MANAGING AND TREATING CANINE HYPOADRENOCORTICISM (ADDISON’S DISEASE)

OCTOBER 6, 2016
SIOUX CITY, IA
Agenda

• Background and Pathophysiology
• Clinical signs & Diagnostics
• Treatment & Monitoring
• Case discussions
• Clinical trial
BACKGROUND & PATHOPHYSIOLOGY
“The Great Pretender”

- First human case described mid-1800’s by Dr. Thomas Addison
- First canine case reported 1953
  - Clinical signs resemble other illnesses
  - Clients often see 2 or more veterinarians before a diagnosis is made
Hypoadrenocorticism

Syndrome of adrenal insufficiency

ACTH

Pituitary Gland

Secondary Addison’s

GC – glucocorticoids
MC - mineralocorticoids

Primary Addison’s

GC and MC deficiency

“TYPICAL”

Adrenal Glands

“ATYPICAL”

GC deficiency

Cortisol
The Adrenal Gland

**Cortex**
- **Glucocorticoids**
  (cortisol / corticosterone)
- **Mineralocorticoids**
  (aldosterone)
- **Androgens**
  (precursors of sex hormones)

**Medulla**
- **Catecholamines**
  (adrenaline / noradrenalin)
Regulation of Secretion

Glucocorticoids

The Normal Hypothalamic-Pituitary-Adrenal Axis

- Positive Effect
- Negative Feedback

Aldosterone

- Renin-Angiotensin Axis
  - $\uparrow$ Angiotensin II
    - Stimulated by $\downarrow$ ECF
  - $\uparrow$ Plasma K$^+$
- $\downarrow$ Plasma Na$^+$
- ACTH concentrations

Dechra Veterinary Products
Adrenocortical Hormone Synthesis

**Mineralocorticoid**
- Cholesterol → SCC → Pregnenolone
  - 3β HSD* → Progesterone
    - 21 OH* → 11-Deoxycorticosterone
      - 11 OH* → Corticosterone
        - 18 OH → 18-Hydroxycorticosterone
          - 18 OH D → Aldosterone
  - 17 OH

**Glucocorticoid**
- 17-Hydroxypregnenolone
  - 17 OH
  - 3β HSD* → 17-Hydroxyprogesterone
    - 21 OH* → 11-Deoxycortisol
      - 11 OH* → Cortisol

**Androgen**
- Dehydroepiandrosterone Sulfate (DHEAS)
  - 17,20 Lyase → Dehydroepiandrosterone
    - 3β HSD* → Androstenedione
      - 17β HSD → Testosterone
        - 17β Estradiol
## Cortisol Actions

<table>
<thead>
<tr>
<th>Liver</th>
<th>Blood</th>
<th>Immune System</th>
<th>Kidney/Urinary</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Increased gluconeogenesis</td>
<td>- Decreases in circulating lymphocytes</td>
<td>- Diminished inflammatory response</td>
<td>- Increased GFR and interference with</td>
<td>- Euphoria, depression, other behavioral changes</td>
</tr>
<tr>
<td>- Increased glycogen stores</td>
<td>- Decreases in circulating eosinophils</td>
<td>- Reduced immune response</td>
<td>vasopressin release or action (polyuria)</td>
<td></td>
</tr>
<tr>
<td>- Induction of certain enzymes</td>
<td>- Increase in circulating neutrophils</td>
<td></td>
<td>- Increased calcium excretion</td>
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<tr>
<td>Muscle</td>
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<tr>
<td>- Increased protein catabolism leads to muscle wasting and weakness</td>
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<tr>
<td>Bone</td>
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<tr>
<td>- Osteopenia associated with increased protein catabolism and neg. calcium balance</td>
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<td></td>
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<tr>
<td>Skin</td>
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<tr>
<td>- Increased protein catabolism – thin skin, poor wound healing and poor scar formation</td>
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<tr>
<td>- Possible calcium deposition</td>
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<tr>
<td>Adipose Tissue</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- Increased lipolysis</td>
<td></td>
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</tr>
<tr>
<td>- Redistribution of fat deposits</td>
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</table>
Aldosterone Actions

