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VETERINARY Emergency Hospital
& Referral Group

Canine Cushings Syndrome: *Diagnostic Approaches and Treatment Options*

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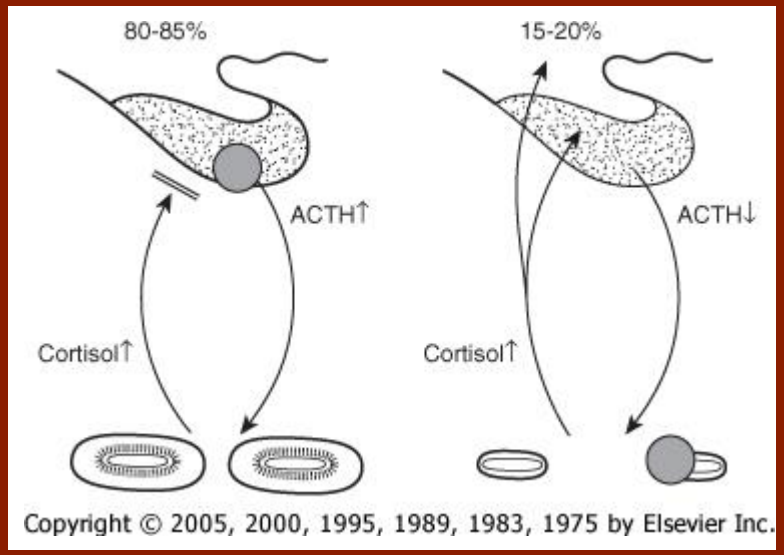
VCA Animal Hospitals

Pathophysiology

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



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

Ettinger and Feldman, 2005. Textbook of Veterinary Internal Medicine, 6th edition

Clinical signs

PU/PD	80-91%
Alopecia	60-74%
Pendulous abdomen	67-73%
Hepatomegaly	51-67%
Polyphagia	46-57%
Panting	30%
Muscle weakness	14-57%
Anestrus	54%
Muscle atrophy	35%
Comedones	25-34%
Hyperpigmentation	23-30%
Testicular atrophy	29%
Calcinosis cutis	8-15%

Inappropriate clinical signs

- Poor appetite, anorexia
- Vomiting, diarrhea
- Coughing, sneezing
- Icterus
- Pruritus
- Pain
- Lameness
- Bleeding

Complications of untreated Cushings

- Hypertension
- Pyelonephritis/chronic UTI
- Urinary calculi
- Calcinosis cutis
- Diabetes mellitus
- Neurologic signs due to large pituitary mass
- Rupture of vessel or caudal vena caval thrombosis with functional adrenal tumour

Clinicopathologic data

↑ ALP	85-95%
Hyperlipidemia	50-90%
↑ ALT	50-80%
↓ BUN	30-50%
Fasting hyperglycemia	30-40%
↓ Phosphorus	38%

Urine specific gravity <1.015-1.020	80%
Proteinuria >1.0	60-80%
Urinary tract infection	40-50%
Glucosuria	10%

Increased ALP

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

Screening tests

- Clinical signs
- Urine cortisol:creatinine ratio
- ACTH stimulation test
- Low-dose dexamethasone test
- Abdominal ultrasound
- Liver biopsy – not useful as sole screening test

Rules of thumb

- Do not test a dog without symptoms
- Do not test a dog with only an increase in ALP if not symptomatic
- Do not test a sick dog
- Remember that no test for Canine Cushings Syndrome is perfect
- Consider results in light of patient

Clinical signs

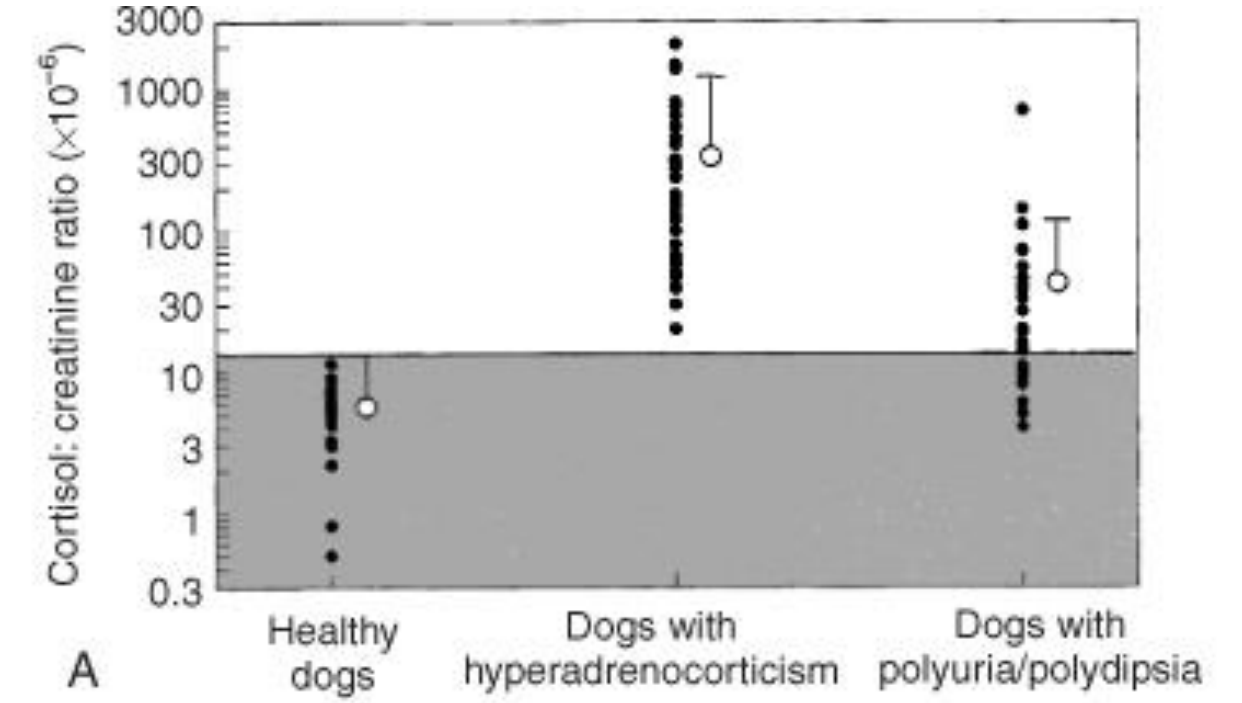
- Polyuria/polydipsia
- Ravenous appetite
- Hair coat changes
- Pendulous abdomen
- Increased panting

Do not test or treat without some of these symptoms

Urine cortisol:creatinine ratio

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

Urine cortisol:creatinine ratio



Ettinger and Feldman, 2005. Textbook of Veterinary Internal Medicine, 6th edition

