Update on Managing Canine Hyperadrenocorticism

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Sioux City, IA

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Agenda

Pathophysiology

Clinical signs

Diagnostic/differentiation test

Treatment/Monitoring

Clinical trials

Q & A

Dechra Veterinary Products

- International and US presence (US home office Kansas City)
- UK based – 14 European countries
- Licensed Pharmaceuticals
- Companion animal & equine focus
- VETORYL® CAPSULES (5,10,30,60,120 mg), Felimazole™(2.5, 5.0 mg)
- Zycortal® Suspension(DOCP)
- Dermapet products acquired Oct 2010
- Phycox®
- Otic/Derm/Ophthalmic – (formerly Pharmaderm)
- Equine - irap, Osteokine , Equidone, OsPhos
- Putney acquisition

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Veterinary Products

The Adrenal Glands

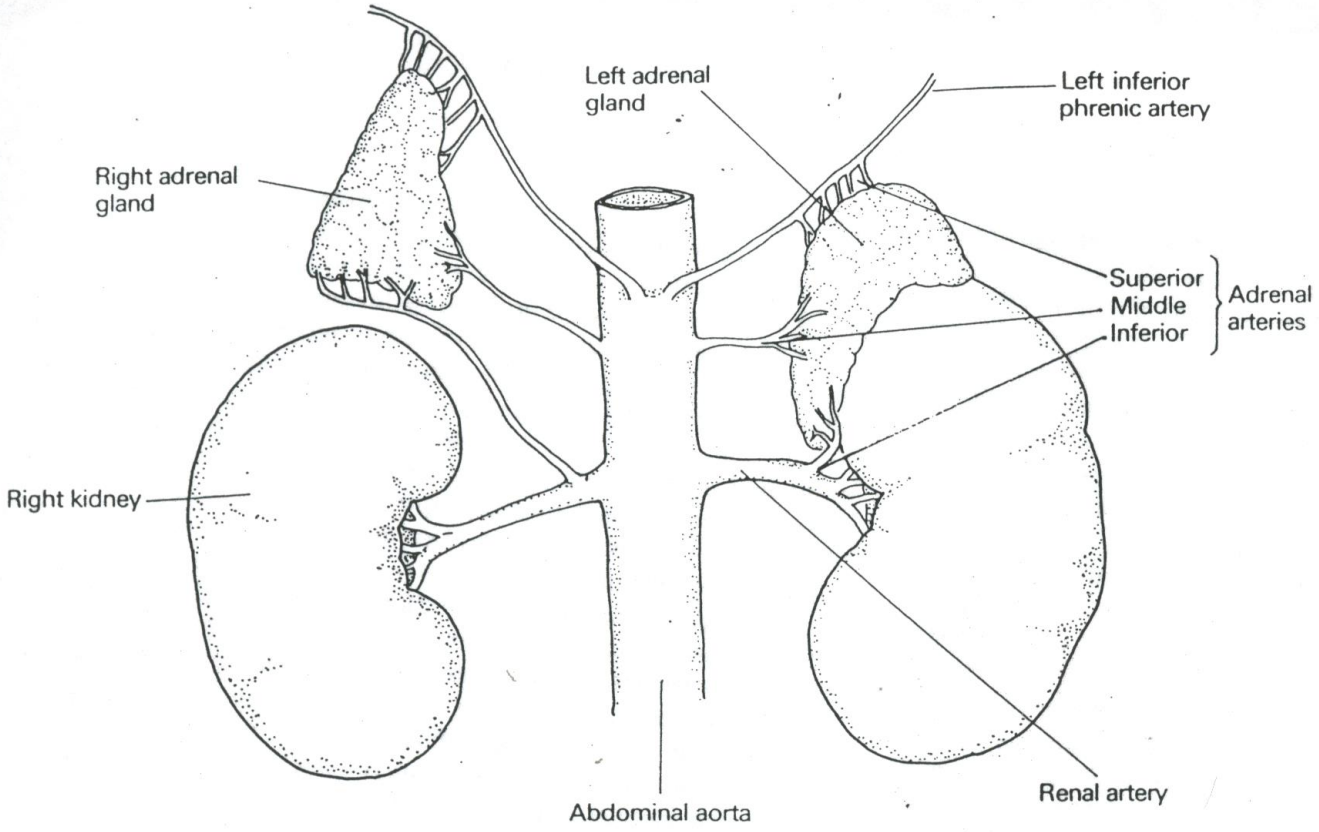

FIG. 19.11. The adrenal glands and their arterial blood supply.

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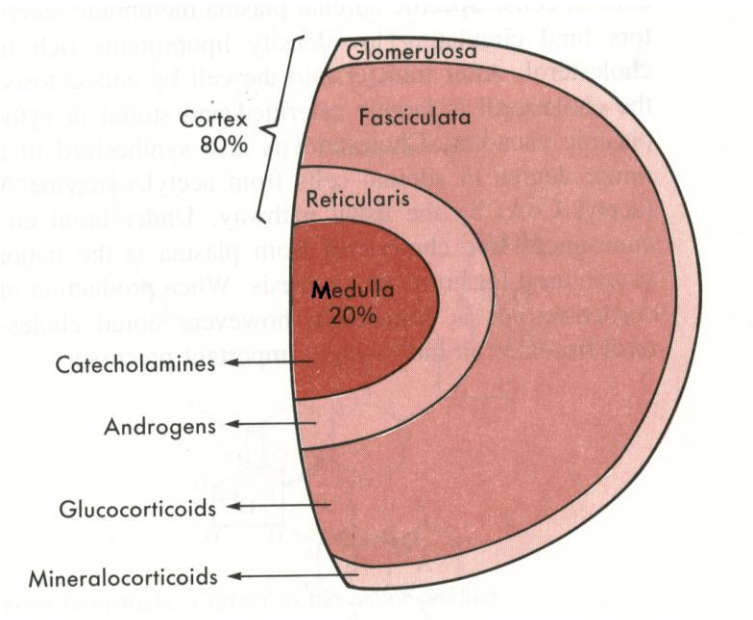
The Adrenal Cortex

80-90% of the entire gland and produces

GLUCOCORTICOIDS
(cortisol / corticosterone)

MINERALOCORTICOIDS
(aldosterone)

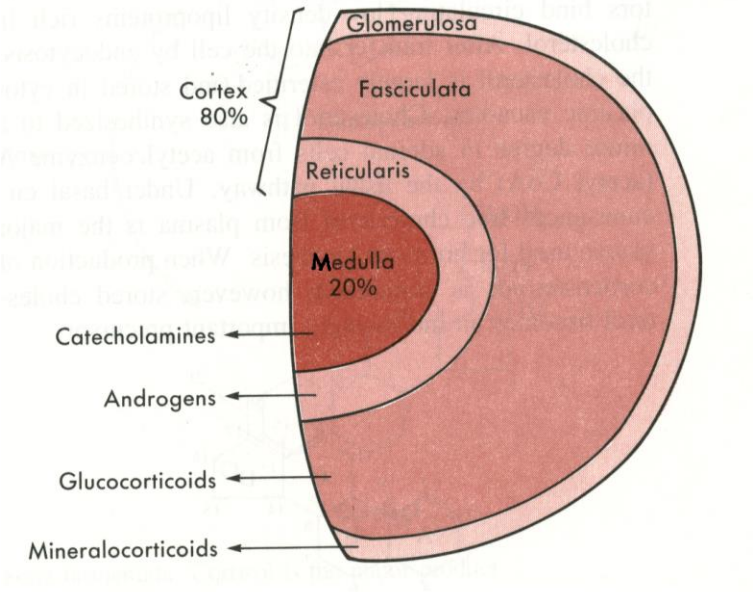
ANDROGENS
(precursors of sex hormones)



The Adrenal Medulla

10-20% of the entire gland and produces

CATECHOLAMINES (adrenaline / noradrenaline)

