Boehringer Ingelheim

Mississauga • Oakville
VETERINARY Emergency Hospital
& Referral Group

Hyperadrenocorticism: *Diagnosis and Treatment*

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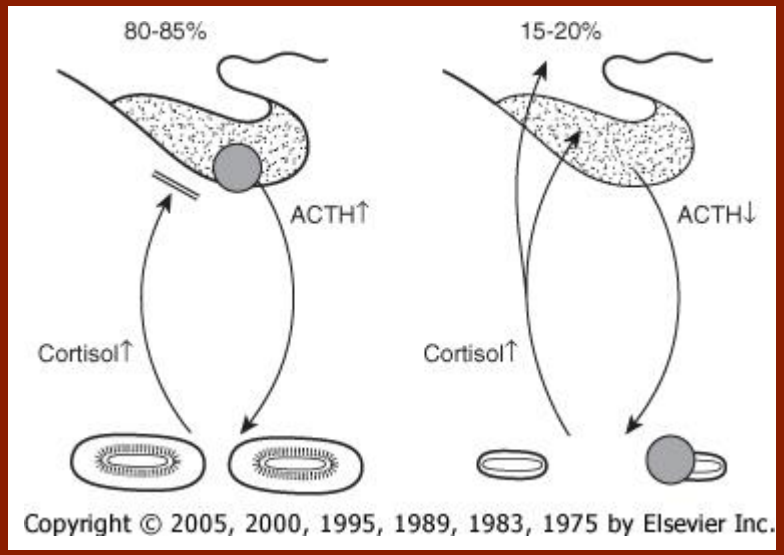
Pathophysiology

- 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%

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

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%

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

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

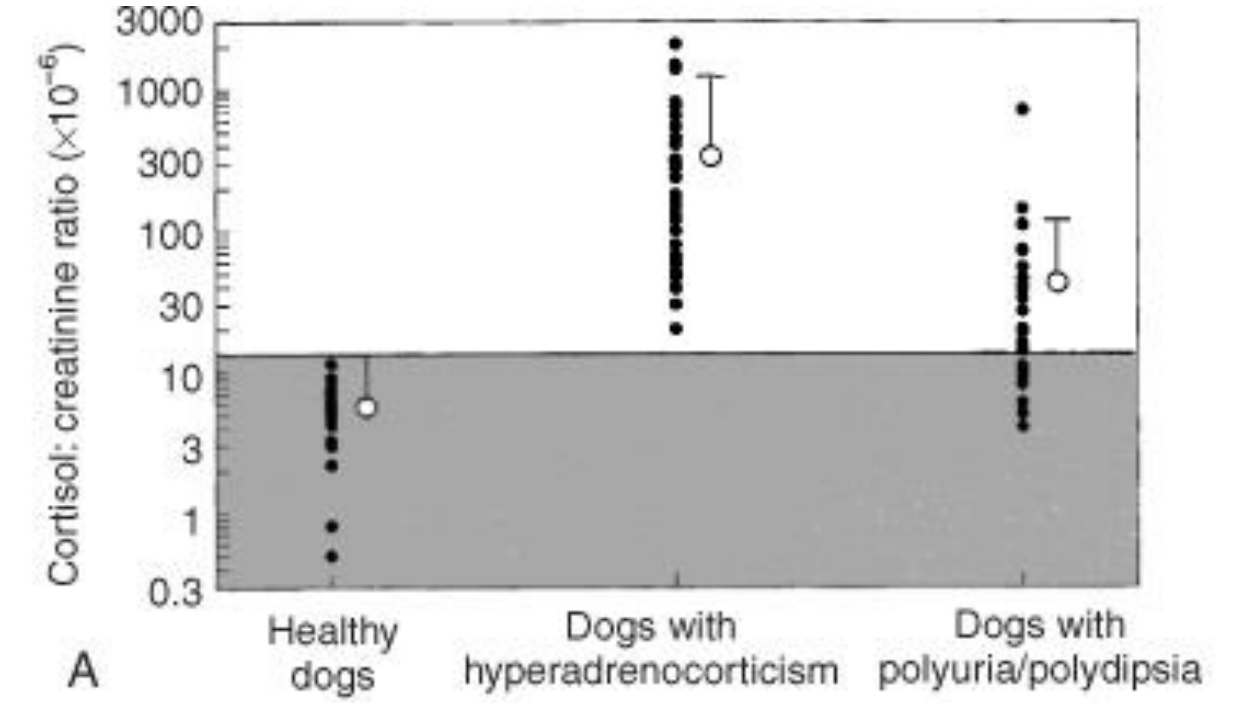
- Polyuria/polydipsia
- Ravenous appetite
- Hair coat changes
- Pendulous abdomen
- Increased panting