- **Primary site of action:**
  - Connecting segment of distal nephron
  - Collecting tubules of distal nephron

- **Stimulates**
  - $\text{Na}^+$ and $\text{Cl}^-$ resorption
  - $\text{K}^+$ and $\text{H}^+$ secretion
Primary Hypoadrenocorticism (Addison’s Disease)

Most Common Etiology
- Adrenal cortex injury/atrophy
  - Immune-mediated
  - Genetic link

Uncommon Etiologies
- Infiltrative Diseases
  - Granuloma, amyloidosis
  - Infarction, hemorrhage
  - Metastatic disease
- Iatrogenic — cytoxic (i.e. mitotane)
  - Usually GC deficiency
  - Aldosterone deficiency possible
Secondary Hypoadrenocorticism

Etiologies

• Impaired hypothalamic-pituitary activity *(tumors/trauma/inflammation/congenital defects)*
• Excessive, exogenous glucocorticoid supplementation

• Normal Na⁺/K⁺ levels
• Dx w/ ACTH stimulation test
• Tx w/ replacement glucocorticoid therapy
Consequences of Adrenal Failure

Cortisol deficiency – Multi-systemic signs
• Inappetence
• Weight loss
• Lethargy
• Gastrointestinal signs
• Hypoglycemia

Aldosterone deficiency – Salt and water
• Electrolyte disturbances
  – HypoNa, HypoCl, and HyperK
• Decreased plasma volume
• Polyuria and increased water loss
Typical Signalment

- Young to middle-aged dog
  - Typically 4 – 7 years (mean age of 4.5 years)
  - Range 5 months to 12 years
- Females overrepresented (70%)
- Any breed including mixed breeds can be affected
  - **Breed predilections:** Great Dane, Westie, Poodle (toy & standard), Basset Hound, Bearded Collie
  - **Breeds less likely to develop:** Lhaso, Yorkie, Boxer, Pomeranian, Boston Terrier, Dalmatian, Pit Bull, Shetland Sheepdog
History

• Usually owners identify a recent stressful event which proceeds onset of clinical signs
• Often chronic and often “waxing-and-waning”
• Majority present with anorexia & GI signs

• Can present in “Crisis”!
  – Hypovolemic shock
Clinical Signs

• Non-specific illness

• Common:
  – Inappetance
  – Lethargy/depression
  – Weakness
  – Dehydration
  – Vomiting
  – Diarrhea
    • Sometimes melena or frank blood
  – Weight loss

85% loss = clinical signs
Clinical Signs

• May be present:
  – Hematemesis
  – PU/PD
  – Anorexia
  – Bradycardia w/ hypovolemia
    • Usually tachycardia seen w/ hypovolemia
  – Weak pulse
  – Slow CRT
  – Hypothermia
  – Shaking/tremors
    • Seizures possible secondary to hypoglycemia
  – Painful/sensitive abdomen
  – Cutaneous hyperpigmentation
Addisonian Crisis

- Progression of disease
- Severe signs
  - Bradycardia
  - Hypovolemic
  - Hypotension
  - Hypothermia
  - Shock
  - Melena
  - Collapses
Diagnostics

- **CBC**
  - Normocytic, normochromic, non-regenerative anaemia
    - Can be masked by dehydration
    - Usually mild
  - Lack of stress leukogram
    - Lymphocytosis, eosinophilia

- **Electrolytes**
  - Metabolic acidosis
    - ↓ renal H⁺ excretion & ↑ lactic acid production
  - Na/K ratio < 27:1  
    *normal in atypical*
  - Hyponatremia
  - Hyperkalemia
  - Hypochloremia
  - Hypercalcemia
  - Hyperphosphatemia
Closer look at electrolytes…

- Na/K ration (normal > 27:1)
  - < 27:1 suspicious (89% sensitivity & 97% specificity)
  - < 20:1 “supportive”
  - Can be affected by numerous factors
    - (urogenital dz, gastrointestinal dz, cardiopulmonary dz)