Endogenous ACTH

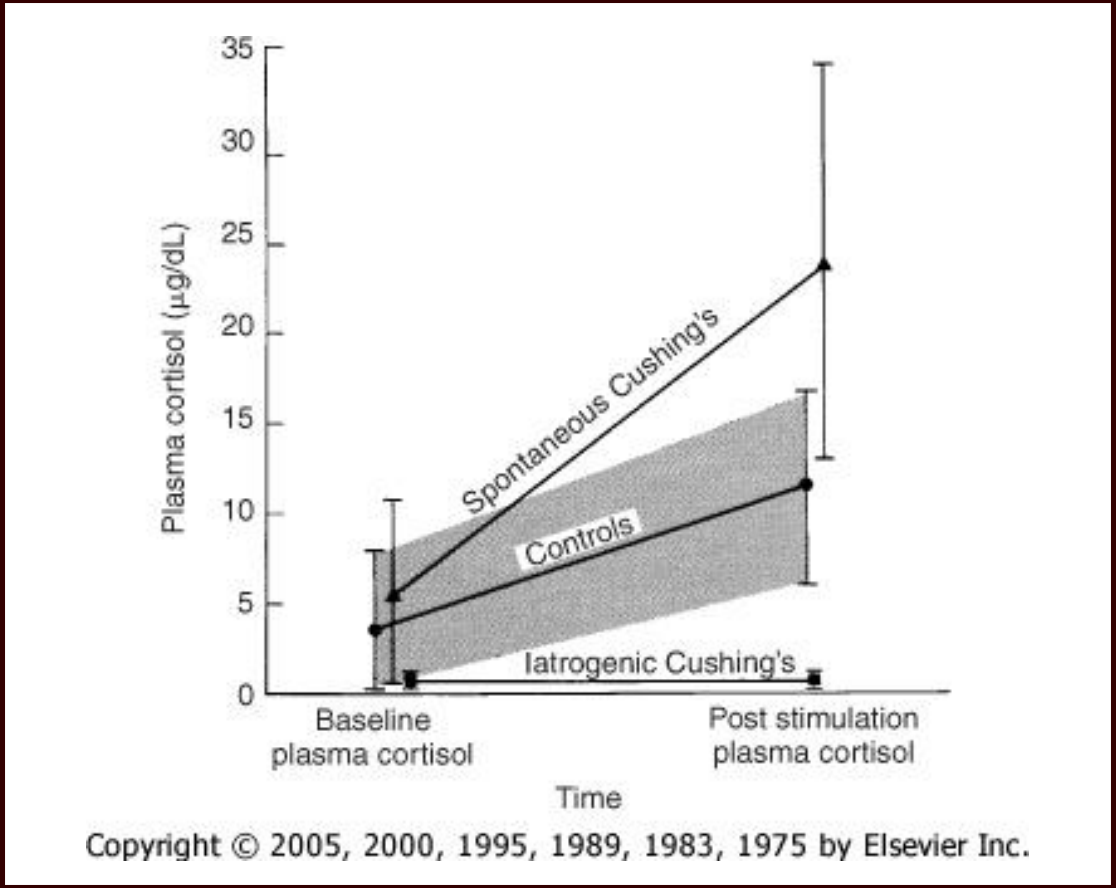
- Only useful for differentiating pituitary-dependent HAC from adrenal-dependent HAC
- Should be low with adrenal-dependent, and high with pituitary-dependent
- Problem is that with PDH, the level can be low, normal or high
- Some problems with stability
- NOT in glass tubes

ACTH stimulation test

- Looking for an exaggerated response
- Only the post-stimulation value is of use
- PDH:
  - Clearly abnormal – 30%
  - Borderline – 30%
  - Normal range – 40%
- FAT:
  - Clearly abnormal – 60%
  - Borderline or normal – 40%

- Normal dogs
  - 15% have abnormal stimulation

ACTH stimulation test



Ettinger and Feldman, 2005. Textbook of Veterinary Internal Medicine, 6th edition

ACTH stimulation test

If high suspicion of hyperadrenocorticism:

- Positive result likely has the disease
- Could still have it with a negative result

- Diagnostic test
- Also used for monitoring when receiving medical therapy

ACTH stimulation test

- New protocol for DIAGNOSTIC test and MONITORING test
- Many previous forms of ACTH are unavailable (ie synacthen)
- Cortrosyn available but expensive
- Options available to reduce cost
- Current backorder issue

Utilizing cortrosyn to reduce $$

1. A cortrosyn vial contains 250 µg / 0.25 mg of synthetic ACTH powder.
2. Reconstitute as directed on vial (add 2.5-ml of sterile saline solution), which results in a concentration of 100 µg/ml (0.1 mg/ml).
3. Aspirate 0.25 ml (25-µg) or 0.5 ml (50-µg) aliquots into plastic syringes. We now make primarily 0.25 ml aliquots (25-µg).

    Please note it is important to use PLASTIC syringes, not glass vials.

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

Utilizing cortosyn to reduce $$

5. Label each syringe with the date reconstituted, amount in that syringe, and name Cortrosyn.
6. Freeze the syringes at -20℃. This is best done in a non frost-free freezer, as they cycle through warmer periods to defrost. Stored in this fashion, the contents can be stored for up to 6 months.
    * If you elect to refrigerate the syringes, they can be stored for up to 4 weeks.