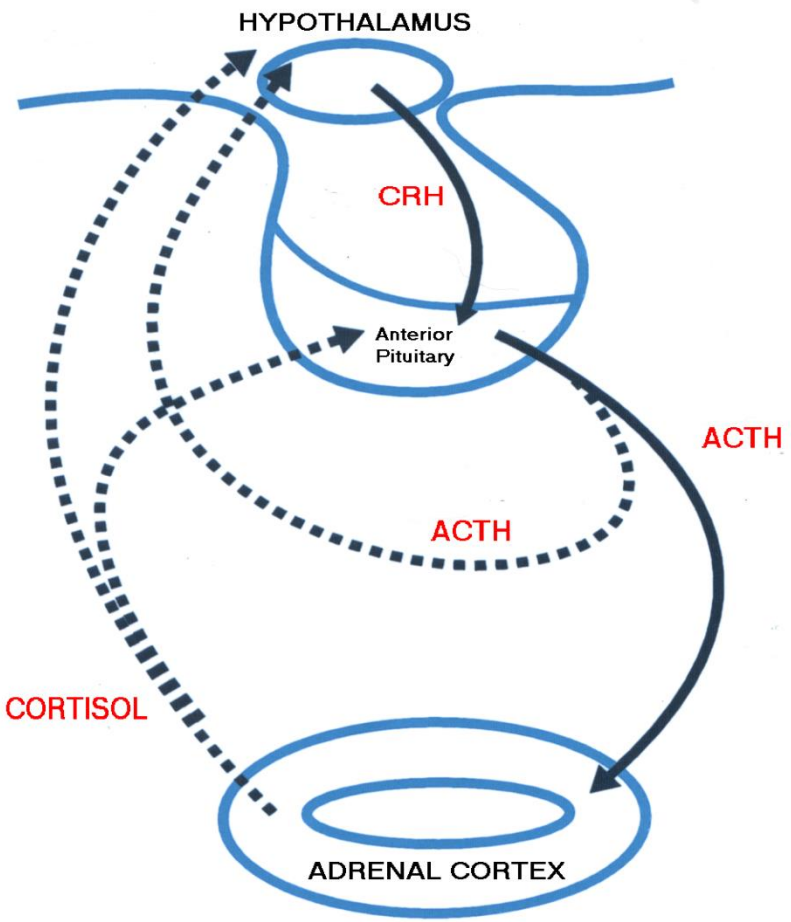


Hypothalamic-Pituitary-Adrenal AXIS

The Normal Hypothalamic-Pituitary-Adrenal Axis

Positive Effect

Negative Feedback



Cortisol has more diverse effects on the body than any other hormone

Cortisol is released in response to **stress.** Long term effects…

Liver
- Increased gluconeogenesis
- Increased glycogen stores
- Induction of certain enzymes

Muscle
- Increased protein catabolism

leads to muscle wasting and weakness

Bone
- Osteopenia associated with increased protein catabolism and neg. calcium balance

Skin
- Increased protein catabolism – thin skin, poor wound healing and poor scar formation
- Possible calcium deposition

Adipose Tissue
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- Redistribution of fat deposits

Blood
- Decreases in circulating lymphocytes
- Decreases in circulating eosinophils
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Immune System
- Diminished inflammatory response
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CNS
- Euphoria, depression, other behavioral changes

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Cortisol in perspective

Cortisol is released in response to stress

Therapeutically, corticosteriods are administered in **MASSIVE DOSES** relatively to physiologic levels.

With prolonged administration, it can take many months for the HPA Axis to return to normal function after these drugs are stopped – risk of Addisonian crisis

Etiology of HAC – spontaneous or iatrogenic

Pituitary dependent (80-85%)

Micro and macro adenomas, (adenocarcinomas)

Adrenal dependent (15-20%)

Functional adrenal adenomas and carcinomas

Iatrogenic

Exogenous corticosteroids

[**Ectopic ACTH**] – very rare(ACTH production by non-pituitary neoplasia - lung)

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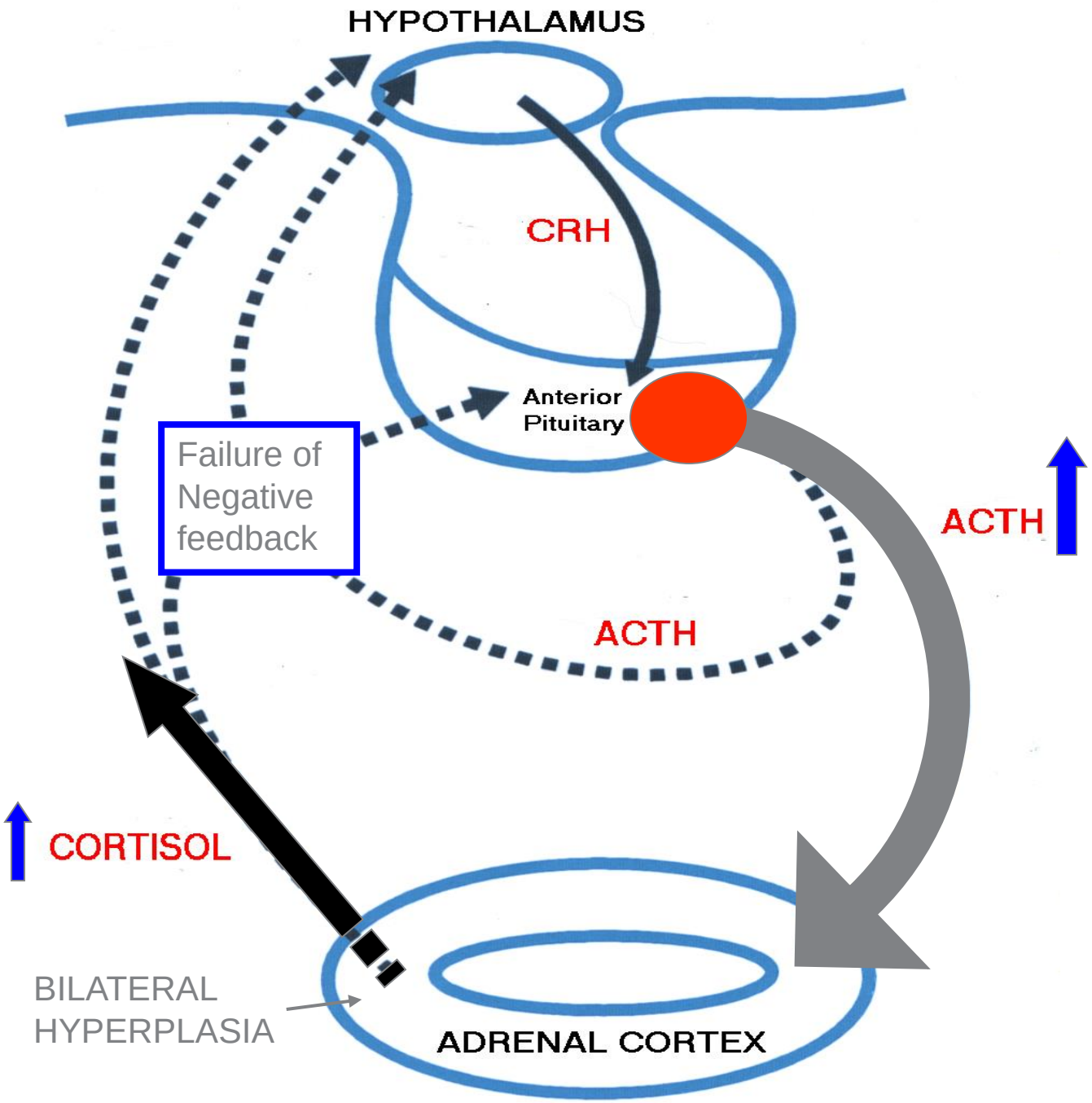
Atypical Hyperadrenocorticism

- Clinical signs suggestive of HAC
- Normal ACTH stim, LDDST and UCCR
- Consider measuring other adrenal steroid hormones – may be increased;may be helpful in diagnosis (Univ of Tennessee Endo lab)
- Have responded to treatment for HAC

Pituitary–dependent HAC(PDH)



Pituitary dependent HAC (PDH)

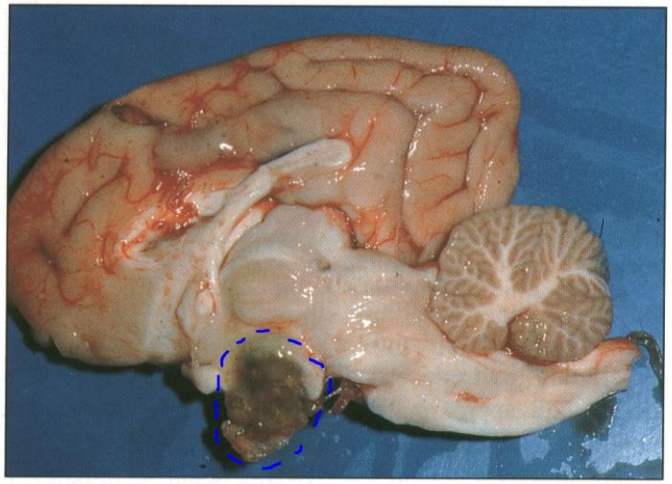
Most (>80%) have a pituitary **adenoma** arising from the pars distalis

Small proportion have a pituitary carcinoma

Most dogs have microadenomas (<1cm)