**Addisons Dz usually causes changes in BOTH electrolytes**

- Significant disturbances are often underappreciated

- Na/K ratio is most useful for increasing suspicion for hypoadrenocorticism
Diagnostics

• Biochemical Profile:
  – Can be unremarkable
  – Hypoglycemia
    • If present, usually mild to modest
    • Can be severe enough to cause neurologic compromise
  – Hypocholesterolemia
  – Serum proteins $\uparrow$ (dehydration) or $\downarrow$ (GI bleeding)
    • Hypoalbuminemia – seen in ~ 39% of cases
  – Mild changes in hepatic enzymes
  – Pre-renal azotemia
    • Usually normal with atypical Addison’s

• U/A – low specific gravity (< 1.030) – despite dehydration
Diagnoses

- Thoracic radiographs
  - Microcardia and pulmonary hypoperfusion
    - Secondary to volume depletion
  - Megaesophagus
    - Uncommon & reversible

- Abdominal ultrasound
  - Undersized adrenal glands
  - Bilateral infiltrative disease *(very rare)*
Diagnostics

• Electrocardiogram (ECG)
  – Serum potassium > 7.5 mEq/l results in:
    • Loss of P waves
    • Tenting of the T waves
    • QRS complexes may be widened
    • Severe hyperkalemia: bradycardia and atrial standstill
Main Differentials

- Renal failure
- Chronic gastrointestinal disease
- Severe intestinal parasitism

**Azotemia + dehydration + dilute urine**

*Misdiagnosed as renal failure*
Increasing Suspicion...

- A repeat pattern of more common signs may suggest progressive adrenal insufficiency
  - Vomiting, diarrhea, weakness
- Response to fluid therapy can be used as an indicator to distinguish between renal failure & hypoadrenocorticism
Definitive Diagnosis

- ACTH Stimulation Test
  - Diagnostic test of choice
    - Not perfect test
    - Expense factor

Infrequently used tests
- Baseline Cortisol level
- Endogenous ACTH level
- Aldosterone level
1. Correct hypotension and hypovolemia
   – Normal saline preferred – shock doses
2. Provide an immediate source of glucocorticoids
   – Dexamethasone preferred (no interference w/ ACTH stim test)
     – 0.5 – 2 mg/kg q 2 – 6 hrs
3. Correct electrolyte imbalances
   – Often correct w/ fluid therapy
4. Correct acidosis
   – Can add bicarbonate to fluids if needed
5. Treat hypoglycemia if present
   – Add glucose to fluids if needed
6. Provide confirmation of the diagnosis
   – ACTH stimulation Test
Next Steps

- Monitor
  - Serum electrolytes and acid-base status
  - Urine output
  - ECG
  - Blood pressure
- Should see rapid improvement w/in 1 – 2 hr
- Start mineralocorticoid therapy once diagnosis confirmed
  - In crisis, can delay until volume and BP improved
  - NaCl fluid therapy can improve electrolytes in short-term
Maintenance Therapy

• Initiated once patient is stable
  – Good appetite
  – No continuing evidence of vomiting, diarrhea, weakness or depression
  – Serum electrolyte concentrations w/in normal range
Maintenance Therapy

Glucocorticoid replacement
• Goal – provide physiologic amount of GC

• Prednisone
  – Replacement dose – 0.1 – 0.4 mg/kg/d
  – Can be divided
  – Taper to lowest effective dose
  – Double dose on days of planned increased exercise or stress

• Only Tx needed for ‘atypical’ Addison’s Dz

• Possible to induce signs of cortisol excess
Maintenance Therapy
Mineralocorticoid replacement

• Fludrocortisone (Florinef®)
  – 0.015 – 0.02 mg/kg/day divided BID
  – Has some GC activity
  – Poor absorption, expensive

  OR

• Desoxycorticosterone pivalate (DOCP)
  – 2.2 mg/kg SC q 25 days initially
  – Max dose 50 mg/dog/dose (?)
  – Slow release of mineralocorticoids
  – Dose can be tapered or intervals adjusted based on clinical response
  – No GC activity

  – Single dose not harmful in dogs without Addison’s
ZYCORTAL® Suspension
(desoxycorticosterone pivalate injectable suspension)