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

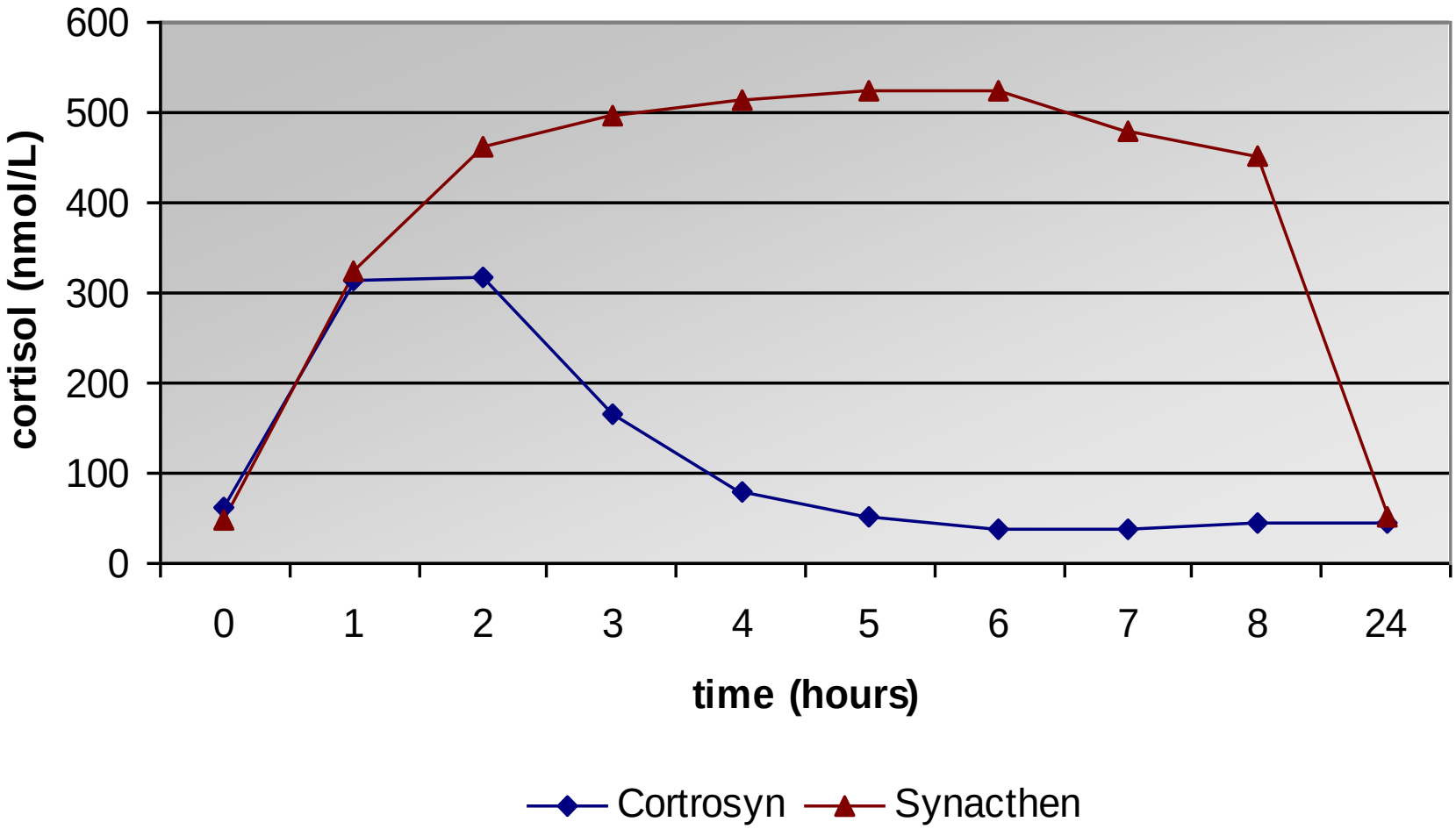
DIAGNOSTIC ACTH stim test

1. Administer at a dose of 5 µg /kg (round up if needed) either ***IM or IV***. Administer ***INTRAVENOUSLY*** in dehydrated dogs and in all cats.
2. Cortisol levels should be measured prior to injection of Cortrosyn (0 hour), and at 1 hour post administration of Cortrosyn.

MONITORING ACTH stim test

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

OVC 2006 study – normal dogs



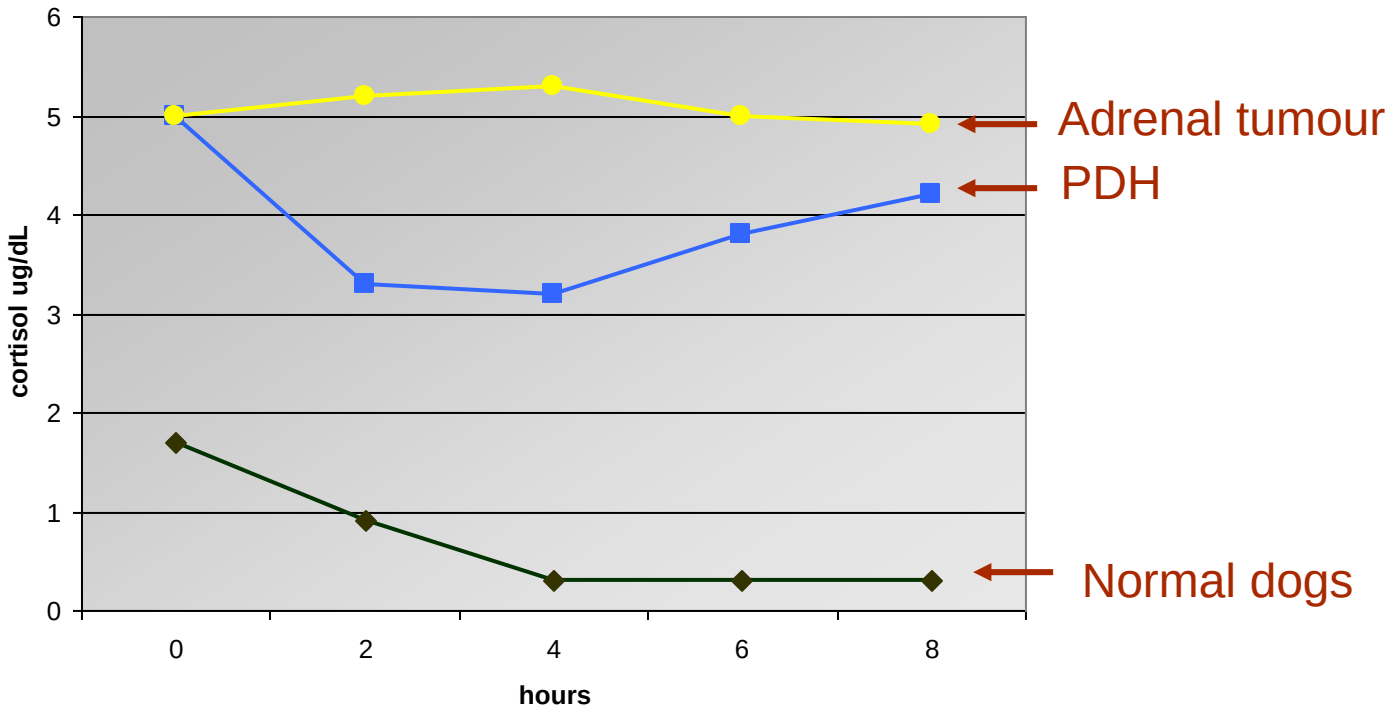
Options with backorder issue

- Compounded ACTH gel 2.2 IU/ml
- Recommended to give 2.2 IU per kg, given IM, and measure at least 0, 1 and 2 hour samples.
- Given lack of knowledge of both quality of product and expected response of cortisol, I would only recommend using this for the diagnosis of hypoadrenocorticism (Addison's disease) until Cortrosyn is off backorder
- Latest information is available week of April 9th through VP, no ETA from CDMV.