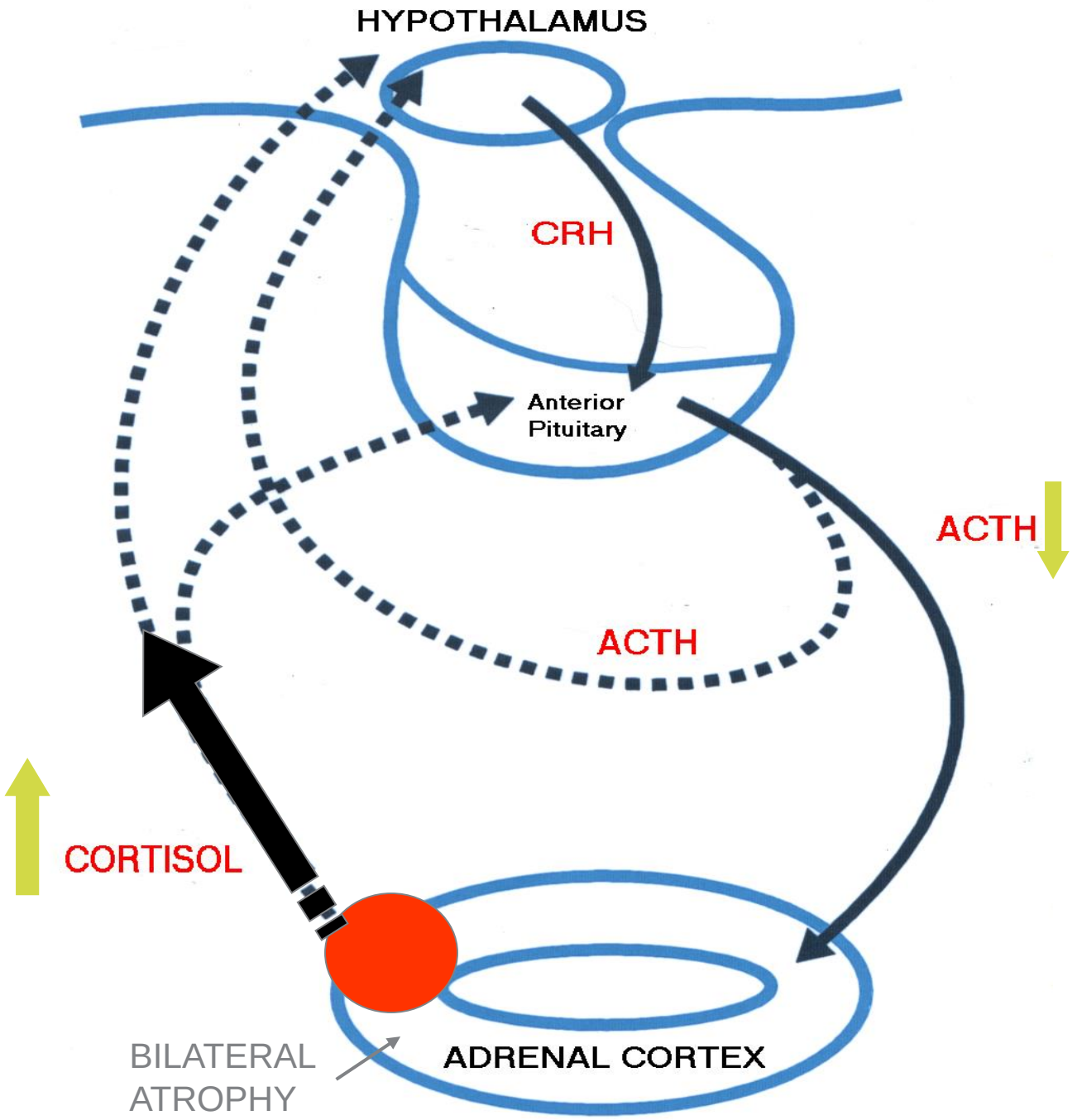
50% of tumors <3mm

10-20% have macroadenomas(>1cm)



From: BSAVA Manual of Canine & Feline Endocrinology 3rd edition, 2004. Chapter 15 'Canine Hyperadrenocorticism' by Michael Herrtage

Adrenal-dependent HAC (ADH)



Adrenal dependent HAC (ADH)

~50% benign, **remainder highly invasive malignancies**

In a series of 41 dogs with ADH, 26 (63%) had adrenocortical **carcinoma** and 15 (37%) had adrenocortical **adenoma** (Reusch, Feldman 1991)

Difficult to distinguish adrenal adenomas from carcinomas

- clinically
- biochemically
- ultrasonographically

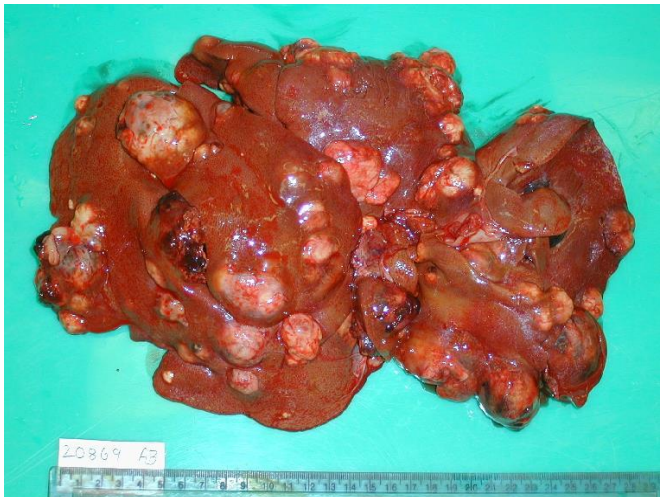


Photo courtesy of Dr Reto Neiger

Hyperadrenocorticism (HAC)

Chronic, progressive; not immediately life-threatening
Quality of life issue for both dog and owner

Signalment:

Middle age to older; male/female
Many breeds; poodles, Dachshunds, various Terrier breeds, G. Shepherd, Labrador commonly represented
Boxer and Boston Terrier ↑ risk (Feldman, Nelson 3rd ed. p 265)

Diagnosis: HAC is a CLINICAL diagnosis! – need more than lab work

Can be difficult to diagnose – not all have “classic” signs

Owners can confuse some signs with aging

HAC “problems” are not acute, nor do they frighten the owner

Confusing diagnostic test results

Without clinical signs – do not treat for HAC

Clinical Signs- depend on the duration and degree of cortisol excess

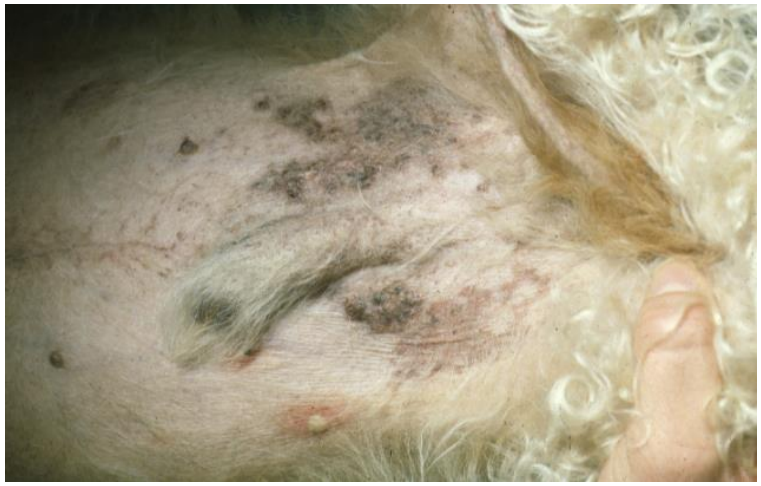
- polydipsia (>100 ml/kg/day)
- polyuria (>50 ml/kg/day)
- polyphagia
- lethargy
- panting
- muscle wasting/weakness
- ‘pot bellied’ appearance

