New Therapies for Pituitary Diseases

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Outline

• Normal anatomy/physiology
• Pituitary disease
  • Pituitary-dependent hyperadrenocorticism
  • Acromegaly

Pituitary Gland

• Posterior Pituitary
  • Pars nervosa
• Anterior Pituitary
  • Pars intermedia
  • Pars distalis

Hormones of the anterior pituitary

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<th>% of secretory cells</th>
<th>Stain affinity</th>
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<td>50</td>
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<td>10-30</td>
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<td>ACTH</td>
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<td>Gonadotrope</td>
<td>FSH, LH</td>
<td>20</td>
<td>Basophilic</td>
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• From Ganong, Review of Medical Physiology

Pituitary Disease

• Tumors
  • Functional - any cell type possible
    • Corticotrope adenoma in the dog
    • Somatotrope adenoma in the cat
  • Non-functional
    • Mass effect
    • Clinically silent
• Other
  • Diabetes insipidus
  • Hypopituitarism

Canine Cushing’s Syndrome (CCS)

• Syndrome characterised by chronic excess of systemic cortisol
  • Pituitary tumor making excess ACTH (most common)
  • Pituitary hyperplasia due to excess CRH (not dogs and cats)
  • Autonomous adrenocortical tumor
  • Iatrogenic
    • Excess ACTH (rare)
    • Excess glucocorticoids (common)
  • (ACTH from non-pituitary sources - not dogs and cats)
Canine Pituitary-Dependent Hyperadrenocorticism (PDH)

- Etiology
- Clinical signs
- Treatment options
  - Adrenals
  - Pituitary

Canine PDH

- 80-85% dogs with HAC
- Most have pituitary tumor in pars distalis
  - Can occur in pars intermedia
- Most microadenomas (< 1 cm)
- 10-20% macroadenomas (> 1 cm)
- Pituitary “hyperplasia” poorly defined and rare
- Little support for hypothalamic cause of PDH

Canine PDH

- Pituitary Tumors: 33 dogs*
  - Adenoma (20 dogs - 61%)
  - Invasive adenoma (11 dogs - 33%)
    - Locally invasive
    - Compress local structures
  - Adenocarcinoma (1 dog - 6%)
    - Evidence of metastasis

*Pollard et al, JVIM, 2010, 24:160-165

Neurological Signs in PDH?

- Wood et al, 2007 - JAVMA
- 157 dogs with PDH
  - 73 had CNS-specific neuro signs
    - 48 (66%) had a detectable pituitary tumor
    - 41 (56%) had no detectable tumor, or a microtumor
  - 84 no CNS-specific neuro signs
    - 60 (71%) had a detectable pituitary tumor
    - 17 (20%) had a macrotumor

Neurological Signs in PDH?

- Wood et al, 2007 - JAVMA
- 157 dogs with PDH
- Vague signs more specific for macrotumor than CNS-specific signs
  - Lethargy, dullness
  - Loss of appetite

Neurological Signs in PDH?

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  - Loss of appetite
PDH Therapy: Mitotane

- (Occasionally used for AT:
  - Pre-surgical stabilization
  - Surgery not an option)

- Effective
- Safe, if used carefully

Mitotane

- 2 phases of therapy:
  - Loading/induction
  - Maintenance

- Monitoring is key:
  - ACTH stimulation test
    - Determine end-point of induction
    - Confirm ongoing successful maintenance

Mitotane: Induction

- Successful induction is achieved when basal and post-ACTH cortisol: both < 4 (5) µg/dl and > 1 µg/dl
- Most cases take 5 - 15 days

Mitotane: Maintenance

- Give daily induction dose weekly (divided)

  - Example:
    - 10 kg dog required 250 mg BID for induction (7 days)
    - Maintenance dose would be 250 mg twice weekly
    - Divide dose (125 mg BID)