Low-dose dexamethasone test

- Administration of 0.01 mg/kg dex
- Dexamethasone does not cross-react with cortisol assay *(prednisone does)*
- PDH:
  - >99% have increased values at 8 hours
  - 35% have increased 4 hour value
- FAT:
  - >99% have increased values throughout
- Normal dogs: >5% to 37-56% abnormal

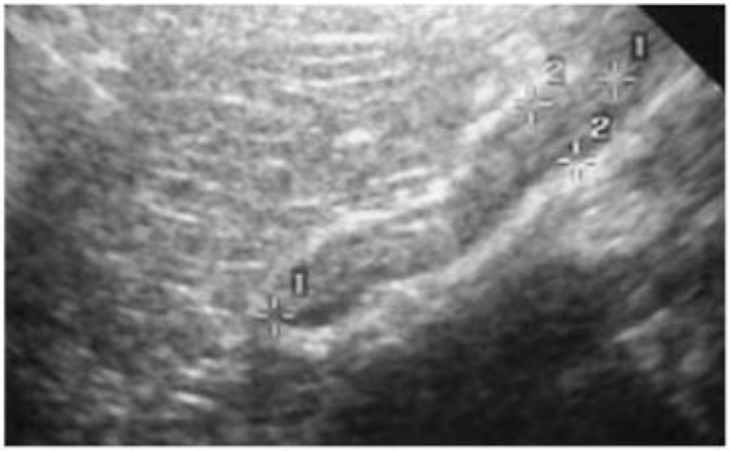
LDDS test


6
5
4
3
2
1
0
cortisol ug/dL
0
2
4
6
8
hours
Adrenal tumour
PDH
Normal dogs

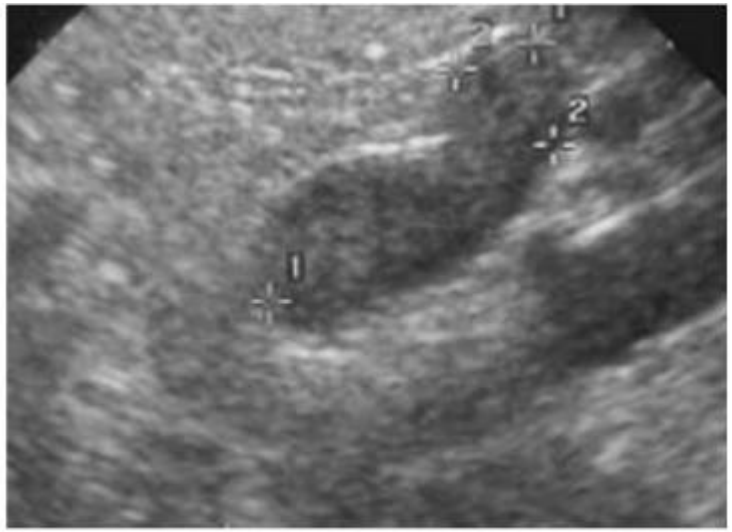
Abdominal ultrasound

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

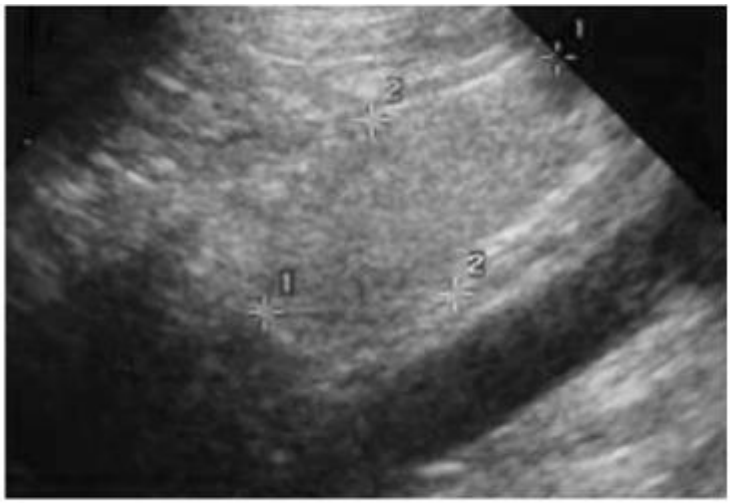
Abdominal ultrasound



Normal dogs



PDH



Adrenal tumour

Differentiating tests (PDH vs FAT)

- Endogenous ACTH
- High-dose dexamethasone test
- Urine cortisol:creatinine ratio
- Abdominal ultrasound
- MRI / CT scan