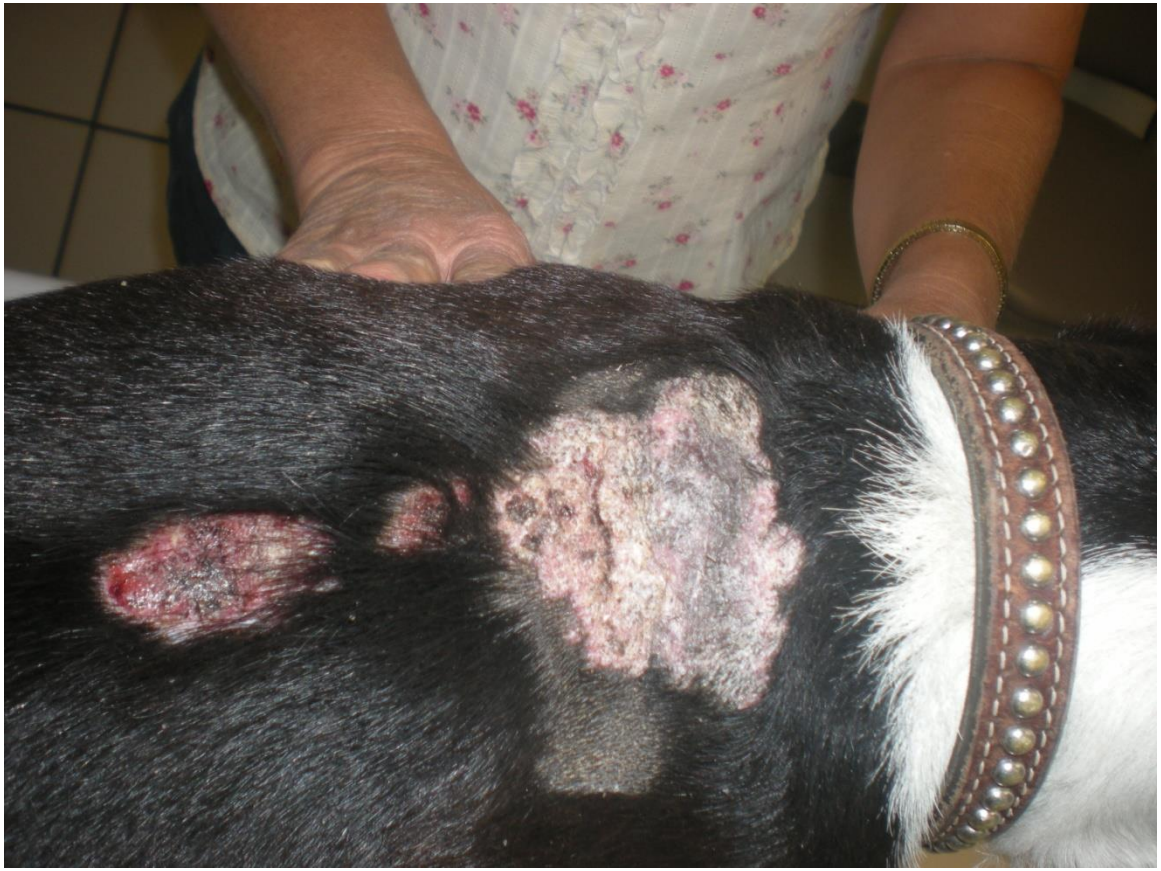

Photo provided by Carlos Melian


Photo provided by Dr Reto Neiger

Clinical Signs –continued

- bilaterally symmetrical, non-pruritic alopecia
- skin thin, inelastic
- poor wound healing
- poor regrowth of hair
- comedomes, calcinosis cutis
- recurrent UTI
- recurrent skin infections
- anestrus/testicular atrophy
- 1st pyoderma in older dog
- Demodex in a older dog
- Ruptured ACL in inactive dog





Calcinosis cutis -

6 yr, male neutered Boston Terrier; on Vetoryl for 4 days
Sometimes develops after treatment has begun.

Clinical Signs - neurologic

Neurological signs with **PDHAC**

- not very common at presentation
- may develop during Tx; probably due to removal of negative feedback inhibition of cortisol on pit/hyp which may allow for rapid enlargement of pituitary tumor = edema and increased intracranial pressure

- dullness, depression, disorientation, loss of learned behavior, anorexia, aimless wandering or pacing, head pressing, circling, ataxia, blindness, seizures, anisocoria

Dogs with MACROADENOMAS may show signs of concurrent CENTRAL DIABETES INSIPIDUS

Clinical Signs - unusual

Myotonia

- persistent active muscle contractions that continue after voluntary/involuntary stimuli
- rigid limbs & stiff stilted gait
- may affect all 4 limbs, but signs usually more severe in the hindlimbs
- bizarre high frequency discharges are noted on electromyography
- Clinical response is not predictable - Cause ? – Feldman, Nelson

Cortisol has more diverse effects on the body than any other hormone

Cortisol is released in response to **stress.** Long term effects…

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Clinical Signs HAC dogs do NOT have

- Poor appetite
- Vomiting and/or diarrhea
- Coughing, sneezing
- Pain
- Seizures
- Bleeding
- Pancreatitis – VERY RARE !
- Renal failure – VERY UNUSUAL

Feldman,Nelson: Canine and Feline Endocrinology and Reproduction p. 266

Non-specific laboratory findings

stress leukogram

- *mature neutrophilia (without left shift)*
- *monocytosis*
- *lymphopenia*
- *eosinopenia (NO EOSINOPHILIA)*

hyperglycemia ± glucosuria

hypercholesterolemia/hypertriglyceridemia

steroid induced ↑ALKP

low urine SG (<1.015), proteinuria, UTI

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Diagnosing Hyperadrenocorticism

Diagnostic tests - does the dog have Cushing's?

Low-dose dexamethasone

ACTH stimulation test

(Urinary cortisol : creatinine ratio (UCCR))

Differentiation tests – if so, is it PDH or ADH?

Dexamethasone suppression

(low / high)

Endogenous ACTH

Ultrasound

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Effects of exogenous steroids on adrenal tests

Assay cross-reaction

- Prednisolone, hydrocortisone cross-react with the measurement antibodies and cause false cortisol results (false high)
- Need to discontinue steroids 24hrs to prevent assay interference
- No cross-rx with dexamethasone

Physiological effect

- Exogenous steroids (even eye, ear, skin) will affect pituitary production of ACTH and cause the adrenals to shrink and less cortisol to be produced
- To study the pituitary-adrenal axis free from this effect, should wait 4 weeks

DO YOU HAVE AN IATROGENIC CASE????

ACTH Stimulation Test

- Measure of adrenocortical reserve capacity
- **PROTOCOL**
- Baseline sample for cortisol (0 hour)
- Inject synthetic ACTH -Cortrosyn (cosyntropin)

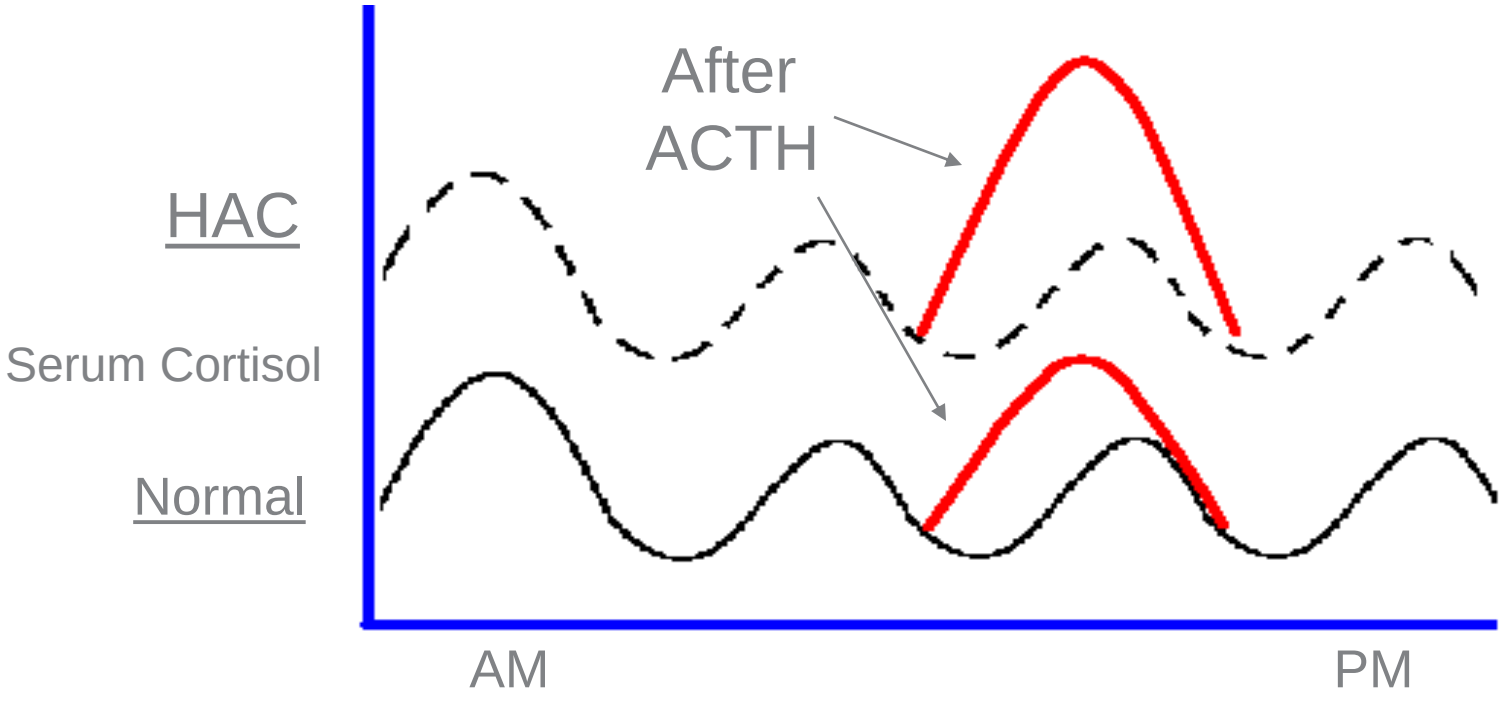
  5 µg/kg IV or IM (max dose = 250 ug)
- Second sample for cortisol taken 1 hour later

