, change to ACTH skin test 1-2 days or return to daily.
- Return to Day 1 if necessary.

**Clinical signs not fully controlled**
- Post-ACTH serum cortisol >48 µg/dl (4.0-5.0 µg/dl) after 24 hours.
- Increase dose 25% (e.g., 1.25 mg/kg) and return to Day 1.
- If clinical signs are not controlled for at least 24 hours, change to ACTH skin test 1-2 days or return to daily.
- Return to Day 1 if necessary.

**Significant improvement**
- Post-ACTH serum cortisol <48 µg/dl (4.0-5.0 µg/dl) after 24 hours.
- Continue treatment at current dose.
- Continue monitoring history, physical examination, and electrolytes.

**Optional treatment**
- If symptoms persist, consider referral to a specialist.
- If symptoms recur, consider repeating ACTH skin test 1-2 days or return to daily.

For more information, contact Dechra Veterinary Technical Services at 1-866-333-3272.
VETORYL® CAPSULE - Changes in Clinical Signs

% Improved Clinical Signs

- Activity (N=33)
- Appetite (N=57)
- Panting (N=47)
- Thirst (N=76)
- Urination (N=74)
Contraindications

- Demonstrated hypersensitivity to trilostane
- Not to be used in animals suffering from primary hepatic disease and/or renal insufficiency – not hepatotoxic or nephrotoxic; based on metabolism and excretion patterns – risk/benefit assessment
- Do not use in pregnant or nursing bitches, or in any animals intended for breeding
- Do not use in animals weighing less than 3kg – caution – originally too few dogs recruited for clinical trial. Now, USE 5 mg!!
- Do not divide or open capsules
Special warnings/considerations

VETORYL® CAPSULES: has anti-aldosterone action (inhibits production); this effect MAY be additive with concomitant use of:

- K+-sparing diuretics /K+ supplements – risk of hyperkalemia
- ACE inhibitors – risk of hyperkalemia – risk/benefit and closely monitor

Concurrent diabetes mellitus – monitor insulin dosages closely; likely to see insulin dose decrease as cortisol levels are controlled - Key Opinion Leaders prefer BID dosing
Changing from mitotane to VETORYL® CAPSULES

• Different modes of action – cytolytic versus enzyme inhibition
• Step 1: Stop mitotane.
• Step 2: Wait until return of clinical signs – plasma ½ life of mitotane in humans is 18-159 days!
• Step 3: Do ACTH stimulation to prove adrenal reserve present. Post cortisol > 9.1 ug/dl (250 nmol/L) or higher
• Step 4: Start Vetoryl at LOW dose
• MONITOR
“Unmasking” underlying disease

- Corticosteroid-responsive problems can be “masked” prior to controlling cortisol
- Osteoarthritis
- Allergic skin disease
- With control of cortisol levels, clinical signs may appear, i.e., limping, scratching
Clinical Trials

• Vetoryl® Capsules: well researched with proven effectiveness
• Six premarketing clinical trials in Europe
  - carefully controlled research
• Field use in Europe since 2005
  - approved in UK 2005, Europe 2006
  - typical use in practice
  - pharmacovigilance data
# Clinical Trials vs Field Use

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<th>Clinical Trials</th>
<th>Field Use</th>
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<td>Inclusion/exclusion criteria</td>
<td>Real world</td>
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<tr>
<td>Strict protocol directives</td>
<td>Possible interaction with concurrent Dx and meds</td>
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<tr>
<td>Small number of patients</td>
<td>Larger number of patients</td>
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<tr>
<td>Thorough evaluation and follow up</td>
<td>Variable ages/ conditions</td>
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<tr>
<td>Committed pet owners and clinical investigators</td>
<td>Variable environments and owner compliance</td>
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<td>Owners tend to be different than real</td>
<td>Post-approval pharmacovigilance</td>
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<td>world – overly committed.</td>
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US Clinical Trial