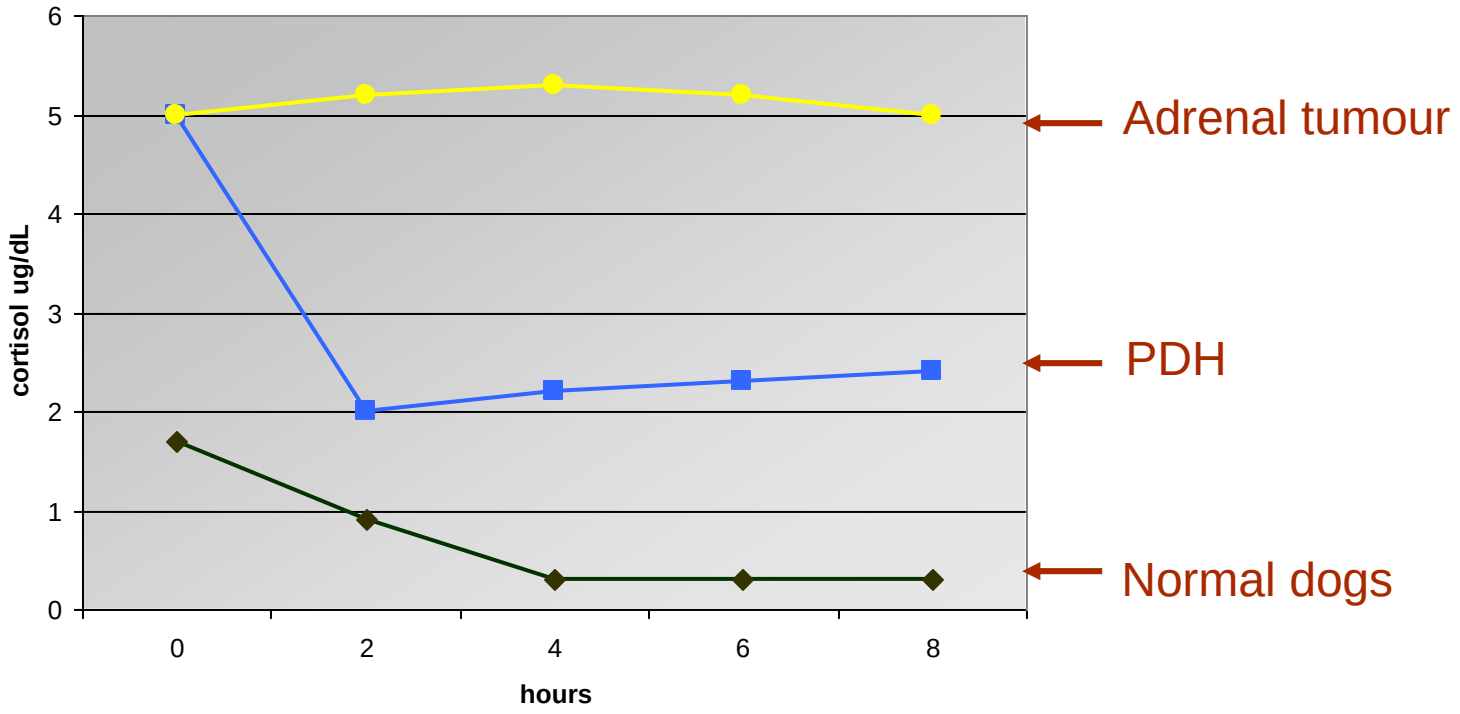
Endogenous ACTH

- Theoretically very useful – high for PDH, low for AT and iatrogenic Cushings disease
- Problems – variation in ACTH throughout day, unstable hormone once collected
- FAT
  - most cases have undetectable levels
- PDH
  - 85% of cases have high levels
  - 15% of cases have non-diagnostic levels

High-dose dexamethasone test

- Administration of 0.1 mg/kg dex
- Criteria for suppression:
  - Cortisol < 50% baseline at 4 or 8 hours
  - Cortisol < 1.4 µg/dl at 4 or 8 hours
- FAT:
  - No suppression (rare cases of suppression)
- PDH:
  - 75% suppress based on one of above criteria
  - No advantage with 1.0 mg/kg dex

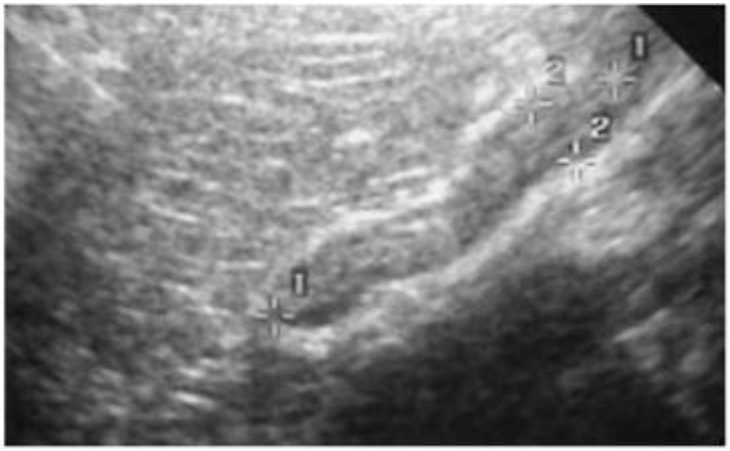
HDDS test


6
5
4
3
2
1
0
cortisol ug/dL
0
2
4
6
8
hours
Adrenal tumour
PDH
Normal dogs

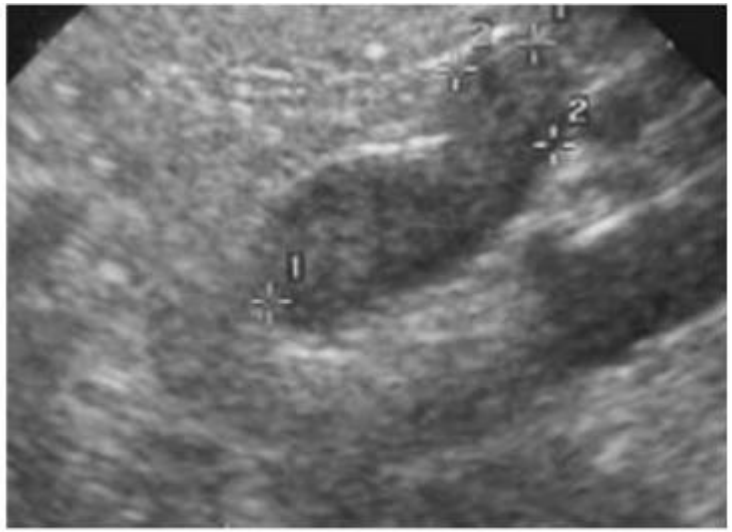
Urine cortisol:creatinine ratio suppression test

- Owners collect urine on 2 consecutive days in the morning for baseline
- 0.1 mg/kg dex given orally q 8 h three times
- Urine collected 8 hours after last dose
- If UC:CR suppresses by >50% → PDH
- If suppression <50% → FAT or PDH