ACTH Stimulation Test

Interpretation

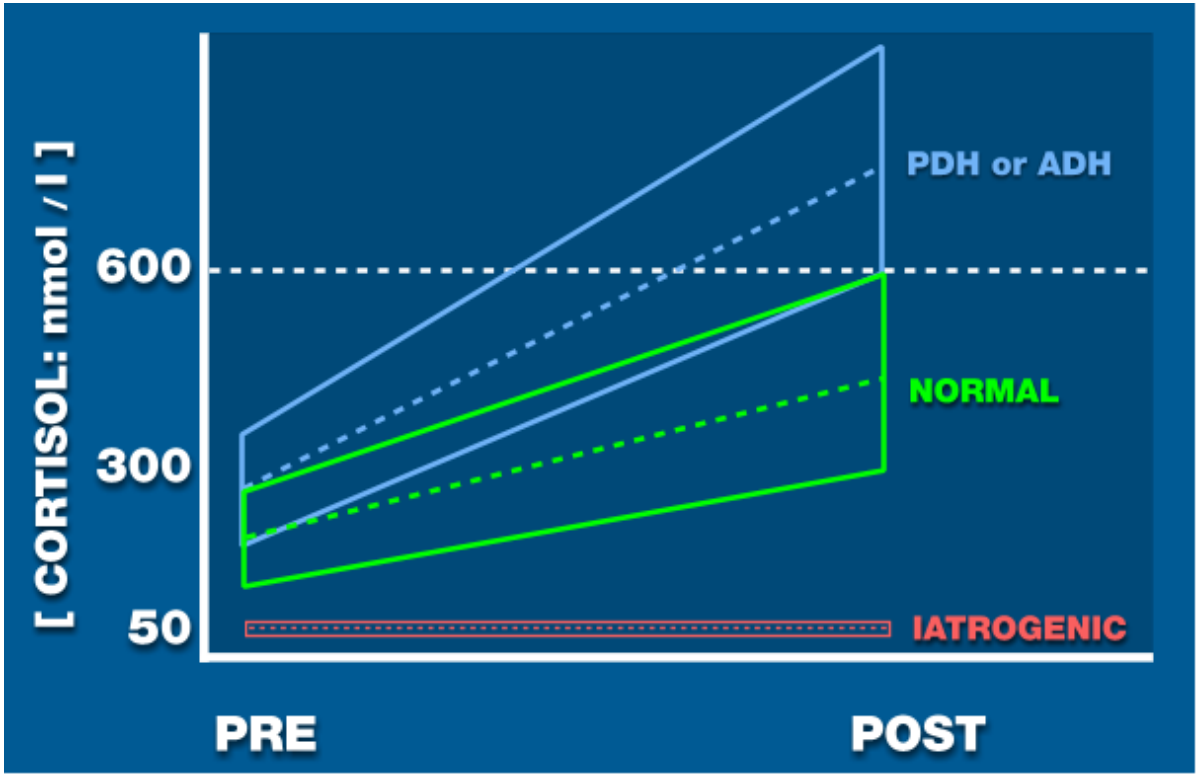
- Post-ACTH cortisol concentration
  - > 22 µg/dl consistent with HAC
  - < 15 µg/dl is not consistent with HAC
- False negatives occur
  - 20-30% of dogs with HAC < 22 µg/dl

ACTH Stimulation Test



HAC dogs demonstrate an **exaggerated** response to ACTH

ACTH Stimulation Test



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ACTH Stimulation Test

Advantages

- Short test (1 hour, => less stress for animal)
- **More specific than LDDST**
  - (more confidence in a positive test result)
- Test of choice in suspect iatrogenic and in monitoring Vetoryl (trilostane) and lysodren

Disadvantages

- **Less sensitive than LDDST** (esp. adrenal HAC)
  - (less confidence in a negative result)
- Cannot provide differentiation

Low-dose dexamethasone suppression test

- Measures the resistance of an abnormal pituitary-adrenal axis to suppression by dexamethasone

- Inject 0.01-0.015 mg/kg dexamethasone iv (dexamethasone sodium phosphate or dexamethasone in polyethlene glycol)

- 3 samples for cortisol @ 0, 3-6 and 8 hrs

8 hr cortisol result **> 1.45 µg/dl = POSITIVE**
(> 40 nmol/L)

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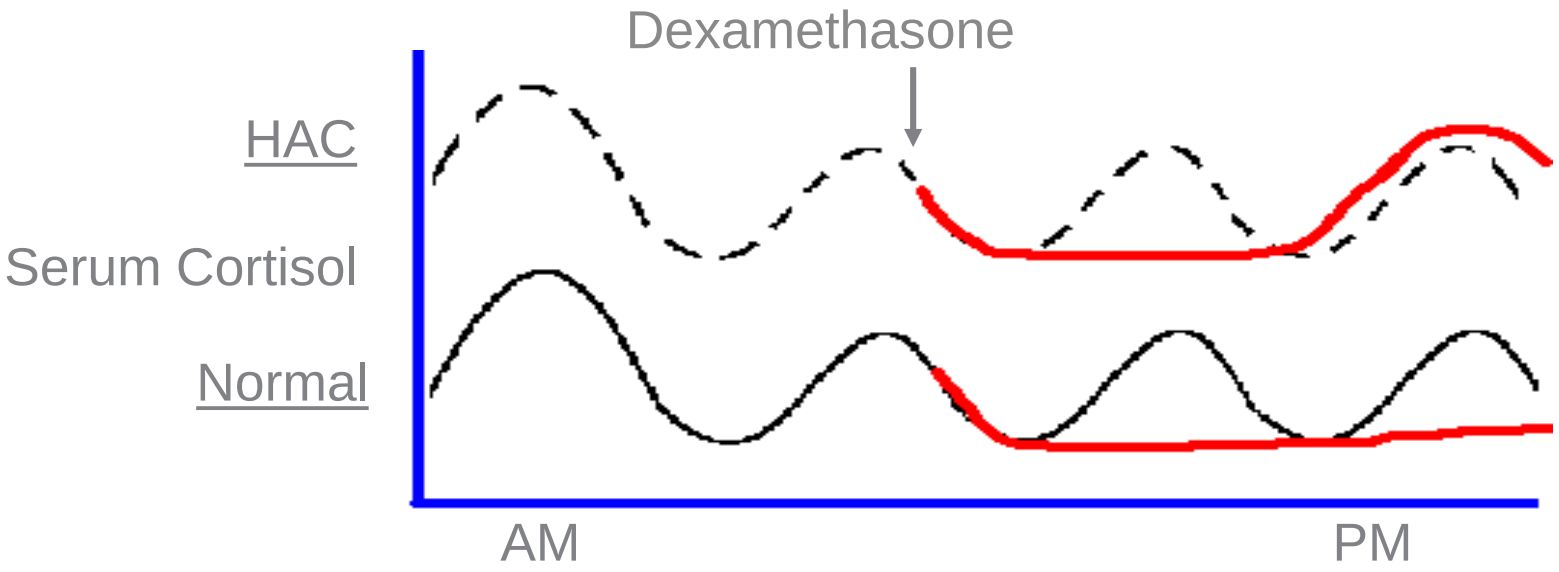
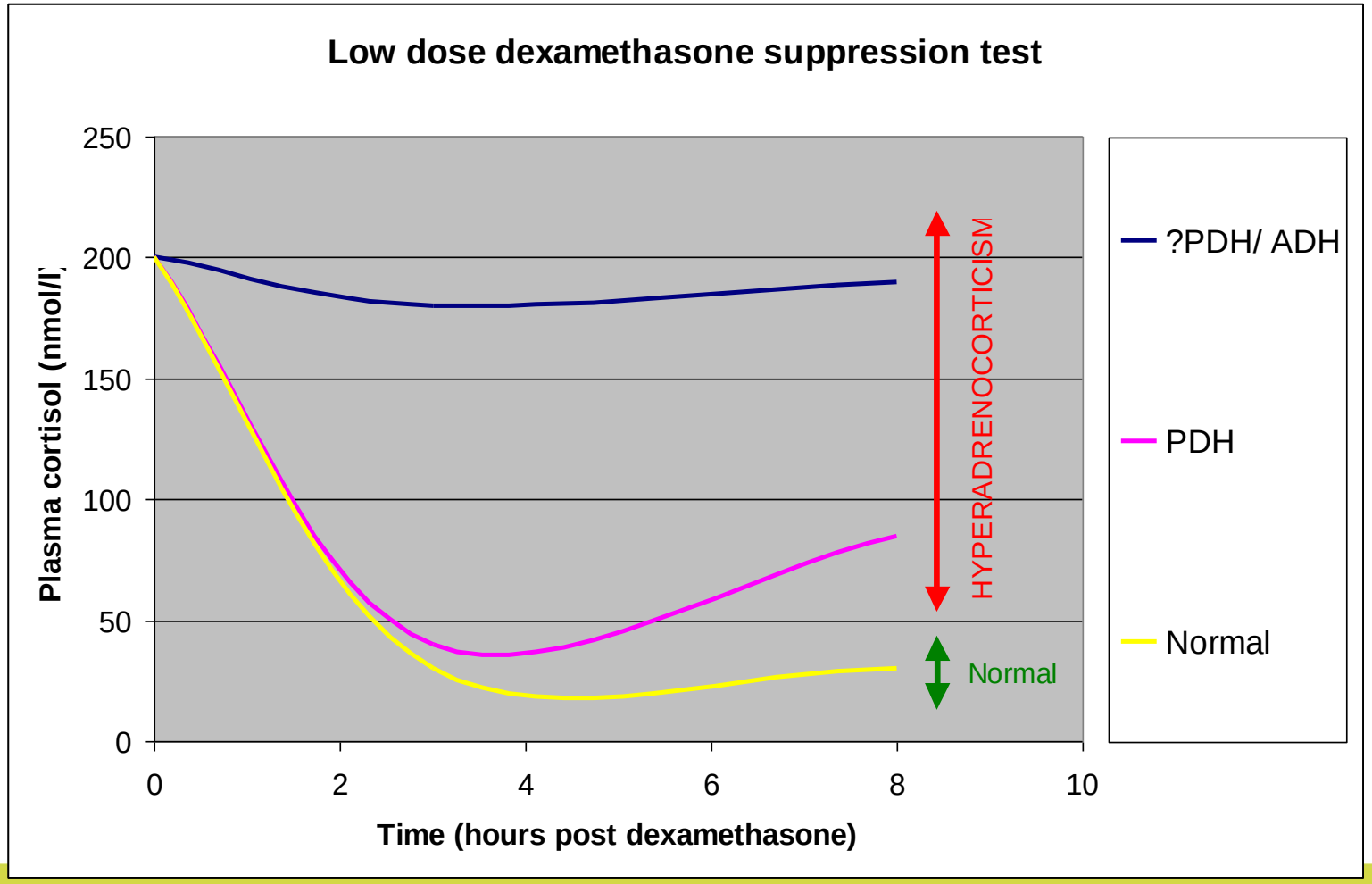
Low-dose dexamethasone