- Received FDA approval December 2015
- A white aqueous suspension
- Shake thoroughly to re-suspend product
- Labeled for SC injection for replacement of mineralocorticoid deficiency in dogs w/ primary hypoadrenocorticism
GETTING STARTED
ZYCORTAL Suspension (DOCP)

- Day 0: initial dose 2.2 mg/kg SC
- Day 10: re-evaluate patient and measure Na⁺/K⁺ ratio
  - $T_{\text{max}}$ of DOCP

Clinical Signs
- Improved
  - Continue prednisone as before and re-evaluate day 25

Clinical Signs not resolved or worsened
- Adjust dose of prednisone and investigate other causes of clinical signs
  - **DO NOT administer additional DOCP**
**ZYCORTAL Suspension (DOCP)**

- **Day 25:** Evaluate patient & repeat Na\(^+\)/K\(^+\) ratio

  Clinically normal patient w/ normal Na\(^+\)/K\(^+\) ratio*

<table>
<thead>
<tr>
<th>Day 10 Na(^+)/K(^+) ratio</th>
<th>Day 25 ZYCORTAL® Dose</th>
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<tbody>
<tr>
<td>≥ 34</td>
<td>decrease dose to 2.0 mg/kg</td>
</tr>
<tr>
<td>32 to &lt; 34</td>
<td>decrease dose to 2.1 mg/kg</td>
</tr>
<tr>
<td>27 to &lt; 32</td>
<td>continue 2.2 mg/kg</td>
</tr>
<tr>
<td>≥ 24 to &lt; 27</td>
<td>increase dose to 2.3 mg/kg</td>
</tr>
<tr>
<td>&lt; 24</td>
<td>increase dose to 2.4 mg/kg</td>
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*If day 25 Na\(^+\)/K\(^+\) ratio > 32, it is possible to increase dosing interval*

Review day 10 Na\(^+\)/K\(^+\) ratio, adjust dose as per guidelines (see chart)
Increasing Dosing Interval

• Dog is clinically normal and Na\(^+\)/K\(^+\) ratio > 32 at day 25…
  – Evaluate electrolytes q 3 – 7 days
  – When Na\(^+\)/K\(^+\) ratio ≤ 32, administer 2.2 mg/kg of ZYCORTAL® Suspension
  – The time from the initial dose (day 0) to the time of 2\(^{nd}\) dose becomes the new dosing interval
    • e.g. if Na\(^+\)/K\(^+\) ratio is ≤ 32 on day 30, then 2\(^{nd}\) dose and subsequent doses are q 30 days.
    • e.g. if Na\(^+\)/K\(^+\) ratio is ≤ 32 on day 60, then 2\(^{nd}\) dose and subsequent doses are q 60 days.
ZYCORTAL Suspension (DOCP)

- Day 25: Evaluate patient & repeat Na⁺/K⁺ ratio

If the patient is not clinically normal and/or Na⁺/K⁺ ratio is abnormal:

1. **Clinical signs of PU/PD**
   - Decrease prednisone dose first; if PU/PD persists, decrease ZYCORTAL® dose

2. **Clinical signs of depression, lethargy, vomiting, diarrhea or weakness**
   - Increase prednisone dose

3. **Hyperkalemia, hyponatremia or Na⁺/K⁺ ratio < 27**
   - Decrease ZYCORTAL® dosing interval by 2 – 3 days

4. **Hypokalemia or hypernatremia**
   - Decrease ZYCORTAL® dose
Long Term Treatment

Reducing costs

• Get good control
  – Reduce hospital costs
  – Healthy patient

• Work to find minimal effective dose
  – Veterinarian works closely with the owner
  – The proximal costs may save long term costs

• Owner administers DOCP at home
  – Successful strategy in majority of cases
  – Must be part of long-term monitoring program with veterinarian.
Long Term Monitoring

Serial evaluation of clinical signs
• Owners’ observations helpful
• Deficiencies result in subtle manifestations

Serial evaluation of electrolytes
• Every 3-4 months
• Used to guide adjustments in mineralocorticoid dose