107 dogs enrolled/223 dogs screened
- Various breeds
- Age range 6-16 years
- Body weight 3-53.5 kg
- Causes of HAC
  - 95 (89%) PDH
  - 5 dogs (5%) ADH
  - 1 dog (1%) PDH + ADH
  - 6 dogs inconclusive localization
US Clinical Trial

➤ Treatment dosages

• Targeted start 2.2-6.7 mg/kg/day (1-3 mg/lb)
• Actual range start 2.5-6.2 mg/kg/day (1.1 – 2.8 mg/lb)
• Actual range end 1.2-15.6 mg/kg/day (0.5 - 7.1 mg/lb)
• Mean actual dose at end 4.81 mg/kg/day (2.2 mg/lb)

➤ Dose adjustments based on clinical response & lab results

• increase - ACTH stim cortisol levels > 9.1 µg/dL and/or no clinical improvement
• decrease - ACTH stim cortisol <1.45 µg/dL @ 4-6 hrs. or if signs of over suppression (anorexia, vomiting, diarrhea, lethargy, depression)
US Clinical Trials

• Pre- and post- clinical trials chemistries

• Significant decreases in ALT, AST, alkaline phosphatase, Na:K ratio, cholesterol (p< 0.0001)- indicative of improvements in hyperadrenocorticism

• ↑ eosinophils, ↑ lymphocytes(counts and %), ↓ segmented neutrophils (counts and %) – represents improvement in stress leukogram associated with hyperadrenocorticism.
US Clinical Trial

80.0% cases remaining at Day 84 were treatment successes

• Success criteria post-ACTH stim <9.1 ug/dL + clinical improvement
US Clinical Trial

Safety assessment (all 107 dogs included)

- Most severe adverse reactions
  - Adrenal necrosis (rupture) 2 dogs
    - 1 dog died; 1 responded to discontinuation and supportive care
  - Hypoadrenocorticism 2 dogs – both responded to discontinuation; 1 needed further Tx

- Five dogs died or euthanized
  - Adrenal necrosis 1 dog
  - Progressive CHF 2 dogs (pre-existing)
  - Progressive CNS signs
  - Cognitive decline – inappropriate elimination
Re: Fear of adrenal necrosis

• “would you withhold insulin from a diabetic because you were afraid of hypoglycemia?” A Cook, TAMU

• “would you prefer to use a drug that had <2% of dogs develop adrenal necrosis, or a drug where 100% developed adrenal necrosis?”

• Importance of monitoring. D Bruyette, VCA West LA
Recent reference on adrenal necrosis

- “Supports the hypothesis that adrenal lesions seen in trilostane-treated dogs with PDHAC are caused by elevated ACTH levels and not be trilostane per se.”
US Clinical Trial

% Dogs Improved Clinical Signs Relative to Day 0
Owner’s perception

<table>
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<tr>
<th>Day</th>
<th>% Improved</th>
<th>Confidence Interval Lower Limit</th>
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<tr>
<td>14</td>
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Survival Times

- 37 animals with ADHAC
- 22/37 trilostane; 13/37 mitotane; 2 both
- Median survival time trilostane 353 days (95-528)
- Median survival time mitotane 102 days (43-277 days)
Survival Times

- 26 dogs who died median survival time – 549 days
- 51 dogs alive at end of 3 year study
- 1 dog lost to follow up after 241 days
Survival Times

• Median survival Trilostane 662 days
• Median survival Mitotane 708 days
Survival Times


• Mean survival time was 930 days
Survival time

- 53 dogs included
- Median age at Dx: 11 yr
- Mean age at Dx: 11 yr, 1 mo. (7-17)
- Median survival time- 304 days
- Mean survival time – 422 days (12-1680)
- 1 year survival fraction – 58%
- 2 year survival fraction – 28%
Prognostic factors for survival

- PDH – 85 dogs treated with trilostane/Vetoryl at one referral center
- Median survival = 852 days
- Clinical signs, liver enzymes, serum cortisol values from testing, proteinuria, systolic hypertension or frequency of trilostane were NOT associated with survival times.
- Hyperphosphatemia was a negative prognostic factor
- Fracassi, Corradini, et al…Vet Record 2014
What if VETORYL® CAPSULE therapy is not going as expected?