Do not test or treat without 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

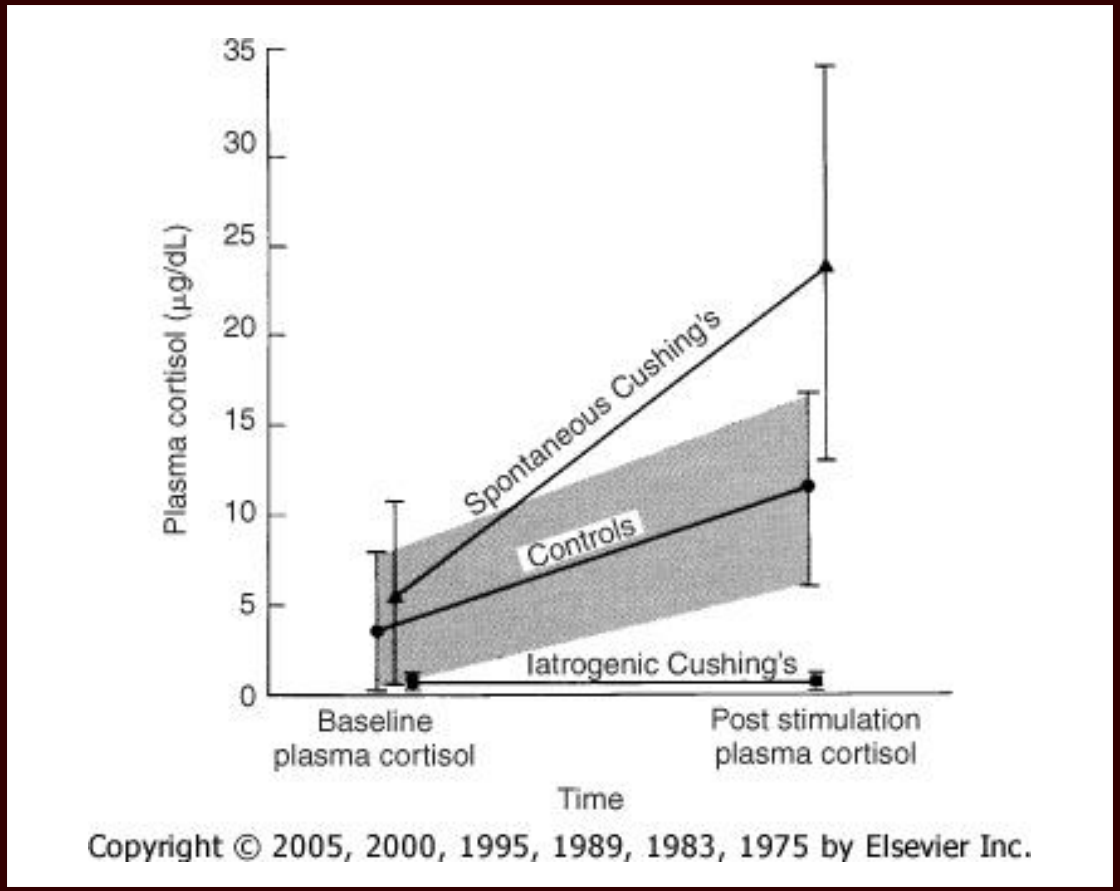
ACTH stimulation test

- 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

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

ACTH stimulation test



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ACTH stimulation test

- Required for monitoring response to medical therapy
- Many previous forms of ACTH are unavailable (ie synacthen)
- Cortrosyn available but expensive
- Options available to reduce cost

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 0.5 ml (50-µg) aliquots into plastic syringes. We will also make a few 0.25 ml aliquots (25-µg) in plastic syringes.