Adjusting GC replacement
• Short-term (2-3d) increase in maintenance dose when stress is anticipated
• Constitutional signs usually need increase in GC
• Decrease GC if there are signs of excess

• NO ROLE FOR SERIAL ACTH STIM TESTS
Excellent Prognosis

If:
Owners are educated about the disease.
Compliance is excellent
Close follow-up is vital for success
Warnings and Contraindications

- Do not use in dogs w/ previous hypersensitivity reactions to DOCP
- Use w/ caution in dogs with:
  - CHF
    - Effectiveness of ZYCORTAL® Suspension may be reduced if K⁺-sparing diuretics, such as spironolactone, are administered concurrently.
  - Edema
  - Severe renal disease
  - Primary hepatic failure
- DOCP may cause:
  - PU/PD
  - Increased blood volume, edema & cardiac enlargement
    - Excessive weight gain may indicate fluid retention secondary to Na⁺ retention
CASE STUDIES

[Image of a ring of dog photos]
Case 1

A Perfect Scenario
Signalment

- Holly
- 6 y.o., FS, Basset, 56# (25.5 kg)
- 2 d Hx
  - Vomiting
  - Lethargy
  - Diarrhea

- No pre-existing conditions
Diagnostics

• **Na⁺, K⁺ and Na⁺/K⁺**
  - Na⁺ = 130 (139-154); K⁺ = 6.3 (3.6-5.5)
  - Na⁺/K⁺ = 20.6 (≤ 27 = Addison’s)
  - Hyponatremia, hyperkalemia, with a low Na⁺/K⁺

**ACTH Stim**

• Baseline = 0.9 µg/dL
• 1-2hr post = 1.3 µg/dL
• Both values < 2µg/dL
• Addison’s
Plan

- **ZYCORTAL® Suspension (DOCP) 25 mg/ml**
  - 1 mg/# (2.2 mg/kg)
- **56#; 56 mg SQ (2.24 ml)**
- **Pred @ 0.2-0.4 mg/kg/day**
  - Taper as indicated
- **Rechecks**
  - 10d, electrolytes ONLY
  - 25d, electrolytes, +/- adjust dose
Recheck Data

- 10d $\text{Na}^+/\text{K}^+ = 30.2 \ (142/4.7)$, patient is well
- 25d $\text{Na}^+/\text{K}^+ = 31 \ (146/4.7)$

Clinically normal patient w/ normal $\text{Na}^+/\text{K}^+$ ratio*

Review day 10 $\text{Na}^+/\text{K}^+$ ratio, adjust dose as per guidelines (see chart)

<table>
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<th>Day 10 Na+/K+ ratio</th>
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<tr>
<td>&lt; 24</td>
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</tr>
</tbody>
</table>

Give same dose, NO Change; Recheck in 14 days
14d Recheck (from 2\textsuperscript{nd} dose)

- $\text{Na}^+/\text{K}^+ = 29.4$ (141/4.8, all normal)

  - Recheck in 14d (28d from her 2nd dose)
  
  - If all is well, this will be her maintenance dose.
Recheck 28d (from 2\textsuperscript{nd} dose):

- \( \text{Na}^+/\text{K}^+ = 28.6 \ (144/5.0) \)
- Dose to remain at 1 mg/#
- Check \( \text{Na}^+/\text{K}^+ \) q6 months as long as she’s well
Case 2

Adjusting Dose to Maintain 28d Interval
Signalment

- Chip
- 4 y.o., MN, Doberman Pinscher, 67# (30.5 kg)
- 2-3 Day History
  - Vomiting
  - Diarrhea
  - Shaking

- Occasional soft stool
  - Ongoing issue
**Diagnostics**

**Na⁺, K⁺, and Na⁺/K⁺**
- Na⁺ = 128 (139 - 154)
- K⁺ = 7 (3.6 - 5.5)
- Na⁺/K⁺ = 18.3 (≤ 27 = Addison’s)

**ACTH Stim**
- Baseline Cortisol = 0.7 µg/dL
- 1-2 hour post = 1.45 µg/dL
- Both < 2 µg/dL
- Addison’s
Plan

• **ZYCORTAL® Suspension (DOCP) 25 mg/ml**
  – 1 mg/# (2.2 mg/kg)
• **67# (30 kg); 67 mg SQ (2.7 ml)**
• **Pred @ 0.2-0.4 mg/kg/day**
  – Taper as indicated