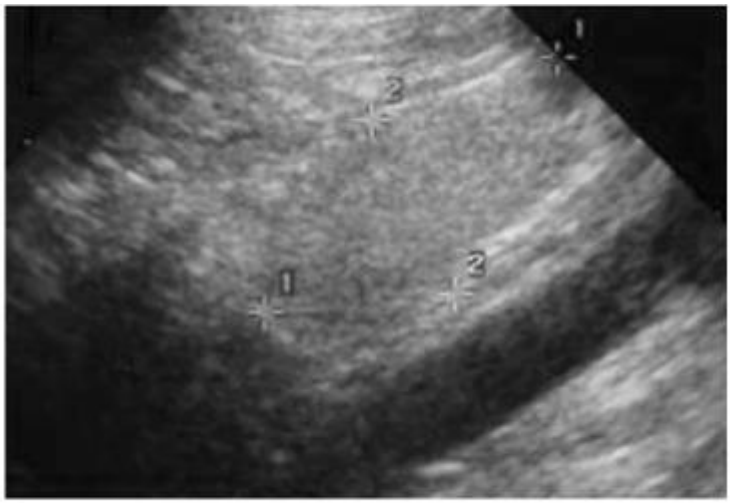
Abdominal ultrasound



Normal dogs



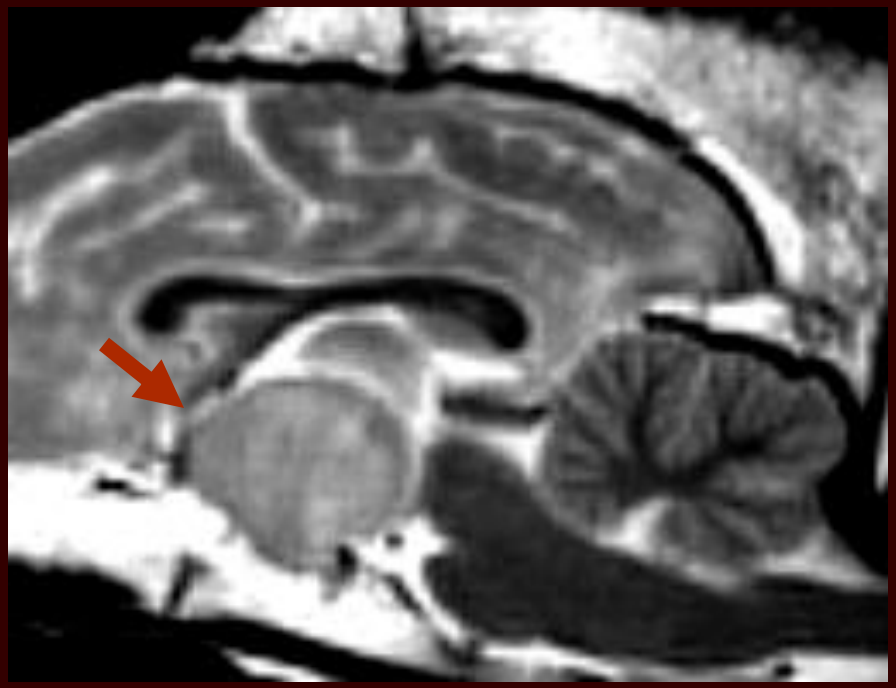
PDH

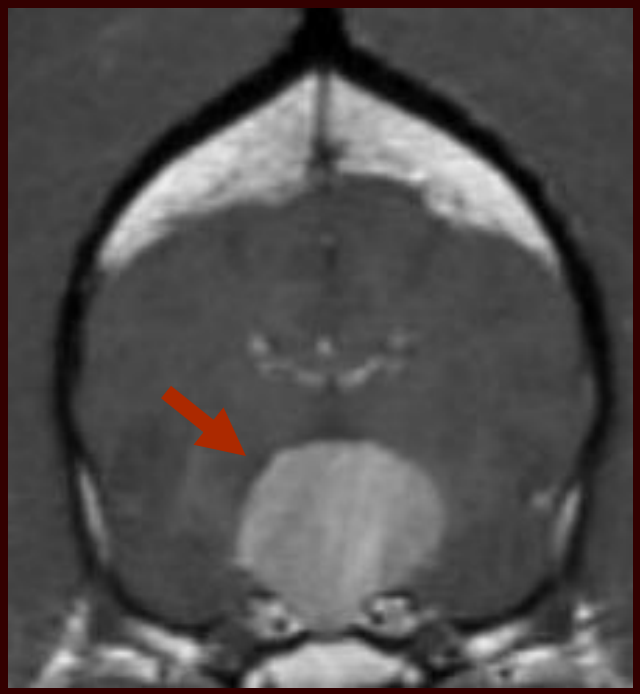


Adrenal tumour

MRI / CT scan

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





Treatment Options

Medical

- Trilostane
- Mitotane

- Other
  - Ketoconazole
  - Selegiline hydrochloride

Surgical

- Adrenal or pituitary tumour

Radiation therapy

- Pituitary tumour

Trilostane

- Steroid analogue
- No innate hormonal activity
- Competitive inhibitor

  ➔ 3β-hydroxysteroid dehydrogenase

- ↓ Glucocorticoid and sex hormones
- Aldosterone production generally spared

Dosing

- Based on body weight categories
  - Starting dose range was 5-10 mg/kg/d
  - More recently recommended 1 mg/kg/d
  - Variable GI absorption

- Short duration of action
  - Suppressed cortisol hypersecretion < 24 hrs
  - Once vs. twice daily; evidence indicates that 80% of dogs need only once daily

(Braddock et al., 2003)

Response to Therapy

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

- Clinical response in >80% dogs with PDH

(Neiger et al., 2002)

Monitoring Response

- ACTH stimulation test
  - Test 4-6 hours after medication administration (0, 1 hr)
  - Clinical remission
    - Post-ACTH cortisol < 250 nmol/L
  - Better control post-cortisol 27-69 nmol/L
  - Recheck ACTH stims @ 1,3,6,13 weeks, then q 6 mos
- Abdominal ultrasound
  - ***Increased*** adrenal gland size

(Mantis et al., 2003)

Monitoring Response

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

Dechra UK Recommendations

Suitable dogs

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

Unsuitable dogs

- Aggressive or stressed dogs
- Unwell dogs

Dechra UK Recommendations

Monitoring Appointment

- Have Vetoryl given at a convenient time from at least the day before (e.g. 9 am), then NOT that day
- Make sure that nothing stressful has happened that morning (e.g. vomiting, injury)
- Ensure the owner has completed a Quality of Life Questionnaire
- Take history and examine the dog, checking for signs of HAC

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Dechra UK Recommendations

Assessing pre-cortisol level – No clinical signs of HAC

- <40 nmol/L
  - Re-evaluate case, lower dose and retest in 10d?
- 40-138 nmol/L
  - Continue current dose, recheck in 3 months
- >138 nmol/L
  - Re-evaluate case
  - Divide twice daily and retest in 10d?
  - Slightly higher dose and retest in 10d?

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Dechra UK Recommendations

Assessing pre-cortisol level – Clinical signs of HAC present

- <40 nmol/L
  - Re-evaluate case, contact Dechra if needed
- >40 nmol/L
  - Increase to twice daily and retest in 10d OR
  - Higher dose and retest in 10d

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Adverse Reactions

- Generally well tolerated & safe
- Cortisol production restored within 24-48 hrs

Neiger et al., 2002 – 78 dogs
- Sudden death (2)
- Hypoadrenocorticism (2)

Braddock et al., 2003 – 30 dogs
- Hypoadrenocorticism (4)