- Continue to monitor with ACTH stimulation tests

Mitotane: Side-Effects

- Vomiting, diarrhea, loss of appetite
  - Not uncommon, often transient

- Lethargy
  - Not uncommon, often transient

- Neurological signs (DDx: pituitary tumor)
  - Very uncommon, usually transient
    - Blindness, ataxia, obtundation, circling, head-pressing
    - Reduce dose, give smaller increments

- Hepatotoxicity
  - Webb, JAAHA 2006
Iatrogenic Hypoadrenocorticism

- Cortisol deficiency alone:
  - Pre- and post-ACTH cortisols both < 0.2 µg/dl
  - Supplement with prednisone (0.1 - 0.2 mg/kg)
  - Follow ACTH stimulation tests
  - Usually recover (may take days, weeks, or months)

- Cortisol and aldosterone deficiency (< 5%):
  - Pre- and post-ACTH cortisols both < 0.2 µg/dl
  - Abnormal electrolytes
  - Do not recover
  - Manage as Addisonian
  - Damage to zona glomerulosa

Prognosis

- Dogs with PDH on mitotane:
  - Feldman and Nelson
  - 1500 dogs
  - Dogs that have died - mean survival 31.6 m
  - (range: few days to several years)
  - >35% relapse
  - 5% mildly overdosed during induction
  - Dogs that died:
    - 37% related to HAC
    - 20-30% due to pituitary tumor
    - <1% due to mitotane overdose

Mitotane Publications

- Remarkably Few!
  - Kintzer and Peterson, 1991
  - 200 dogs with PDH
  - 80% efficacy
  - 31% adverse effects
  - 6% Addisonian crisis (none died)
  - 58% relapsed
  - Median survival = 620 days

Cushing’s Therapy: Other Medications

- Ketoconazole
  - Inhibits steroid synthesis in adrenal cortex
  - 5 mg/kg BID for 7 days, then 10 mg/kg BID - 20 mg/kg BID
  - Monitor with ACTH stimulation test
  - Works in about 50% PDH cases
  - Side-effects (vomiting, anorexia, diarrhea, elevated liver enzymes)

Cushing’s Therapy: Other Medications

- l-deprenyl
  - PDH only
  - Poor efficacy
  - “L-Deprenyl should not be used in the treatment of dogs with PDH” (Feldman and Nelson, 3rd Edition, 2004)

Cushing’s Therapy: Trilostane

- Vetoryl®
  - Tested and licensed in Europe and USA for canine Cushing’s
  - Competitively inhibits steroid synthesis
    - Inhibits 3β-hydroxysteroid dehydrogenase
    - Converts pregnenolone to progesterone
    - Converts 17-OH pregnenolone to 17-OH progesterone
Cushing’s Therapy: Trilostane

- Vetoryl®
  - Appears safe and effective
  - Monitor with ACTH stimulation tests
  - Adrenals keep getting bigger
  - Some reports of adrenal necrosis
  - One case report of successful therapy of adrenal tumor (80 weeks)
  - One case series of 3 dogs with adrenal metastasis (survived 11m, 16m, and 10 m)
  - Has been used in small number of cats

  - 78 dogs with PDH
  - 2 became hypoadrenocortical
  - 1 resolved when trilostane stopped
  - Dose:
    - < 5 kg: 30 mg; 5-20 kg: 60 mg; > 20 kg: 120 mg
    - BID dosing better (short duration of action)?

