Diagnosis: Cushing’s Disease….
Now What?

Alyssa Mourning, DVM
Raking in the CE
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Outline
• Review of pathophysiology, signalment and clinical signs
• Diagnostic testing
• Treatment options

Pathophysiology
• Corticotropin Releasing Hormone (CRH)
  – Hypothalamus
• Adrenocorticotropic Hormone (ACTH)
  – Pituitary
  – Stimulates glucocorticoid from adrenal cortex
  – Suppressed by high doses of exogenous corticosteroids
  – Negative feedback by cortisol
  – Negative feedback by ACTH
**Pathophysiology**

- **Adrenal gland**
  - Cortex
    - Cortisol
      - Fasciculata and reticularis
        - 17\(^\alpha\)-hydroxylase
        - Cholesterol to pregnenolone – rate limiting step
        - Major site of ACTH action
  - Aldosterone
    - Zona glomerulosa
    - Renin-angiotensin system
    - Potassium concentration

**Adrenal gland**

<table>
<thead>
<tr>
<th>Mineralocorticoid</th>
<th>Glucocorticoid</th>
<th>Androgen</th>
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<tr>
<td>Cholesterol</td>
<td>17-OH</td>
<td>Androstenedione</td>
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<tr>
<td>Progesterone</td>
<td>17-OH</td>
<td>Androstenedione</td>
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<tr>
<td>11-Deoxy cortisol</td>
<td>11-OH*</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Cortisol</td>
<td>18-OH</td>
<td>Testosterone</td>
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<tr>
<td>18-Hydroxy cortisol</td>
<td>18 OH D</td>
<td>17(\alpha)-Oxosterol</td>
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**Pathophysiology**

- Pituitary Dependent Hyperadrenocorticism (PDH)
  - 80-85% of cases
    - Most are benign adenomas; microadenomas (< 1 cm)
      - Pars distalis
    - 15-25% can be large and have invasive tendencies
      (macroadenoma, > 1 cm)
      - Dorsal expansion (hypothalamus)
    - Malignant
      - rare
Pathophysiology

- **PDH**
  - Chronic excessive secretion of ACTH
  - Adrenal gland hyperplasia
    - 5-10% of all cases have adrenocortical nodular hyperplasia (not adrenal dependent)
  - Excessive cortisol secretion
    - Inhibits normal pituitary and hypothalamic function
      - TSH (secondary hypothyroidism)
      - GH (failure to grow in puppies)
      - LH, FSH (failure of females to cycle, testicular atrophy in males)

Pathophysiology

- **Adrenal tumor hyperadrenocorticism (AT)**
  - Adenomas vs carcinomas
  - Cortisol secretion
    - Episodic, random
  - Retain ACTH receptors
    - Respond to ACTH
  - Typically unresponsive to manipulation of hypothalamic-pituitary axis with drugs
    - dexamethasone
  - Cortical atrophy of other adrenal gland
    - negative feedback

Pathophysiology

- **AT**
  - Adenoma
    - 1-6cm
    - Calcification
      - 50% of tumors
  - Carcinomas
    - Tend to be larger than adenoma
    - Highly vascular
    - Partial calcification
      - 50%
    - Metastasis (liver, lungs, other)
Pathophysiology

- Adrenocortical tumor
  - Bilateral adrenal neoplasia
    - rare
  - In conjunction with pheochromocytoma?
    - Can have both…
      - PDH and AT
      - Extremely rare, but reported

Signalment

- Middle aged, older
  - AT > PDH
- 55-60% PDH ♂, 60-65% AT ♂
- Breeds
  - Poodles
  - Dachshunds
  - Terrier breeds
  - Beagles
  - GSD
  - Boston terrier, Boxer at increased risk
- Weight
  - 75% of PDH are < 20kg
  - 50% AT are > 20kg

Clinical signs

- Clinical disorder, therefore need for clinical signs
- PU/PD
- PP
- Enlarged abdomen
- Muscle weakness/lethargy/lameness
- Skin
- Obesity
- Respiratory
- Other, rare symptoms
PU/PD

- 80-85% of HAC cases
- Normal water intake
  - 40-60ml/kg/day
- Cortisol interference with release of ADH
  - Form of central diabetes insipidus

Polyphagia

- > 90% of dogs
- Direct effect of increased glucocorticoid

Abdominal Enlargement

- Potbelly/pendulous abdomen
- > 80% of cases
- Increased weight of abdominal organs
  - Redistribution of fat (to omentum)
  - Hepatomegaly
- Decreased strength of abdominal muscles
  - Catabolic effects of cortisol
Muscle Weakness and Lameness