Normal dog : cortisol secretion inhibited within 2-3 hours and suppression lasts as long as 24–48 hours

HAC dog : variable or transient inhibition of cortisol secretion initially
a) **FIRST** √ 8 hr result first: **if 8 hr > 1.45 ug/dl (40 nmol/L) = positive** b) √ escape from suppression by 8 hours (if > 50% suppression from base line at 4 or 8 hr – PDHAC.
c) if < 50% or minimal suppression = PDH or ADH

Low-dose dexamethasone



Low-dose dexamethasone

Advantages

Highly sensitive

(extreme confidence in a negative test result)

(up to 10% of PDH dogs have normal LDDST- D. Bruyette)

May differentiate as well as diagnose (60% of HAC cases)

Disadvantages

Long test (8 hours)

Poor specificity

(up to 56% false positives in Non-adrenal illness)

Not appropriate if history of exogenous steroids

Urinary cortisol : creatinine ratio

Collect one (or more) morning urine samples at home in a non-stressed environment . Consult with your laboratory for their normal values.

ADVANTAGE

Inexpensive; Convenient for owner

HIGH SENSITIVITY (extreme confidence in negative results)

DISADVANTAGE

POOR SPECIFICITY (positive result not confirmatory – false positives relatively common)

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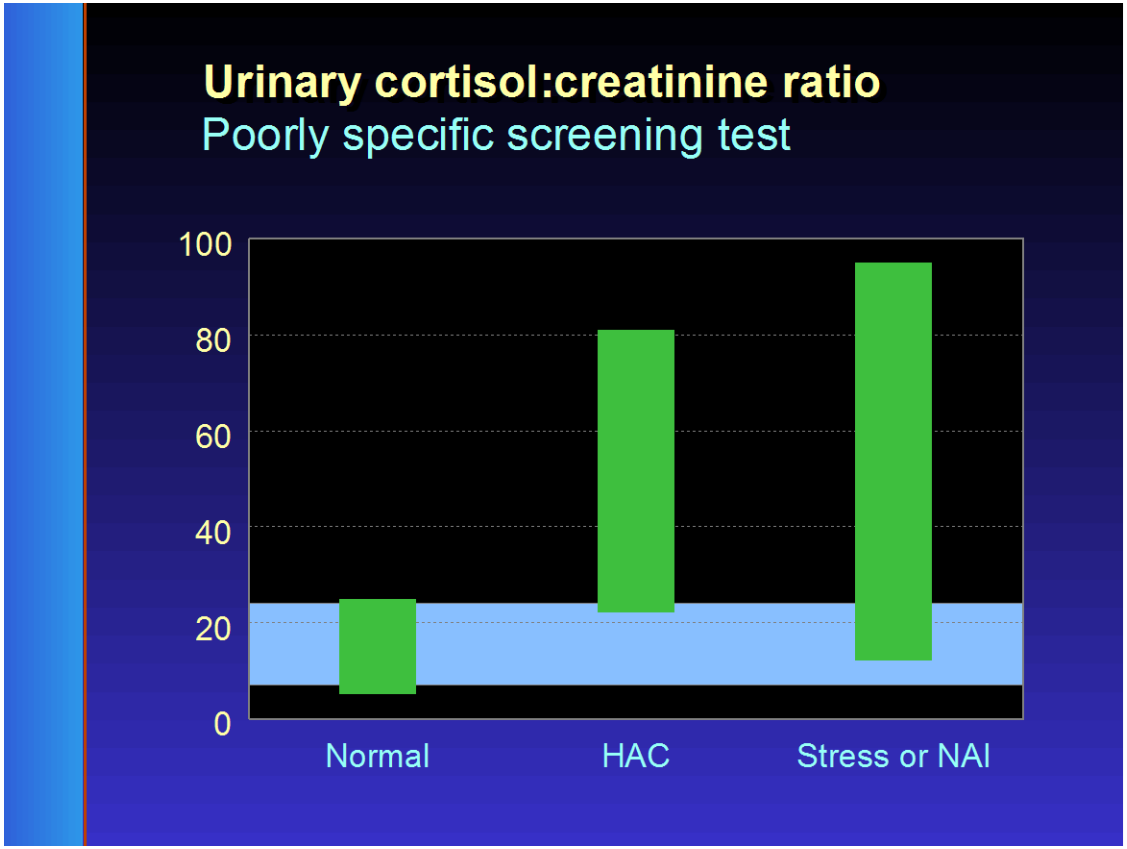
Urinary cortisol : creatinine ratio

DISADVANTAGE

Very poor specificity (some as low as 24%)



Differentiation Test: PDH vs ADH

Low dose dexamethasone

sufficient suppression for differentiation in 60% of positive LDDST

Endogenous ACTH – contact lab or sample handling

Imaging

Ultrasound : bilateral adrenal enlargement in PDH, unilateral in ADH

CT/MRI : adrenal tumour, adrenal hyperplasia or pituitary tumour

Radiography: adrenal enlargement or mineralisation

High dose dexamethasone

0.1 to 1.0 mg/kg iv - sample at 0, 3-6 and 8 hours

>50% suppression rules out adrenal source

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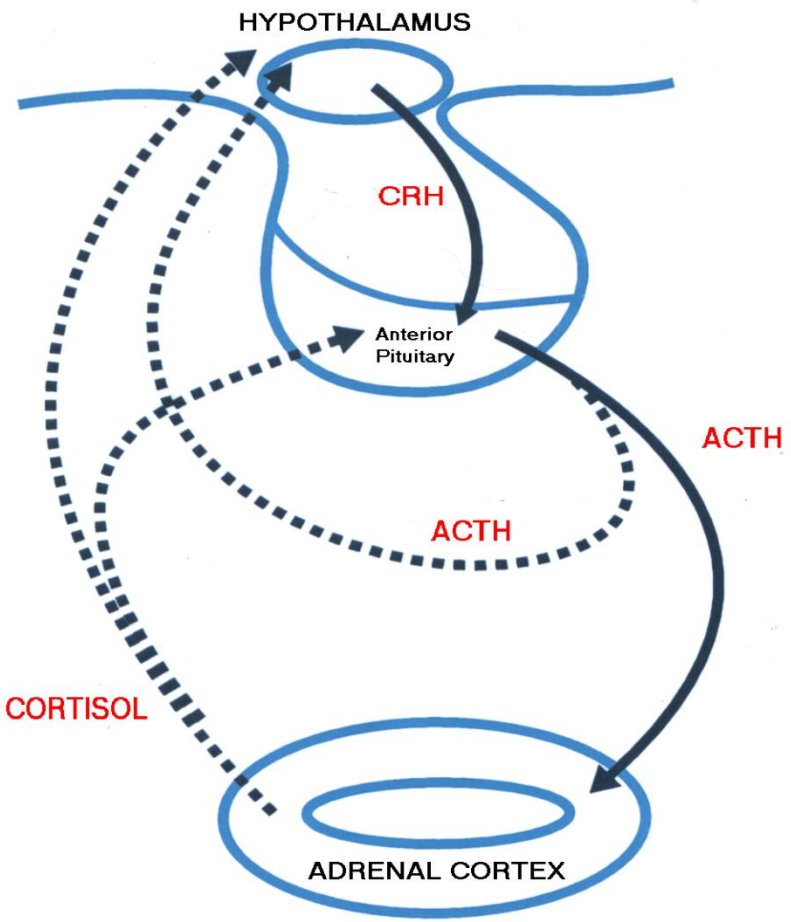
Endogenous ACTH Test