  - Long-term efficacy of trilostane administered twice daily in dogs with pituitary-dependent hyperadrenocorticism
  - 44 dogs with PDH
  - Followed for 6 - 42 months
  - 15 dogs died
    - 8 unrelated diseases
    - 2 from HAC complications
    - 4 unknown
    - 1 lost to follow-up
  - 5 dogs: treatment stopped due to low cortisol
    - 1 required mineralocorticoid and glucocorticoid

- Vaughan et al., JAVMA, 2008
  - Evaluation of twice-daily, low-dose trilostane administered orally in dogs with naturally occurring hypoadrenocorticism
  - 90% responded well
  - 9% adverse effects
  - 2 dogs were sick with high K and low Na
    - Had some cortisol secretion
    - Differential effects on aldosterone and cortisol

- Feldman, JAVMA, 2011
  - Evaluation of twice-daily, lower-dose trilostane administered orally in dogs with naturally occurring hypoadrenocorticism
  - 38 dogs with PDH
  - Started at 0.84 (+/- 0.22) mg/kg
  - Mean dose at 1 yr: 1.7 mg/kg BID, or 1.1 mg/kg TID

Using Trilostane

- Start with lower dose
  - 1 mg/kg BID
- ACTH stimulation tests
  - Start 4-6 hours post-pill
  - 10-14 days
  - Monthly
  - Whenever clinical signs change
Using Trilostane
- ACTH stimulation test
  - Aim for pre and post values between 2 and 6 ug/dl
  - ACTH response may decrease over time
  - Do not be too quick to increase dose

Using Trilostane
- SID or BID?
  - No good comparisons performed
  - May depend on size of dog and size of capsule
  - Use BID if ACTH stim results are good on SID, but clinical signs persist
  - Interpret ACTH stim results and clinical signs together

Using Trilostane
- Just use Vetoryl!
- Compounded trilostane?
  - No!
  - Recent study
    - Marked variability within batches of medication
    - Marked variability between batches of medication
    - Several pharmacies evaluated

Mitotane or Trilostane: Which to Use?
- Effectiveness?
- Side-effects?
- Cost?
- Owner preference
  - Costs
  - Protocol/dosing

Mitotane vs. Trilostane Effectiveness
- Barker et al., JVIM, 2005
  - Median survival = 708 days (M)
  - Median survival = 662 days (T)

- Clemente et al., Vet Rec, 2007
  - Median survival = 720 days (M – non-sel)
  - Median survival = 900 days (T - BID)

Mitotane vs. Trilostane Side-Effects
- Mitotane
  - Kintzer and Peterson
    - 31% adverse effects (usually mild)
    - 6% addisonian crisis
  - Feldman and Nelson
    - 5% mild overdose in induction
    - < 1% died from mitotane overdose
### Mitotane vs. Trilostane Side-Effects

- **Trilostane**
  - Neiger
    - 5% serious adverse effects (4 died; 1 Addisonian)
  - Alenza
    - 11% Addisonian
  - Vaughan
    - 9% Addisonian
  - Braddock
    - 13% Addisonian
  - Feldman
    - 10% ill (2% hospitalized)

### Mitotane vs. Trilostane Cost Comparison

- **CSU**
  - Mitotane 500 mg = $8.91
  - Trilostane 10 mg = $1.88
  - Trilostane 30 mg = $2.34
  - Trilostane 60 mg = $3.05
  - Cortrosyn = $112 (1 vial)
  - Cortisol = $31

### 10 kg dog – month 1

- **Mitotane**
  - 50 mg/kg/day for 10 day induction
    - $8.91 \times 10 = $89.10
  - 50 mg/kg/week for 3 weeks
    - $8.91 \times 3 = $26.73
    - $115.83 (+ 1 ACTH stim test)
  - 50 mg/kg/week for 3 weeks
    - $8.91 \times 3 = $26.73
    - $115.83 (+ 1 ACTH stim test)

- **Trilostane**
  - 1 mg/kg BID for 31 days
    - $1.88 \times 2 \times 31 = $116.56 (+ 1 ACTH stimulation test)
    - Assume no dose increase!