• Questions to ask?
• Why might this happen?
• Key information to determine
• What information do you need to obtain from the owner?
Vetoryl “logistics”

- Is the owner able to medicate the dog?
- Is the dog spitting out the capsule?
- How are the owners medicating the dog? As recommended? Something weird, such as mixing weekly dose in water and dosing with a syringe! Or sprinkling on food; dog not eating?
- Is Vetoryl being given with food?
Questions related to ACTH stimulation results

• When was the test performed relative to dosing with Vetoryl – MUST be 4-6 hr after.
• On day of ACTH monitoring, someone in practice must ask a) did dog receive Vetoryl that morning, and b) when? If not given, reschedule ACTH stimulation testing.
• Make sure dog is not being dosed at night
? Re: ACTH stim results (cont.)

- Was testing done in-house or sent out (Antech, Idexx, Marshfield, etc). If in-house, might suggest sending it out. (Equipment maintainance or calibration might be issue)

- Is the vet using Cortrosyn or ACTH gel? If gel, should probably repeat with Cortrosyn
ACTH stim results (cont.)

- Are symptoms still present? Is there any improvement? How long has the dog been on Vetoryl? Perhaps a dosage adjustment is needed (CALL TECH SERVICES!)
- Is concurrent disease present, such as diabetes, kidney disease, etc. All clinical signs of Cushing’s but *maybe* one can be caused by something else – (calcinosis cutis may be the exception.)
- Does the dog have Cushing’s?
How do you know the dose is too high?

- Anorexia and lethargy – common early signs
- Post-cortisol below 1.45 ug/dl
- Evidence of hyperkalemia, hyponatremia, and Na:K ratio < 27
Example 1 of actual calls to Tech Services

- 25 pound Beagle; 30 mg Vetoryl SID for 2 wks
- ACTH stim: pre 6.7  post 18.0 (1.45-9.1)
- Why this result?
  - 1) was Vetoryl given the morning of test
  - 2) is dog being dosed at night?
  - 3) are owners giving with food?
  - 4) are clinical signs improving?
Example 2

- 50 pound dog; 60 mg once a day.
- After 2 weeks therapy;
  ACTH post- 1.5 ug/dl (1.45-9.1) – this result is near the bottom of our range.
  Is this a concern and if so, why?
Case 3

- 35 pound mix breed; 30 mg Vetoryl SID for 8 weeks. Dosed in morning
- ACTH pre 2.5, post 7.0
- Clinical signs improving, but owners mention pu/pd, panting in the evening.
- Rec: 30 mg am, 10 mg pm
Baseline cortisol vs ACTH stim

- 50 lb dog; 60 mg SID. Doing well clinically, on Vetoryl for 10 months.
- ACTH stimulation pre 0.7; post 3.0
- What would you do if you only had baseline?
- What would you do if you have full ACTH stim?
Vetoryl® vs compounded trilostane

- **Vetoryl® Capsules**
- FDA approved®
- Tech support
- Consistency
- Confidence in content of capsule
- Liability – using approved product

- **Compounded**
- Not FDA approved
- No tech support
- Variability in dissolution and content
- Liability – VET!

Learnings from the “field”...

- Get the diagnosis RIGHT- don’t treat if not symptomatic
- There is NO induction period
- Start low end of dose guidance – SID adequate for vast majority
- If BID - start low, determine total daily dose and divide THAT dose in half.
- Never miss early monitoring (10d)
- Don’t dose increase at initial monitor (10d) unless patient is extremely symptomatic and high ACTH post-cortisol
- Over-suppression and glucocorticoid withdrawal most common avoidable consequences
- Beware of long-term decrease in dose requirements
Beau (left) and Cody Pre Tx
Beau(left) and Cody After TX
US Clinical Trial

Conclusion – Vetoryl highly effective for HAC and generally well-tolerated. Serious adverse events can occur, but appear to be rare. Monitoring very important.
Question? I'm all ears!
Questions?

Please feel free to contact:
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