   Please note it is important to use PLASTIC syringes, not glass vials.
4. Label each syringe with the date reconstituted, amount in that syringe, and name Cortrosyn.

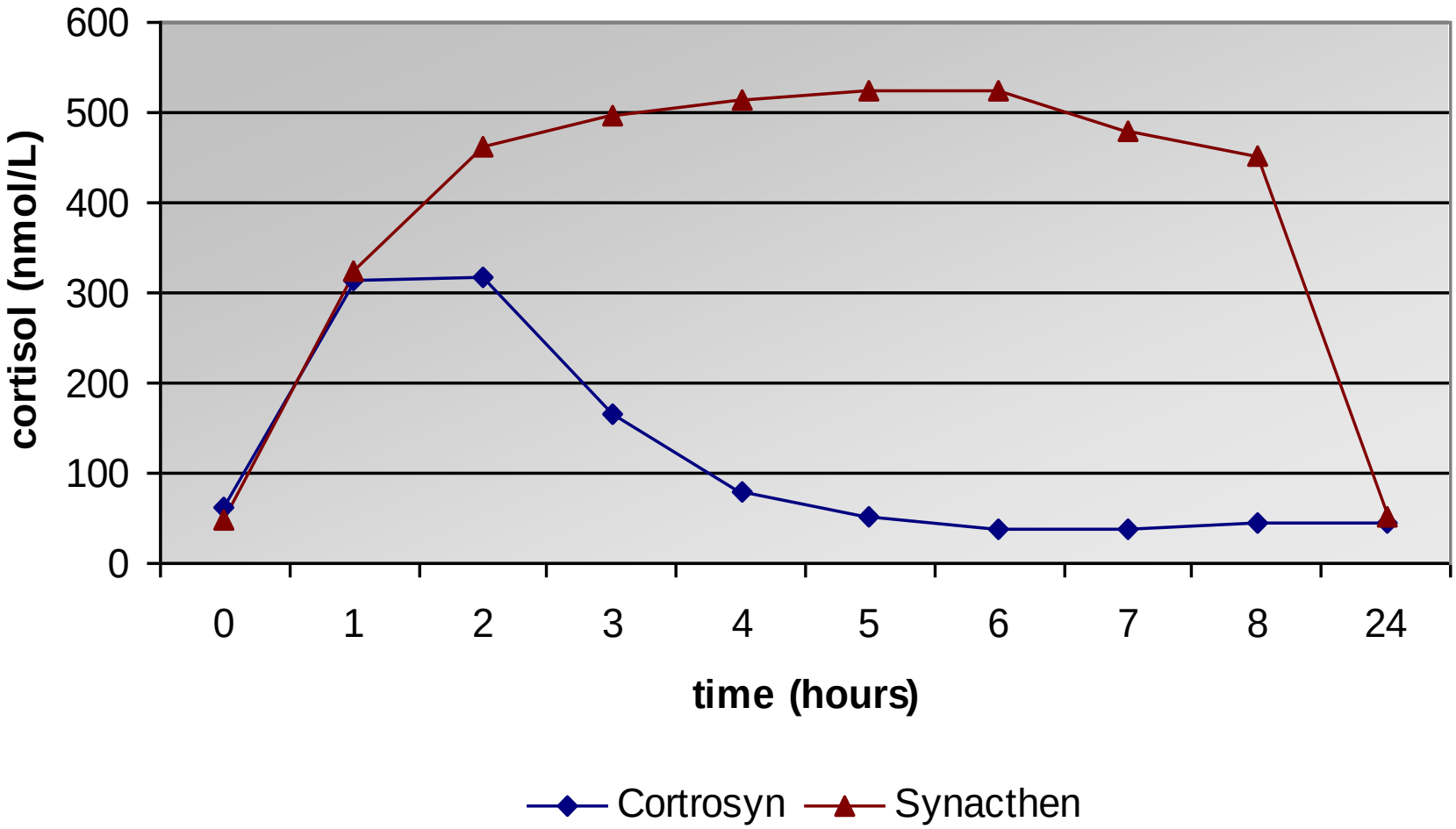
http://www.endocrinevet.info/2011/03/how-to-extend-your-supply-of-cortrosyn.html