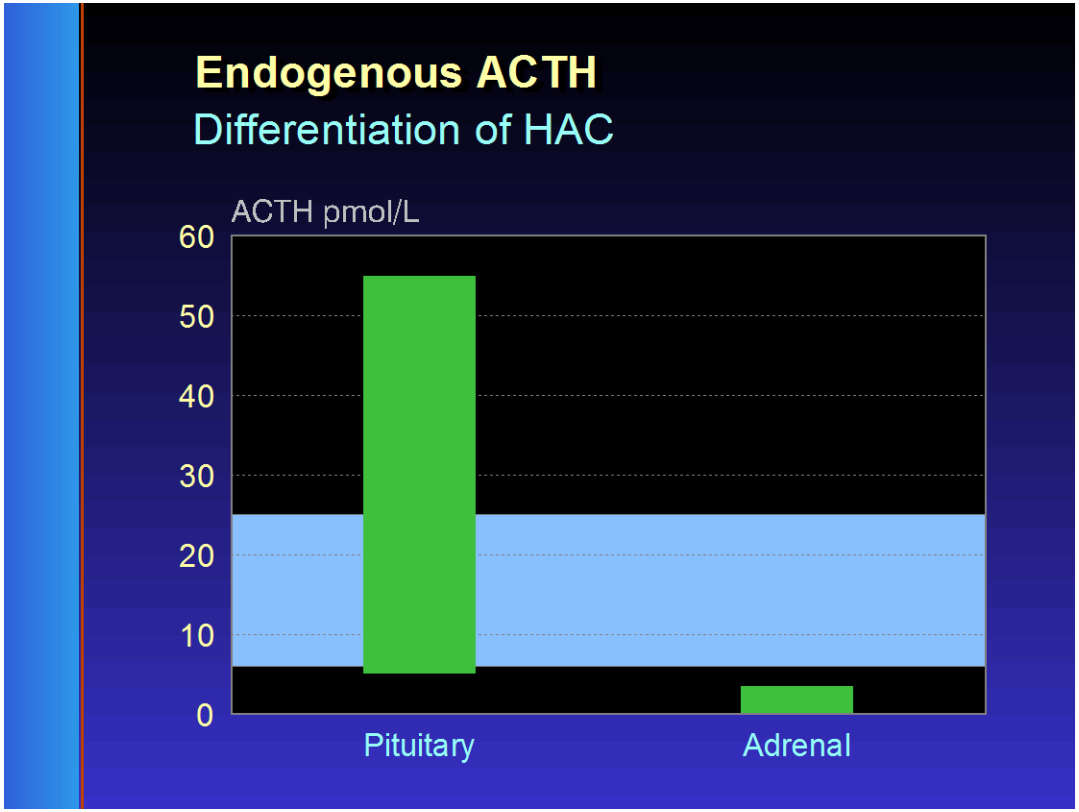
The Normal Hypothalamic-Pituitary-Adrenal Axis

Positive Effect

Negative Feedback



Endogenous ACTH



Area of overlap does exist

Meticulous handling important as tube must be kept **frozen**.

Aprotinin tubes can be used without freezing sample – ask reference lab

Contact laboratory for supply of an insulated container.

PDH vs ADH

Why discriminate between PDH & ADH?

PDH & ADH are treated the same way medically

However; adrenalectomy, bilateral adrenalectomy are possible depending on patient, client, etc

(hypophysectomy- very rarely done)

If appropriate, Important to give clients the option of surgery

Adrenalectomy

- Indicated if:
- No evidence of metastases/invasion of abdominal vessels
- Dog in good enough shape to have surgery
- Surgeon who can do the surgery
- Owner will to pay.
- Strong recommendation: Vetoryl for 4-8 weeks prior to reverse metabolic derangements of hyperadrenocorticism

ADHAC - adrenalectomy

- Consider: VETORYL Capsule therapy for 3-4 weeks before surgery
- Decreased perioperative mortality

(R. Nelson – Midwest Vet Conference 2010)

- Adrenocortical tumors are quite sensitive to trilostane – treat prior to adrenalectomy – 9/9 dogs underwent successful adrenalectomy after 8-10 weeks trilostane therapy

(E. Feldman – JAVMA June 1, 2011

Additional medical concerns with HAC

Hypertension

- has been clearly associated with HAC (>50% untreated HAC dogs)
- cause unknown
- doesn't resolve with control of excess glucocorticoid

Hypercoagulable State

- HAC has been associated with pulmonary thromboembolism, aortic thrombosis & iliac thrombosis
- cause incompletely understood; probably multifactorial including: obesity, hypertension,↑ hematocrit, sepsis, prolonged periods of recumbency, ↑procoagulation factors, ↓decreased antithrombin)

Adrenal tumours can sometimes rupture

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IMPORTANT CONSIDERATIONS

Reconsider diagnosis /treatment if :

- Anorectic
- Eosinophilia
- Normal UCCR
- No clinical signs consistent with HAC

- Most sensitive and specific diagnostics tests are history and clinical examination
- Without clinical signs present, treatment is not warranted
- Dechra does not recommend trial therapy

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Medical options for PDH & ADH

VETORYL CAPSULES(trilostane) - approved by FDA for

PDH and ADH, short acting enzyme inhibitor, reversible

Mitotane - not approved, cytotoxic effect

Ketoconazole - not approved, steroid synthesis inhibition, expensive

Anipryl (selegiline hydrochloride) – approved for PDH; increase dopamine concentration, decrease ACTH; poor efficacy