• **Rechecks**
  – 10d, electrolytes only
  – 28 d, electrolytes, +/- adjust dose
Recheck Data

- 10d Na+/K+ = 31.7 (143/4.5), patient well
- 28d Na+/K+ = 28.2 (139/4.9)

Review day 10 Na⁺/K⁺ ratio, adjust dose as per guidelines (see chart)

Clinically normal patient w/ normal Na⁺/K⁺ ratio*

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</table>

- NO dose change
- Recheck in 28d
Recheck
Goal = Maintain a 28d Interval

• $\text{Na}^+ / \text{K}^+ = 33.3 \ (145 / 4.4)$

• **Delay dose**
  – Due to elevated ratio

• **Recheck 7d**
  – Electrolytes
Recheck

Goal = Maintain a 28d Interval

Last Zycortal dose 35 days ago @ 1 mg/#

• $\text{Na}^+/\text{K}^+ = 33.9 \ (146/4.3)$

• Decrease dose
  – 0.95 mg/# (vs 1 mg/#)

• 64 mg (2.6 ml) SQ

• Recheck 14d
Recheck

Goal = Maintain a 28d Interval

Last Zycortal dose 14 days ago at 0.95 mg/#

• $Na^+ / K^+ = 30.2$ (142/4.7), patient is well

• No changes
• Recheck 14d
Recheck

Goal = Maintain a 28d Interval

Last Zycortal dose 28 days ago; 0.95 mg/#

• $\text{Na}^+/\text{K}^+ = 35.4 \ (149/4.2)$

• **Decrease dose**
  - 0.9 mg/# (vs. 0.95 mg/#)
  - 60 mg SQ (2.4ml)

• Recheck in 28d
Recheck

Goal = Maintain a 28d Interval

Last Zycortal dose 28 d ago; 0.9mg/#

• $\text{Na}^+/\text{K}^+ = 36.3(149/4.1)$

• **Decrease dose**
  – 0.85 mg/# (vs 0.9 mg/#)
  – 57 mg SQ (2.3 ml)

• **Recheck in 28d**
Recheck

Goal = Maintain a 28d Interval

Last Zycortal dose 28 days ago; 0.85 mg/#

• Na⁺/K⁺ = 35.0(154/4.4)

• Decrease dose
  – 0.8 mg/# (vs 0.85)

• 54 mg SQ (2.1 ml)

• Recheck in 28d
Recheck
Goal = Maintain a 28d Interval

- $\text{Na}^+/\text{K}^+ = 30.0(142/4.7)$
- Within the target range!
- Stay at final dose
  - 0.8 mg/# (1.76 mg/kg)
- Administer q28 days
Chip - Summary

• Electrolyte range (Na/K)
  – 36.3 - 30.0

• Dose range
  – 1 mg/# - 0.8 mg/#

• 4 dosage adjustments required to maintain the desired 28 day interval
Case 3

Extending Dose Interval
Stella

- 4 y.o., FS, Pit Bull, 56# (24kg)
- 2 Day History
  - Vomiting
  - Lethargy
  - Inappetance
- No pre-existing conditions
Diagnostics

**Na⁺, K⁺, and Na⁺/K⁺**
- Na⁺ = 139 (141 - 156 mmol/L)
- K⁺ = 5.6 (4.0 - 5.6 mmol/L)
- Na⁺/K⁺ = 24.8 (≤ 27 = Addison’s)

**ACTH Stim**
- Baseline Cortisol = 0.5 µg/dL
- 1-2 hour post = 0.5 µg/dL
- Both < 2.0
- Addison’s
Plan

- **ZYCORTAL® Suspension (DOCP) 25 mg/ml**
- 1 mg/# (2.2 mg/kg)
- 56#; 56 mg SQ (2.2 ml)
- Pred 0.2-0.4 mg/kg/day