### 10 kg dog – month 2

- **Mitotane**
  - 50 mg/kg/week
    - $35.64
  - 4 weeks
  - 1 ACTH stimulation test

- **Trilostane**
  - 1 mg/kg BID
    - $105.28
  - 4 weeks
  - 1 ACTH stimulation test

### 20 kg dog – month 1

- **Mitotane**
  - 50 mg/kg/day for 10 day induction
    - $8.91 \times 20 = $178.20
  - 50 mg/kg/week for 3 weeks
    - $8.91 \times 6 = $53.46
    - $231.66 (+ 1 ACTH stim test)
  - 50 mg/kg/week for 3 weeks
    - $8.91 \times 6 = $53.46
    - $231.66 (+ 1 ACTH stim test)

- **Trilostane**
  - 1.5 mg/kg BID for 31 days
    - $2.34 \times 2 \times 31 = $145.08 (+ 1 ACTH stimulation test)
    - Assume no dose increase!

### 20 kg dog – month 2

- **Mitotane**
  - 50 mg/kg/week
    - $71.28
  - 4 weeks
  - 1 ACTH stimulation test

- **Trilostane**
  - 1.5 mg/kg BID
    - $131.04
  - 4 weeks
  - 1 ACTH stimulation test
30 kg dog – month 1

- Mitotane
  - 50 mg/kg/day for 10 day induction
    - $8.91 x 30 = $267.30
  - 50 mg/kg/week for 3 weeks
    - $8.91 x 9 = $80.19
    - $347.49 (+ 1 ACTH stim test)

- Trilostane
  - 1 mg/kg BID for 31 days
    - $2.34 x 2 x 31
    - $145.08 (+ 1 ACTH stimulation test)

30 kg dog – month 2

- Mitotane
  - 50 mg/kg/week
    - $106.92
    - 4 weeks
    - 1 ACTH stimulation test

- Trilostane
  - 1 mg/kg BID
    - $131.04
  - 2 mg/kg BID
    - $170.80
    - 4 weeks
    - 1 ACTH stimulation test

Cost Comparison

- Small dog
  - Mitotane and trilostane equivalent in first month (mitotane induction is expensive)
  - Mitotane much less expensive in maintenance phase

Cost Comparison

- Medium to large dog
  - Mitotane more expensive in first month
    - Differential is greater for larger dogs
  - Mitotane less expensive in maintenance phase

Cost Comparison

- Assumes no dose increase
- Have to consider cost of reinduction on mitotane – this is not needed with trilostane
- Have to consider cost of ACTH stimulation tests
  - $120 for small dog
  - $180 for large dog

Transitioning Between Medications

- Stop first medication
  - Monitor clinical signs and ACTH stimulation tests
  - Start second medication when have clinical signs and exaggerated response to ACTH (high normal or above normal post-ACTH cortisol)
    - Probably happens more quickly with trilostane
### What about the pituitary tumor?

- Will progress over time

  - Bertoy, 1996
    - 13 dogs – MRI at time of diagnosis
      - 8 had a pituitary mass
      - None had clinical signs of the tumor
    - 1 year later
      - 4 of 8 tumors had enlarged
      - 2 dogs had newly visible tumors
      - 2 of 13 dogs had neurological signs

### Treatment of the tumor?

- Surgery
  - Treatment of choice in humans
  - Not widely available in the US for dogs or cats
  - Is used in Europe
    - Case series of 150 dogs
    - 65% success overall
    - 127 in remission – 32 relapsed
    - 53% developed central diabetes insipidus

### Treatment of the tumor?

- Radiation therapy
  - Adjunctive therapy in humans
  - Several case reports in dogs
    - Tumor size decreases
    - Reduces neurological signs
    - Increases survival
    - Endocrine benefits are unclear

### Treatment of the tumor?

- Stereotactic radiation therapy (SRT)
  - Used in humans
  - Better endocrinological cure rates than conventional radiation therapy?
  - Some use in dogs and cats

### SRT Background

- Stereotactic Radiosurgery
  - Geometrically accurate delivery of very high doses of radiation
  - Target defined by high resolution stereotactic imaging
  - Development driven by neurosurgeons to give single large dose of radiation to brain lesion
    - Gamma knife