Chapman et al., 2004 – 1 dog
- Bilateral adrenal necrosis

Obtaining Trilostane

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

Obtaining Trilostane

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

Quality of Trilostane

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

Cook et al 2012 JAAHA

Quality of Trilostane

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

Cook et al 2012 JAAHA

% of Label Claim

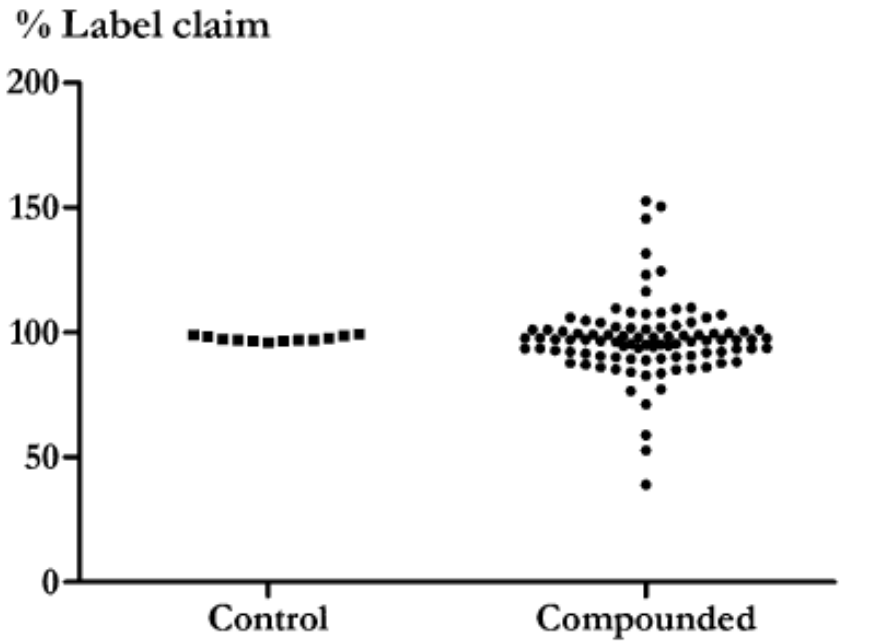


FIGURE 1 *Average percent label daim (% LC) for control (n=12) and compounded (n=96) batches of trilostane.*

Cook et al 2012 JAAHA

Control
96.1 - 99.6 %

Compounded
39 - 152.6 %

% of Label Claim

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

Control
96.1 - 99.6 %

Compounded
39 - 152.6 %

Cook et al 2012 JAAHA

% of Impurities

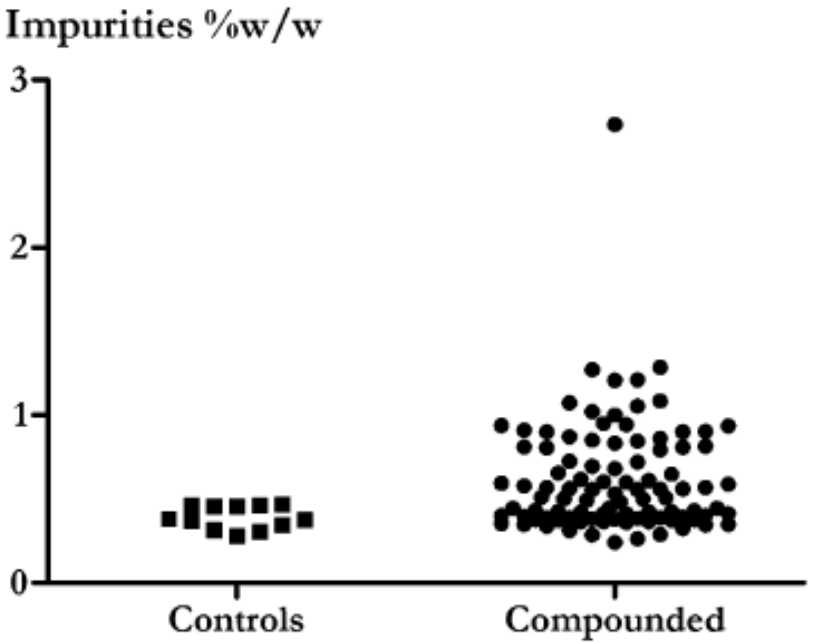


FIGURE 2 *Average percent (% weight/weight [w/w]) impurities/ related substances for control (n=12) and compounded (n=96) batches of trilostane.*

Control
0.392%

Compounded
0.624%

Cook et al 2012 JAAHA

% of Impurities

Only 1 batch of compounded trilostane considered unacceptable

Control
0.392%

Compounded
0.624%

Cook et al 2012 JAAHA

% Dissolution

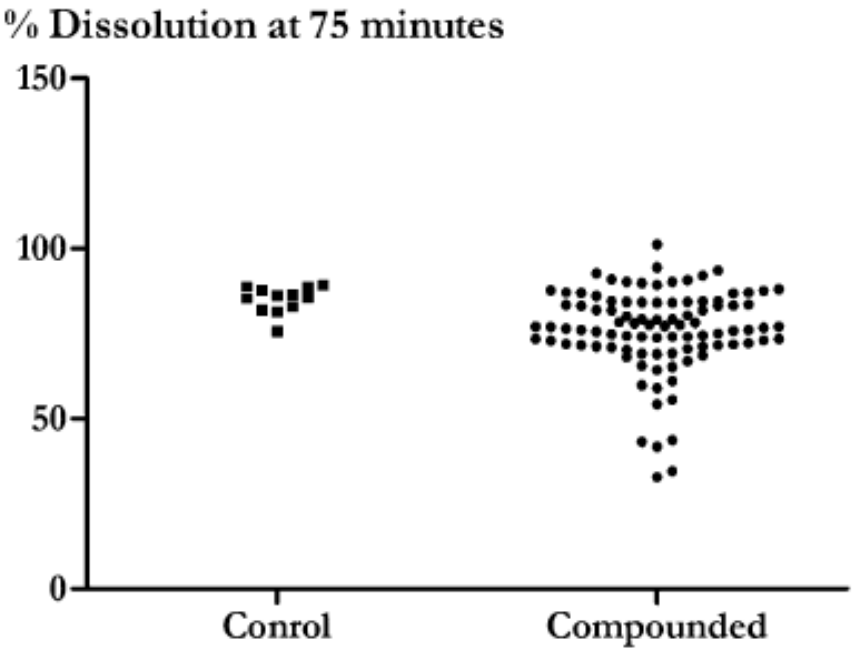


FIGURE 3 *Average dissolution based on % LC for control (n=12) and compounded (n=96) batches of trilostane at 75 min.*

Control
0% failed >70% at 75 mins

Compounded
20% failed >70% at 75 mins

Cook et al 2012 JAAHA

Bottom Line

- Consider using Vetoryl if possible

OR

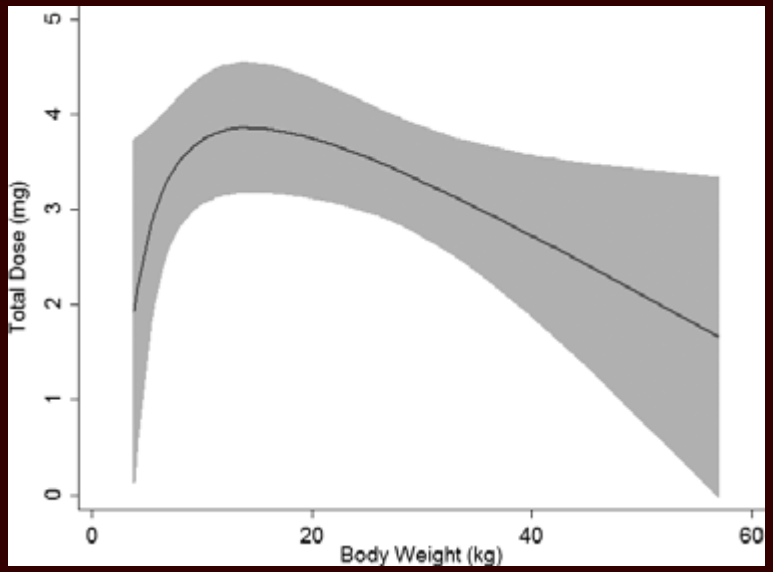
- Use a compounding pharmacy that you trust