- **Rechecks**
  - 10d, electrolytes only
  - 25d, electrolytes, +/- dose adjustment

- **Goal = Extend dose interval beyond 28 days**
Recheck Data

- 10d Na+/K+ = 42.2 (152/3.6), patient well
- 28d Na+/K+ = 43.1 (155/3.6)

Review day 10 Na⁺/K⁺ ratio, adjust dose as per guidelines (see chart)

Clinically normal patient w/ normal Na⁺/K⁺ ratio*

Day 10 Na+/K+ ratio | Day 25 ZYCORTAL® Dose
--- | ---
≥ 34 | decrease dose to 2.0 mg/kg
32 to < 34 | decrease dose to 2.1 mg/kg
27 to < 32 | continue 2.2 mg/kg
≥ 24 to < 27 | increase dose to 2.3 mg/kg
< 24 | increase dose to 2.4 mg/kg

- Delay dose
- Recheck 7 day
- Goal = Extend dose interval
Recheck

Goal = Extend dose interval

• Goal = $\frac{Na^+/K^+}{K^+} \leq 32$

• $Na^+/K^+ = 40.8 \ (155/3.8)$

• Delay dose
  – 35 days from last dose

• Recheck in another 7d
Recheck
Goal = Extend dose interval

• \( \text{Na}^+/\text{K}^+ = 39.7 \ (151/3.8) \)
• Delay dose
  – 42 days from last dose

• Recheck in 14 days (vs 7) since electrolytes are consistently high
Recheck
Goal = Extend dose interval

• $\text{Na}^+ / \text{K}^+ = 34.2 \ (154/4.5)$
• Delay dose
  – 56 days from last dose

• Recheck in 7 days
Recheck
Goal = Extend Dosing Interval

- 63 days from last Zycortal Suspension
- $\text{Na}^+ / \text{K}^+ = 31.6 \ (152/4.8)$
- Wt. = 60#
- Dose 1 mg/# (2.2 mg/kg)
- 60 mg SQ (2.4 ml)
- Recheck at 28d
Recheck
Goal = Extend dose interval

- Na\(^+\)/K\(^+\) = 47.6 (157/3.3)

- Recheck in another 42d
  - 60 days from last dose
Recheck
Goal = Extend dose interval

• $\text{Na}^+/\text{K}^+ = 32$ (153/4.7)

• Wt. = 60.8#

• 1 mg/# (2.2 mg/kg)
  – 60.8 mg SQ (2.4 ml)

• Maintain 65d interval
Stella - Summary

- 10d Na+/K+ = 42.2 (152/3.6), patient well
- 28d Na+/K+ = 43.1 (155/3.6), delay, recheck 7d
- Na+/K+ = 40.8 (155/3.8); delay dose, recheck 7d
- Na+/K+ = 39.7 (151/3.8); delay, recheck 14d
- Na+/K+ = 34.2 (154/4.5); delay, recheck 7d
- Na+/K+ = 31.6 (152/4.8); treated, recheck 28d
- Na+/K+ = 47.6 (157/3.3); delay, recheck in 42d
- Na+/K+ = 32 (153/4.7); treated, maintain 65d interval
Clinical Trial

• Multi-center
• 152 dogs of various breeds
  • Age range: 6 mo to 12.4 yr
  • 2.1 to 134.6 lb
  • 74 male (9 intact, 65 castrated)
  • 78 female (10 intact, 68 spayed)
    – 133 newly diagnosed
    – 19 existing cases
      • tx w/ fludrocortisone or deoxycorticosterone acetate for at least 30 days prior to enrollment
• Dx based on
  – ACTH stim ≤ 2 mg/dl both pre & post
  – Na⁺/K⁺ ratio ≤ 27
  – One or more clinical signs consistent w/ primary hypoadrenocorticism
Clinical Trial