- Stereotactic Radiation Therapy (SRT)
  - New generation of technology
Background

- Varian Trilogy™ System
  - On-board imaging
  - Ensures accurate patient positioning for multiple fractions
  - Treatment planning
  - High doses to tumor
  - Rapid drop-off of dose to normal tissues
  - Fractionated
    - Biological benefits
    - Fewer fractions (2-4)

SRT for Feline Acromegaly

- Disease background
- Signalment
- Clinical signs
- Diagnosis
- Prognosis
- Treatment options
- Results at CSU

Feline Acromegaly

- Rare/Uncommon/Common?
- Pituitary Tumor
  - Adenoma
  - Somatotrope cells
  - Secretes GH
  - Usually visible on CT or MRI
  - Acidophil hyperplasia?

Growth Hormone

- GH = somatotropin
- Pulsatile secretion from pituitary
- Induces IGF-1 production by the liver

Feline Acromegaly

- Anabolic effects
  - Growth of bone, cartilage, soft tissues and organs
- Catabolic effects
  - GH antagonises insulin at post-receptor level
  - Insulin-resistant diabetes mellitus
Feline Acromegaly

• Older male, DSH or DLH cats
  • Median age = 9 years
  • Mean age = 10 years

Feline Acromegaly

• Clinical Signs
  • PUPD
  • Polyphagia
  • Insulin resistant DM
    • Insulin dose > 2 U/kg
    • Often 12-15 units BID
    • Sometimes > 20 units BID
  • Weight gain
    • Despite unregulated diabetes

Feline Acromegaly

• Clinical Signs
  • Enlarged facial features
  • Enlarged feet
  • Abdominal distension
  • Altered dental spacing
  • Distorted joints
  • Thickened soft tissues around airway
    • Stridor/snoring
    • Very common

Feline Acromegaly

• Clinical Signs
  • Hypertension
  • Myocardial disease
  • Neurological signs uncommon
    • Mental dullness

Feline Acromegaly

• Clinical Pathology
  • Hyperglycemia
  • Glucosuria
  • Elevated cholesterol
  • Elevated phosphorus
  • Erythrocytosis
  • Proteinuria
    • Glomerulonephropathy

Feline Acromegaly

• Diagnosis
  • History/clinical signs/PE
  • Look at an old photo!
A disease of Photoshop®?

Feline Acromegaly

• Diagnosis
  • GH levels
    • Not currently available
    • (Very helpful in diagnosis)
  • IGF-1
    • Readily available

Feline Acromegaly

• Diagnosis
  • CT or MRI
  • MRI more sensitive
  • Negative study
    • Small mass
    • Hyperplasia?

Feline Acromegaly

• Prognosis
  • Guarded to good in short-term
  • Poor for long term
  • Typically survive 1.5-3 yr
  • Neurological signs uncommon

Feline Acromegaly

• Cause of death
  • Renal failure
  • Cardiac failure
  • Hypoglycemic coma

Acromegaly Therapy

• Goals (Humans)
  • Tumor removal
  • Relief of symptoms
  • Reduction of systemic complications
  • Control mass effect of the tumor

• Multidisciplinary approach
Acromegaly Therapy

• Goals (Feline)
  • Relief of signs
  • Reduce systemic complications
  • Quality of life
    • Patient and owner

Acromegaly Therapy

• Surgery
  • Primary therapy in humans
  • Rarely performed in cats in the US

• Medical Therapy
  • Commonly used in humans
  • Poor results in cats so far

Stereotactic Radiation Therapy (SRT)

• Used in humans as adjunct therapy
• Recent experiences in cats

SRT Study at CSU

• Optimise SRT protocol for feline acromegaly
• Monitor IGF-1 (and GH) levels
• Follow endocrine function after SRT
• Evidence of hypopituitarism?
• Monitor insulin requirements