Utilizing cortosyn to reduce $$

5. 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.
   5b. If you elect to refrigerate the syringes, they can be stored for up to 4 weeks.
6. Administer at a dose of 5 µg /kg (round up if needed) either IM or IV. Administer IV in dehydrated dogs and in all cats.
7. Cortisol levels should be measured prior to injection of Cortrosyn (0 hour), and at 1 hour post administration of Cortrosyn.

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

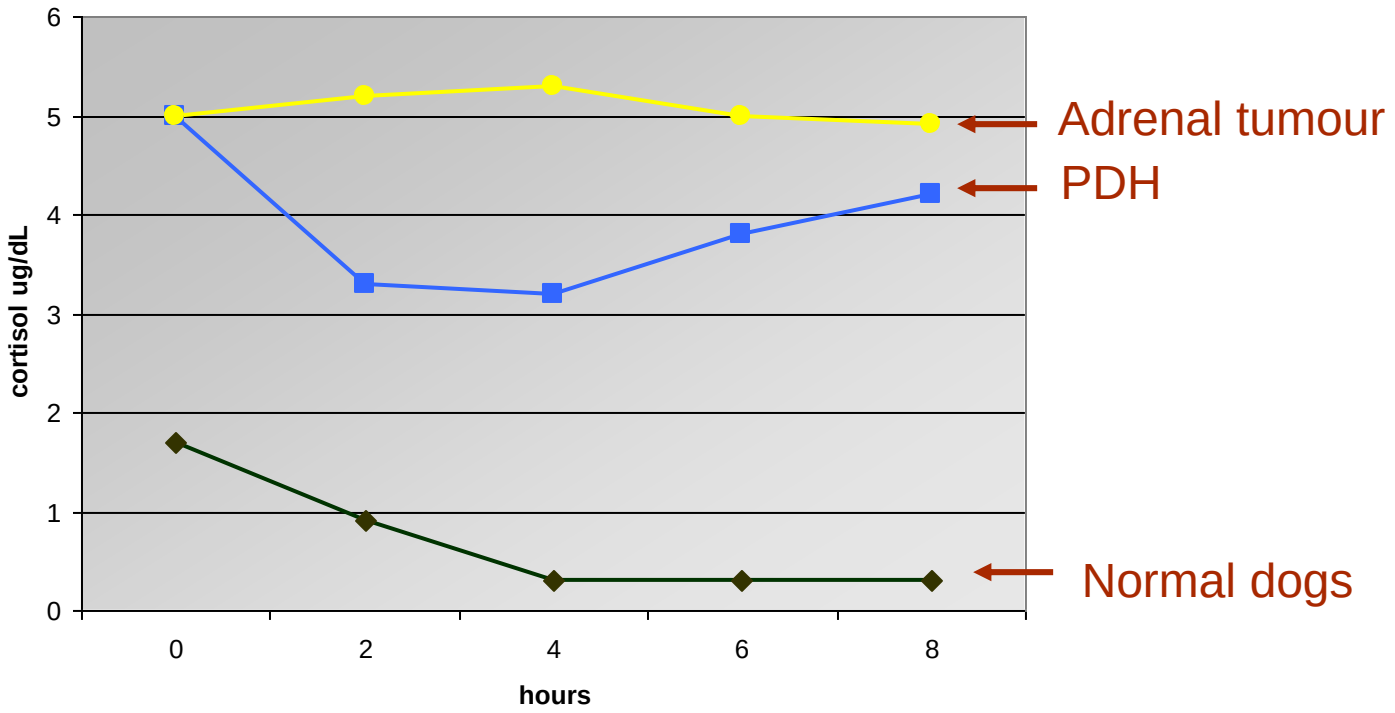
OVC 2006 study – normal dogs



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

Differentiating tests (PDH vs FAT)