- 113 of 152 received ZYCORTAL® Suspension
- 39 of 152 received active control
- Initial dose of either 2.2. mg/kg then dose adjusted based on needs of patient
- Mean final dose:
  - ZYCORTAL®: 1.93 mg/kg (1.15 – 2.53 mg/kg)
  - Active control: 1.96 mg/kg (1.39 – 2.8 mg/kg)
- Mean final dose interval:
  - ZYCORTAL®: 38.5 days (20 – 99 days)
  - Active control: 38.8 days (23 – 70 days)
Clinical Trial

• Dogs evaluated at days 25, 60, 90, 120, 150 & 180 days
  – PE, clinical assessment, in-house serum Na\(^+\) & K\(^+\) concentrations & ratio calculation
  – Hematology & biochemical profile day 25
  – Biochemical profile & U/A day 90 & 180

• Tx Success:
  1. Investigator determined dog clinical normal or had reduced clinical signs compared to baseline
  2. Na\(^+\) & K\(^+\) concentrations w/in reference range or ratio between 27 - 32
Clinical Trial

- 135 dogs included in statistical analysis
  - 101 ZYCORTAL®
  - 34 Active control group

- ZYCORTAL® Suspension: 86.2% success rate

- Active control group: 85.1% success rate

- Adverse events similar in both
  - Related to signs of Addison’s
    (PU/PD, depression, V/D, etc.)
Diagnostic Algorithm

Step-by-step diagnosis of hypoadrenocorticism

Courtesy of Professor Ian Ramsey, University of Glasgow

- Clinical history
  - No previous relevant medical history
  - Tachycardia, obesity
  - Normal Thr and R
  - Increased white blood cell count with stress leukogram
- Physical examination
  - Slower heart rate, thinner or more dehydrated than expected
- Routine biochemistry (remember electrolytes)
  - Low Na and/or high K (important), Na : K ratio < 1.7, low albumin, glucose and/or increased ana and creatinine
  - Anaemia and low white blood cell count with relative lymphocytosis, eosinophilia and neutrophilia, lack of stress leukogram
- Haematology (blood smear)
- ACTH stimulation test
  - Post-ACTH cortisol > 55 nmol/L*
    - Hypoadrenocorticism can be ruled out
  - Post-ACTH cortisol < 55 nmol/L*
    - No history of steroid application confirmed
    - Hypoadrenocorticism highly likely

*Veterinarians should use the specific reference ranges of their diagnostic laboratory.
Monitoring & Dose Adjustment Algorithm

Zycortal monitoring and dose adjustments

Day 1
- First dose

Day 10
- Interim monitoring
  - Check clinical signs and electrolytes. If clinically abnormal, adjust glucocorticoid dose and/or look for other causes.

Day 25
- Second dose
  - Check clinical signs and electrolytes

Clinically normal
- Adjust dose according to Day 10 Na/K ratio as described in table below

Clinically abnormal
- Abnormal electrolytes or abnormal Na/K ratio
- PUPD
  - Depression, lethargy, vomiting, diarrhea or weakness
- Other clinical signs

If the Day 10 Na/K ratio is:
- ≥ 34: Decrease dose to 2.0 mg/kg body weight
- 32 to < 34: Decrease dose to 2.1 mg/kg body weight
- 27 to < 32: Continue 2.2 mg/kg body weight dose
- ≥ 24 to < 27: Increase dose to 2.3 mg/kg body weight
- < 24: Increase dose to 2.4 mg/kg body weight

Instead of changing the dose, the dose interval can be changed as well.
For more information contact technical services at technical@dechra.com

Subsequent doses and long-term management:
Once the dog is optimally controlled, keep the same dosing regimen. In case of abnormal clinical condition or abnormal electrolytes at subsequent visits continue to titrate the dose in similar increments as described above. In times of stress the glucocorticoid dose may need to be increased.
Additioinal Resources

- ZYCORTAL® Suspension package insert
- Technical & Client Brochures
- Addison’s Case Studies
- Dechra Technical Services Team: 866-933-2472
- Dechra online CE: www.DechraCE.com
- Dechra technical brochures
- Dr. Mark Peterson blog: http://endocrinevet.blogspot.com
- Dechra Field Sales Managers
- Website: www.dechra-us.com
Resources

QUESTIONS?