Dosing

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

Dosing

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



Dosing

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

Dosing – Bottom Line

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

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

- If you are having trouble getting control, consider twice daily dosing

Bottom line - Trilostane

- Considered by some as the standard of medical treatment for PDH
- Much less difficult to obtain
- Requires long-term monitoring to determine dose
- Occasional side effects

Mitotane (o,p'-DDD)

- Chemical related to insecticide DDT
- Adrenocorticolytic
  - Binds covalently to adrenal proteins
  - Converted to reactive metabolite
- Drug intolerance
  - Anorexia, vomiting, diarrhea, weakness, ataxia
  - Hypoadrenocortical crisis

Mitotane (o,p'-DDD)

- Two protocols:
  - Partial adrenocortical destruction
    - Induction phase, monitor clinical signs closely
    - Maintenance phase long-term
  - Complete adrenocortical destruction
    - Require glucocorticoid and mineralocorticoid replacement therapy for life
- Long-term monitoring
  - ACTH stimulation tests, initially every 1-3 months

Bottom line - Mitotane

- Previous standard of medical treatment
- Still widely used
- More common and serious side effects
- Some practitioners are more comfortable with mitotane
- Many practitioners these days have not used mitotane

Anipryl (L-Deprenyl, selegiline hydrochloride)

- Useful for treatment of canine cognitive dysfunction
- Increases dopamine, which inhibits ACTH release

- CVT XIII chapter – take with a grain of salt!
- Controlled clinical trial (10 dogs with PDH):
  - Improvement in 2 dogs
  - No change in 4 dogs
  - Worsening clinical signs in 4 dogs
- Bottom line – do not use for Cushing's

APPROX COST – 10 kg dog

Vetoryl:	$47 per month
Compounded:	$34 per month
Lysodren:	$40-50 per month

Future of medical therapy

- Targeted approach to problem – suppressing ACTH from pituitary mass
  - Cabergoline – useful in 42.5% of cases
  - Retinoic acid – not enough research
  - Pasireotide – not enough research
- Bottom Line – not enough data yet to recommend switching from our current treatments

FAQ

What is the best test for HAC?

- Difficult question, but likely the LDDS is slightly better than the ACTH stimulation test.

I have a geriatric dog with PU/PD, an elevated ALP and an elevated UCCR. Can I start treatment for HAC?

- No. Many older pets will have an elevated ALP and UCCR. This pet MAY have HAC, but further testing is needed.

FAQ

Why is there not a panel that includes endogenous ACTH with provocative testing?

- Endogenous ACTH is really only used to differentiate PDH from an adrenal mass. It has issues with stability, interpretation and cost.

I have a pet with uncontrolled diabetes mellitus where I suspect HAC. Help!

- Ideally try to control the DM as best as possible, and then you may need to utilize several tests for HAC (LDDS and U/S, for example).

FAQ

Should I use Vetoryl, compounded trilostane or mitotane for PDH cases?

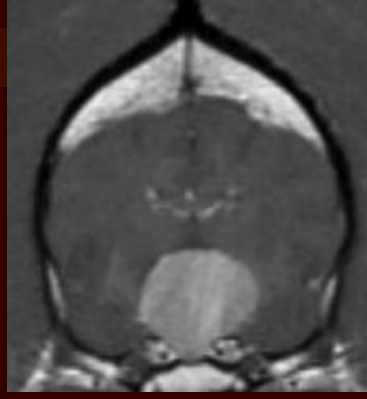
- I would use Vetoryl if possible, then compounded trilostane if there is a reason not to use Vetoryl. Mitotane has more risk of side effects, but some practitioners are still comfortable with its use.

How should I monitor my Cushingnoid dogs?

- Continue to utilize the ACTH stimulation in general, however consider trying the cortisol level only approach with well controlled cases.

Where does surgery or radiation therapy fit in?

Pituitary Macroadenoma



- **Size**
  - > 10 mm in height = macroadenoma
  - does not equate to clinical signs in all dogs
- **Concern**
  - 50% of pituitary tumours have tendency to grow
  - 15-20% of pituitary tumours will result in neurologic signs

Treatment

- Transsphenoidal hypophysectomy
  - Complete removal of pituitary gland
  - Residual corticotropes in sella turcica
  - Targeted removal of tumour TOC in people
- Radiation therapy
  - Cobalt 60 or megavoltage
  - Linear accelerator

Post-operative Complications

- Diabetes insipidus-like syndrome
- Hypothyroidism
- Keratoconjunctivitis sicca
- Glucocorticoid deficiency

Bottom Line - Hypophysectomy

- Likely to increase in use as more surgeons perform procedure
- Should be considered in dogs with larger tumours
- Should be considered in younger dogs

Radiation Therapy

	Response Rate	Survival	Disease Free Fraction
Hypo-physectomy	65% (97/150)	1yr – 84% 2 yr – 76% 3 yr – 72%	1 yr – 88% 2 yr – 75% 3 yr – 44%
Radiation	50% (3/6)	MST 21 weeks (n=8)	10 months (n=2)

- We need more published cases and more data to make recommendations

Hanson et al., 2005, Neiger et al., 2002, Brearley et al., 1999

Conclusions - Testing

- LDDS test – very sensitive, questionable specificity
- ACTH stimulation test – many chances for false negatives and positives
- Ultrasonography very useful
- Some cases can be challenging!

Conclusions - Treatment

- Trilostane and mitotane are effective treatments, both have pros and cons
- Surgery or radiation therapy indicated for some cases
- Do not treat without clinical signs

Functional Adrenal Tumour

- Adrenocortical adenomas and adenocarcinomas
- No clinical signs or biochemical features to predict adenoma vs carcinoma
- One study indicated that masses greater than 2 cm are more likely to be carcinoma
- Presence of mineralization increases likelihood of malignancy
- Evaluate for invasion of caudal vena cava and metastatic disease

FAT - Surgery

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

FAT – Mitotane

- Control or destroy tumour
- Can be used after surgery if metastatic disease is documented
- Tend to require higher doses, usually 50-75 mg/kg/day
- Higher incidence of side effects

FAT – Trilostane

- Control clinical signs of tumour
- Less indicated as it suppresses precursors rather than destroy tumour
- Less side effects
- Anecdotally has controlled clinical signs well
- Recent study of three cases showed survival of 10, 11 and 17 months with good quality of life
- Usually requires higher dosages

Questions?

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