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

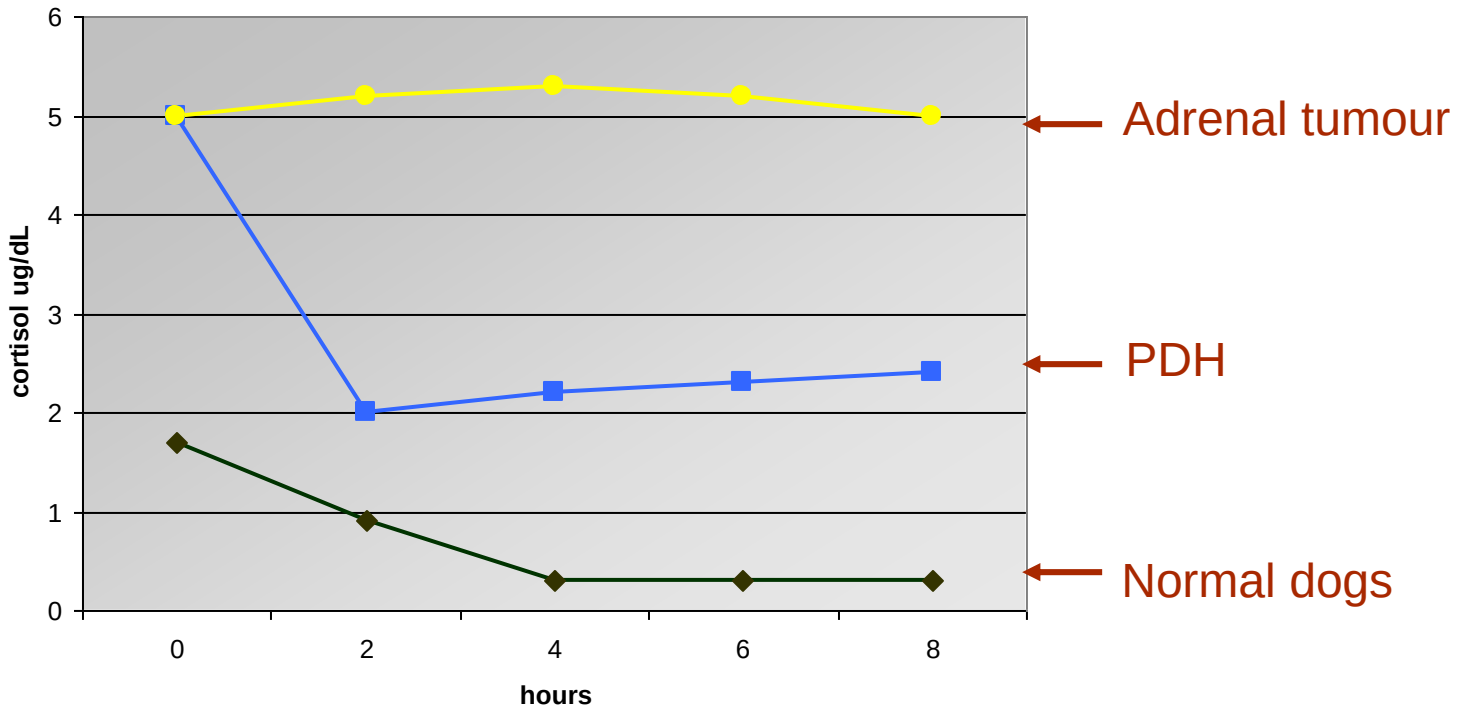
Endogenous ACTH

- 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

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
  - Recent talk suggests 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)