• Muscle wasting
• Rarely are these signs significant

• Cruciate ruptures
• Patellar luxation

Skin disease

• Alopecia
  – Atrophy of hair follicles
    • Points of wear; flanks, perineum, abdomen
    • Failure to regrow hair after shaving
• Thin skin, pyoderma
  – Comedones (keratin plugged follicles)
• Poor healing
  – Decreased fibrous tissue

Calcinotis cutis

• Dystrophic calcium deposition in dermis, subcutis
• Firm, irregular plaques
• Locations
  – Temporal region of head
  – Dorsal midline
  – Neck
  – Ventral abdomen
  – Inguinal area
Obesity

- Owner complaint; usually not true weight gain
  - Fat redistribution
  - Pot belly

- Truncal obesity
  - Loss of muscle and fat from extremities

Respiratory signs

- Panting
  - Increased fat deposition over thorax
  - Muscle wasting
  - Weakness of muscles involved in breathing
  - Increased pressure on diaphragm
  - Pulmonary interstitial mineralization
  - Thromboembolism

Myopathy

- Rare
- Persistent, active, muscle contraction after voluntary effort
  - Stiff gait
  - Non-inflammatory degenerative myopathy
  - Cause not known
  - Resolution after treatment unpredictable
PE findings

- Hyperpigmentation (increased melanocytes)
- Skin alterations
- Hepatomegaly
  - Centrilobular vacuolation
  - Hepatocellular glycogen accumulation
- SARDS
- Acute weakness/painful abdomen
  - Rupture of adrenal mass

Laboratory findings

- CBC
  - Neutrophilia, monocytosis, lymphopenia, eosinopenia
- Mild increased glucose
  - Hepatic gluconeogenesis
  - Anti-insulin effects

Laboratory findings

- Increased ALT
  - Mild, < 400 IU/L
    - Damage due to swollen cells, glycogen accumulation, interference with blood flow
- Increased ALP
  - Increased rate of production
    - Hepatic glycogen deposition, vacuolization
    - Steroid induced ALP
      - isoenzyme
Laboratory findings

- ↑ cholesterol, triglycerides, lipemia
  - Lipolysis

- Urinalysis
  - Dilute (likely < 1.020)
  - Proteinuria
    - Typically UP:C < 3, but rarely can be higher (up to 8-10)
    - Likely consequence of hypertension
  - UTI (immunosuppression, polyuria, muscle weakness)

Imaging

- Radiography
  - Hepatomegaly
  - Adrenal mass
    - 15% of cases are adrenal
      - Of these, only 50% are calcified
  - Mineralization
    - Bronchial, tracheal ring
    - Calcinosis cutis
  - Generalized interstitial lung pattern

Imaging

- Ultrasound
  - Adrenal size (normal = < 0.75cm)
  - Adrenal echogenicity = hypoechoic to renal cortex
  - Adrenal tumors = enlarged, irregular, rounded
    - < 2cm likely malignant
    - > 4cm malignant
  - Incidental mass?
    - Reassess in 4-6 weeks if not invading vital structures
Complications from HAC

- Hypertension
  - Hypervolemia

- Pyelonephritis
  - Immunosuppression

- Urinary calculi
  - Increased calcium excretion

- CHF
  - Hypervolemia, myocardial workload increases, followed by hypertrophy

Complications from HAC

- Diabetes
  - Insulin resistance

- Pulmonary thromboembolism (PTE)
  - Hypercoagulable state

- Obesity, hypertension, increased HCT, sepsis

Pituitary macrotumors

- Signs – typically subtle, slowly progressive
- Dull, listless, inappetant
- Disorientation
- Altered mentation, ataxia, pacing
- Circling, head pressing, blindness, seizures, coma
- Diagnosis – advanced imaging (CT, MRI)
  - Endocrine tests cannot help not differentiate
Diagnostic Testing

- Screening tests: Does he or doesn't he?
  - ACTH stimulation
  - Low Dose Dexamethasone Suppression (LDDS)
  - Urine cortisol:creatinine

  Sensitive, but not specific
  - Good negative predictive value
    - (if negative, unlikely HAC)
  - Collect at home?