SRT Study

• Planning CT on day 0
• Stereotactic Radiation Therapy
  • Trilogy™ linear accelerator
    • 2 fractions: days 1 and 3
    • 4 fractions: days 1, 2, 3, and 4
• Monitoring:
  • IGF-1
  • GH
  • eACTH
  • ACTH stim testing
  • Thyroid panels
  • Insulin dose

SRT Set-Up
Results: Cats
- 7 cats enrolled over one year for the initial study
- 10 more cats treated after study
- All had typical acromegaly signs
- Longest follow-up: 30 months

Results: CT Scan
- Pituitary mass detected in 5 of 7 study cats
- No mass detected in cats 3 and 7
- Owners elected SRT

Results: SRT
- Cats 1-3: 2 fractions
  - 36 Gy (2 cats)
  - 28 Gy (1 cat)
- Cats 4-7: 4 fractions
  - 28 Gy
- Cats 8-17: 3 or 4 fractions
  - 15 - 20 minute duration of anesthesia per fraction

Results: Adverse Effects
- 15 of 17 cats had no adverse effects
- 2 cats mentally dull immediately post SRT
  - Responded to short course of prednisolone
  - Returned to pre SRT status
- All owners reported steady improvements in attitude and energy level
- No delayed effects seen so far

Results: Survival
- 4 of initial 7 cats euthanised
  - Cat 1
    - 6.5 months
    - Episodes of severe hypoglycemia with seizures
    - Renal disease
  - Cat 2
    - 6.5 months
    - Intussusception and intestinal leiomyoma
  - Cat 3
    - 5.5 months
    - CKD
  - Cat 4
    - 19 months
    - CKD
    - Diabetic remission at 17 weeks
### Results: Insulin Requirements

- All study cats (7)
  - Initially 1.9 - 3.2 U/kg per dose
  - 3 detemir, 3 glargine, 1 PZI
- All cats
  - Insulin dose < 6 U at 8 wk - 7m
- For cats alive at 1 yr
  - Insulin dose < 0.5 U/kg at 1 year
- 3 cats
  - Diabetic remission
  - 17 wk, 19m, 19m

### Results: IGF-1

- All cats
  - IGF-1 fell slowly over time
  - Never into normal range
  - Surviving cats followed > 1yr
  - IGF-1 increased after initial decline

### Results: GH

- Available for 1st year of study (7 cats)
  - Increased pre-SRT in all cats
  - > 10 ng/ml
  - In all surviving cats
  - < 10 ng/ml by 30 weeks

### Results: Long-Term

- Cat 5
  - Still in diabetic remission at 30 months post-SRT
- Cat 6
  - Still in diabetic remission at 30 months
  - On levothyroxine
- Cat 7
  - On 2.5 U detemir q 24 hr at 17 months post-SRT
  - On levothyroxine

### Results: Additional Cats

- 10 additional cats treated
  - 2 lost to follow-up
  - 1 in diabetic remission at 2.5 months post-SRT
  - 6 on < 6U insulin
  - 1 not responding by 9 m post-SRT

### Results: Endocrine Testing

- Diabetes insipidus
  - No cats
- Hypoadrenocorticism
  - No cats
- Hypothyroidism
  - 2 cats
  - At 6 months post-SRT
  - Responded to supplementation
Results: Physical Changes

SRT Conclusions

- Stereotactic Radiation Therapy: 1 year+ findings for feline acromegaly
  - Safe and well-tolerated
    - Few anesthetic events
    - No significant adverse effects
  - Convenient
    - Can be completed within one week
    - Avoids extensive hospitalisation

SRT Conclusions

- Insulin Resistance
  - Improves within 12-16 weeks
  - Diabetic remission possible
    - Even after > 18 m

Disadvantages of SRT?

- Availability
- Cost (disadvantage of all forms of RT)

SRT for Canine PDH?

- Yes!
- One dog successfully treated
- Ongoing study at CSU
  - See me for details!
  - kathylunn@me.com