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

- Currently can obtain through Vet Purchasing in 10, 30 and 60 mg sizes
- However, Compounding Pharmacies have many sizes available, liquid format
- This allows slight increases or decreases in dosing

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

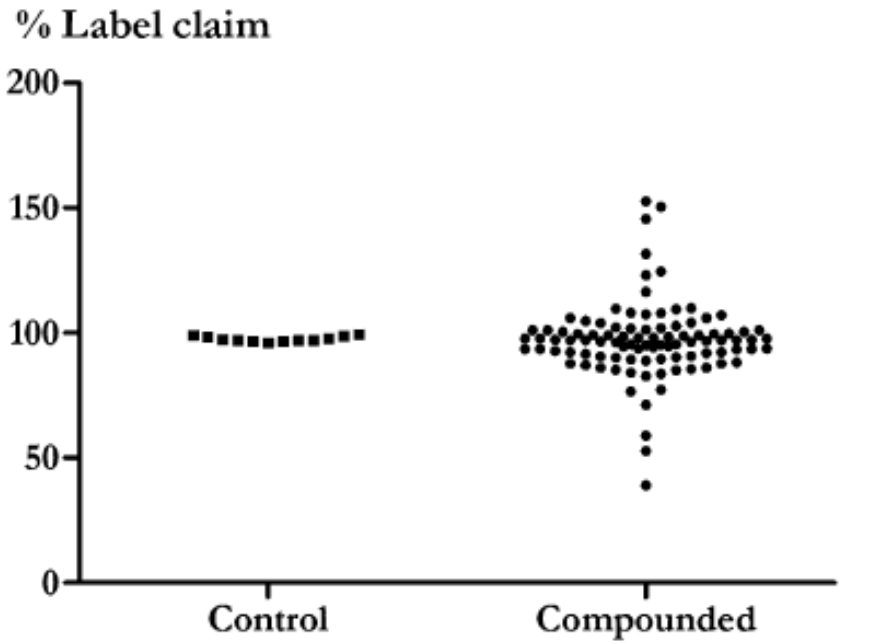


FIGURE 1 *Average percent label daim (% LC) for control (n=12) and compounded (n=96) batches of trilostane.*

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

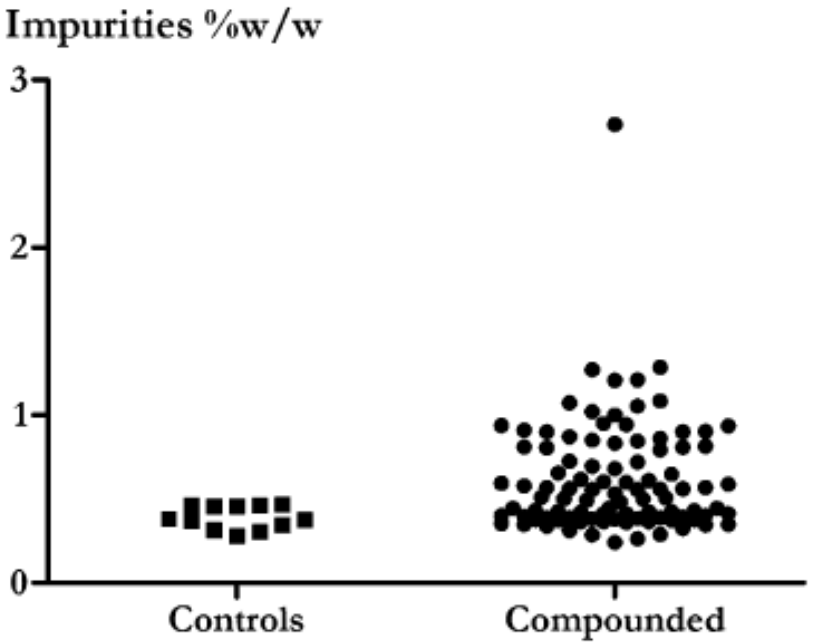


FIGURE 2 *Average percent (% weight/weight [w/w]) impurities/related substances for control (n=12) and compounded (n=96) batches of trilostane.*