Urine cortisol:creatinine

ACTH stimulation

- Thought process
  - Either PDH or AT, adrenal cortex has capacity to secrete more cortisol when stimulated by ACTH
- Protocol
  - No prep needed
  - Draw sample, give ACTH, draw sample 1-2 hours later
    - Synthetic, draw 1 hour post
- HAC?
  - Should capture 60% of HAC
  - False positive in up to 15% of cases (non-adrenal disease)
  - Iatrogenic HAC
  - Response to treatment
Low Dose Dexamethasone Suppression

- Inhibits pituitary secretion of ACTH via negative feedback
  - Decreases endogenous cortisol secretion for up to 24-48 hours
  - Do not run on ill dogs
  - When used appropriately, sensitivity can reach 99%
  - Affected by more variables than ACTH stimulation

Low Dose Dexamethasone Suppression

- PDH
  - Resistant to normal negative feedback mechanism

- AT
  - Already producing excessive cortisol
  - Already negative feedback to ACTH

Low Dose Dexamethasone Suppression

- PDH
  - Cortisol > 1.4µg/dl @ 8 hour
  - Results
    - Unchanged (35%)
      - Greater than basal
      - Same as basal
      - Suppressed, but greater than 50% of basal (lack of suppression)
    - Decreased (65%)
      - < 1.4µg/dl @ 4 hour
      - < 50% of basal @ 4 hour
      - < 50% of basal @ 8 hour
Low Dose Dexamethasone Suppression

• AT
  – Cortisol > 1.4µg/dl @ 8 hour
  – Cortisol levels do NOT suppress at any time

Diagnostic Testing

• Discriminating tests
  – LDDS
  – Endogenous ACTH
  – High dose dexamethasone suppression (HDDS)
  – CT/MRI (macroadenoma)

LDDS

• Cortisol > 1.4µg/dl @ 8 hour
• Dexamethasone transiently suppresses ACTH (60-65%)
  – 3-6 hours duration (rather than 24-48 as in normal dogs)
• 1 of 3 things needs to happen (already confirmed HAC) to be consistent with PDH (60-65%)
  – 4 hr cortisol less than 1.4µg/dl
  – 4 hr cortisol less than 50% of basal level
  – 8 hr cortisol concentration less than 50% basal
• Lack of suppression = non-specific
Endogenous ACTH

- AT, iatrogenic HAC
  - Suppressed ACTH
- PDH
  - Increased ACTH

Careful handling/sampling required

HDDS

- AT
  - Never suppresses
- PDH
  - May be dose dependent (larger doses may suppress ACTH via negative feedback)

Suppression:
- Cortisol < 50% baseline at 4 OR 8 hours
- Cortisol < 1.4µg/dl at 4 OR 8 hours

- 75% of PDH cases meet the above criteria

HDDS

- AT
  - No suppression

- PDH
  - 60% of cases will have cortisol < 50% baseline at 4 and/or 8 hours
MRI/CT scan

• Dogs with PDH with neurologic signs

• Testing for prognostic purposes in PDH dogs
  – Irradiation of tumors

Treatment

• Medical therapy
  – Mitotane
  – Trilostane
  – Ketoconazole

• Surgical therapy
  – Adrenalectomy
  – Hypophysectomy

• Confirm HAC

• Differentiate between pituitary vs adrenal
  – Treatment options
  – Prognosis
  – Client expectations
Mitotane

- Adrenocortico lytic drug
  - Necrosis to zona fasciculata and zona reticularis
- Most dogs respond within 5-9 days

Mitotane

- Loading
  - 50mg/kg/day, DIVIDED
  - Give with food
  - Phase should be stopped/discontinued if:
    - Appetite
      - Feed 2/3 of normal intake, divided
      - Once any sign of reduction in appetite, phase is complete
    - Water intake
      - Takes < 66ml/kg/day
    - Vomiting
    - Diarrhea
    - Lethargy

Mitotane

- Communicate with owner
- Recheck patient within a week of starting drug

- Goals
  - Clinically normal dog
  - ACTH
    - Pre < 5µg/dl
    - Post > 1µg/dl, but < 5µg/dl
Mitotane

- What can an owner expect:
  - Increased activity within a week
  - Decreased PU/PD within a week or two
  - Improved muscle strength in days to weeks
  - Improved pot bellied appearance days to weeks
  - Months before improvement noted in thin skin, panting, alopecia, calcinotis cutis
  - Months for liver enzymes, cholesterol
  - Blood pressure improvement 3-6 months

Mitotane and the Adrenal tumor

- Same initial treatment protocol
- One week
  - Improved ACTH stim, but not ideal: continue on 50mg/kg/day, divided
  - If results similar to that prior to therapy, increase to 75-100mg/kg/day, divided
- Recheck ACTH stim @ day 14
  - Repeat as above
  - May need to continue to increase dose until response is documented
- ~60% response rate
- Median survival 16 months

Mitotane: maintenance dosing

- Respond, but post ACTH stim < 1µg/dl
  - Stop for 2 weeks
  - 25mg/kg/week
- Post ACTH stim >1µg/dl but < 3µg/dl
  - 25mg/kg/week
- Post ACTH stim > 3µg/dl
  - 50mg/kg/week
- Doses should always be divided into what is practical
Mitotane: maintenance dosing

• Recheck ACTH stim 1, 3 months after maintenance therapy
• If post > 5µg/dl, then can increase dose by 25%
• Recheck patients, if stable, every 3-4 months
  – Physical examination
  – ACTH stimulation testing

Mitotane: prognosis

• Median life span after diagnosis and treatment
  – 31.6 months
  • Median age of diagnosis is 11 years
• Relapses are common
• Overtreatment can occur
  – Crisis

Trilostane

• Inhibits 3β–hydroxysteroid dehydrogenase
  – inhibits the synthesis of several steroids in the adrenal cortex, including glucocorticoids and mineralocorticoids
• Dosing
    • Low dose twice daily (~1mg/kg bid)
      – Better tolerated, but slower to improve
    • Higher dose once daily (30mg/dog)
      – Improved more rapidly, but also developed signs of hypoadrenocorticism in 2/7 dogs
Trilostane - compounded

  - Trilostane content of compounded capsules may vary from the prescribed strength, and dissolution characteristics may not match those of the licensed product
  - The use of compounded trilostane products may therefore negatively impact the management of dogs with hyperadrenocorticism.

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!

Trilostane

- Monitoring
  - 2-6 hours after dosing
  - ACTH stimulation
  - Goals — post stim: 1-5 µg/dL

- Expectations
  - 60-100% improvement within 3-6 months
How do you know the dose is too high?

- Anorexia and lethargy – common early signs
- Post-cortisol below 1.45 µg/dl
- Evidence of hyperkalemia, hyponatremia, and Na:K ratio < 27

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 µg/dl)
- Vet/owner not satisfied with progress
- Difficulty in managing concurrent hypertension with SID Vetoryl and/or anti-hypertensive medications

Timing of ACTH stimulation samples

4-6 hr post dosing
VETORYL® 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

VETORYL® CAPSULES

available in: 10 mg, 30 mg, 60mg, and 120mg

Mitotane vs Trilostane

- Barker, et. al
  - 148 dogs with PDH
  - 2 groups
    - Mitotane
    - Trilostane
  - Median survival
    - Mitotane = 708 days
    - Trilostane = 662 days
    - *no statistical difference
Mitotane vs. Trilostane

- Helm, et. al
  - 37 dogs with AT
  - 3 groups
    - Mitotane
    - Trilostane
    - Both
  - No statistical difference

Key differences between a dog on Vetoryl versus Lysodren

1) NO induction period with Vetoryl
2) Target ranges:
   - Vetoryl 1.45 – 9.1 ug/dl
   - Lysodren 1.45 – 4.5 ug/dl
   - Target range is broader with Vetoryl
3) ACTH stim: 4-6 hour dosing with Vetoryl
   - ACTH stim: anytime with Lysodren

Ketoconazole

- Affects steroid biosynthesis at high doses
  - 30mg/kg/day
- Indications?
  - Not tolerating traditional therapy
- Cons
  - Expensive
  - Failure to respond
  - BID dosing indefinitely
Adrenalectomy

- Prognosis: Excellent
  - IF tumor can be removed and patient survives 1st 2 weeks
  - Average life expectancy = 36 months
- Adrenal tumors spread to liver, lungs
- Advanced imaging
  - Small (= ½ kidney) = likely benign
  - Large (≥ 1 kidney) = not likely to be benign
- Surgical candidate?
  - BP, UP, UC
  - Tumor size
  - Metastasis
  - Owner understanding – thromboembolic complications

Hypophysectomy


- 150 dogs
- Survival rates
  - 1year – 84%
  - 2year – 76%
  - 3year – 72%
  - 4year – 68%
- 8% died
- 6 had incomplete surgeries
- Relapse free rates
  - 1year – 88%
  - 2year – 75%
  - 3year – 66%
  - 4year – 58%
- Risks
  - CDI
  - KCS

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