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

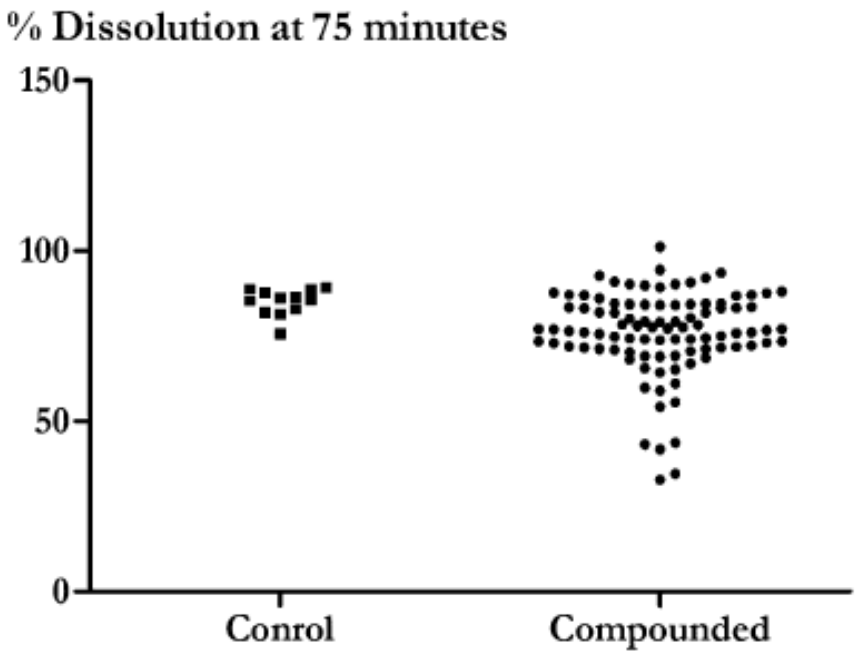


FIGURE 3 *Average dissolution based on % LC for control (n=12) and compounded (n=96) batches of trilostane at 75 min.*

Control
0% failed >70% at 75 mins

Compounded
20% failed >70% at 75 mins

Cook et al 2012 JAAHA

Bottom Line

- Use a compounding pharmacy that you trust

OR

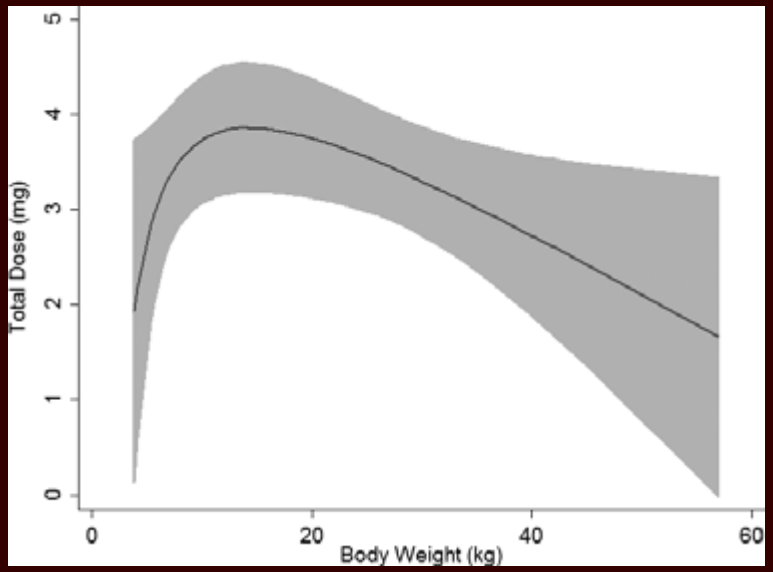
- Use a brand name product

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
  - Recent 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 – 20 kg dog

Vetoryl:	$124 per month
Compounded:	$114 per month
Lysodren:	$100 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

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