Vetoryl is now in 5 sizes

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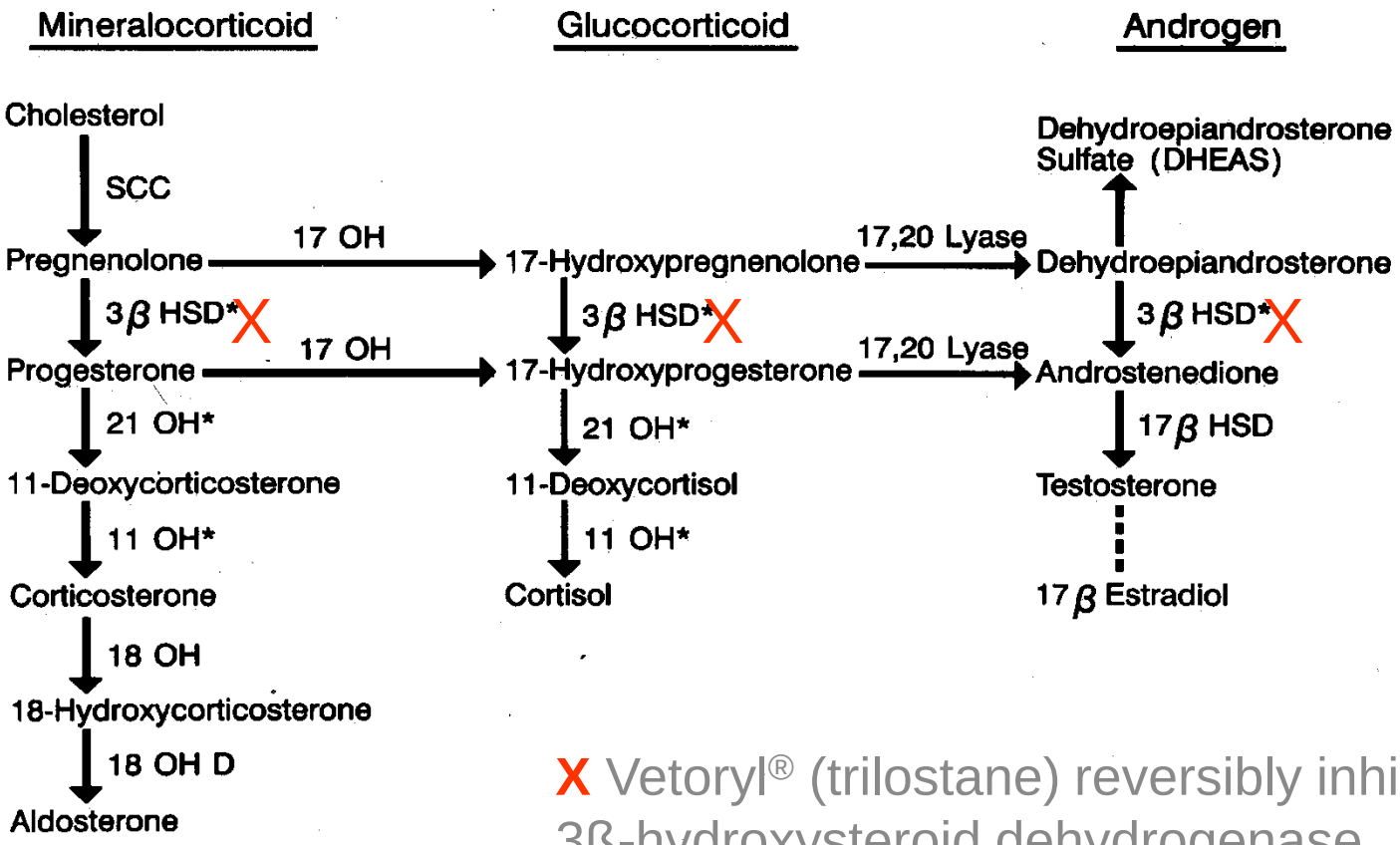
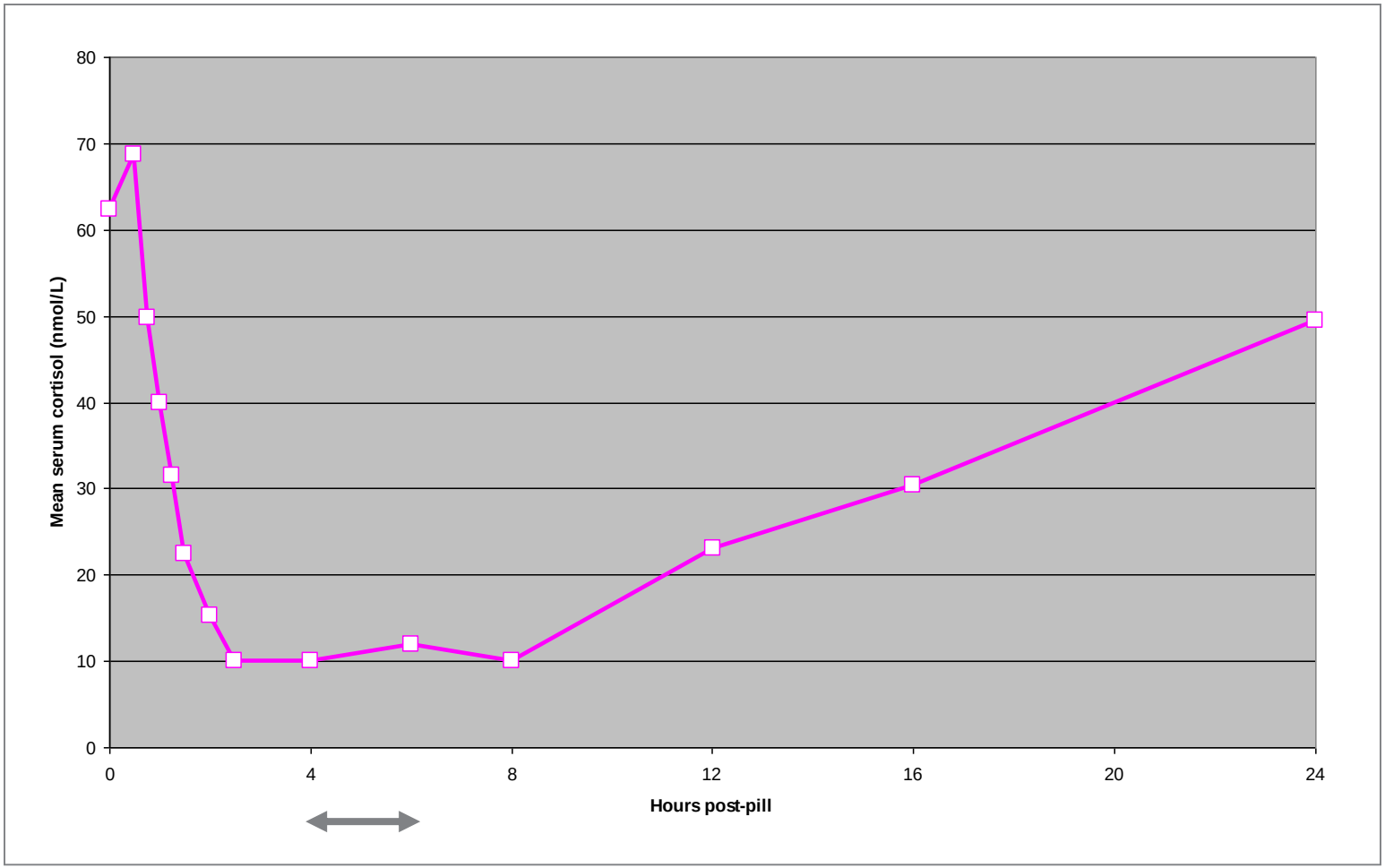
VETORYL® CAPSULES(trilostane)



X Vetoryl® (trilostane) reversibly inhibits 3ß-hydroxysteroid dehydrogenase, blocking the production of cortisol and corticosterone

VETORYL® CAPSULE(trilostane) activity – cortisol levels



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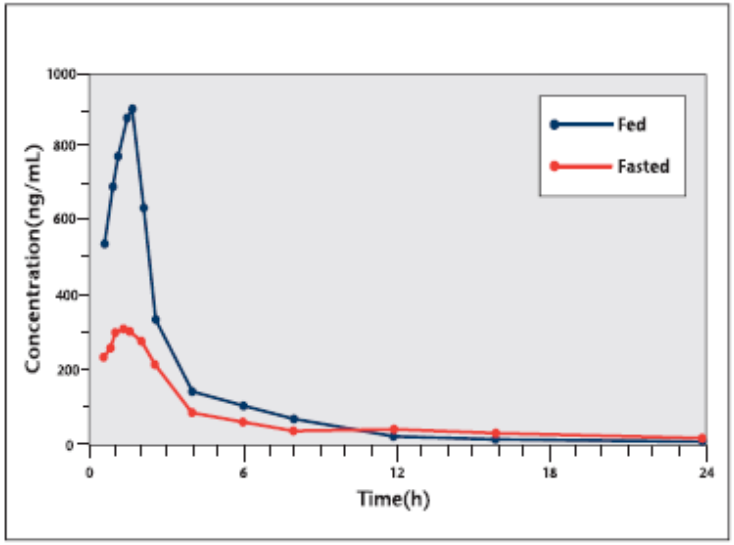
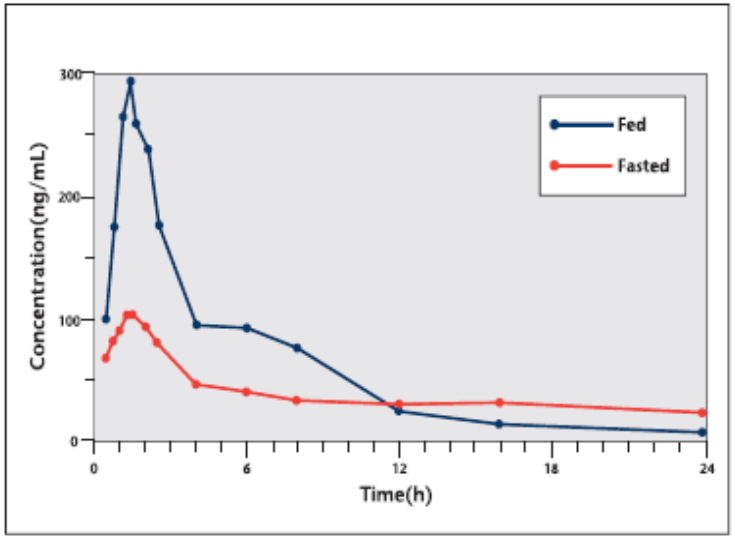
VETORYL® CAPSULE(trilostane) activity

Mean plasma concentration-time plot for Trilostane



Mean plasma concentration-time plot for Ketotrilostane



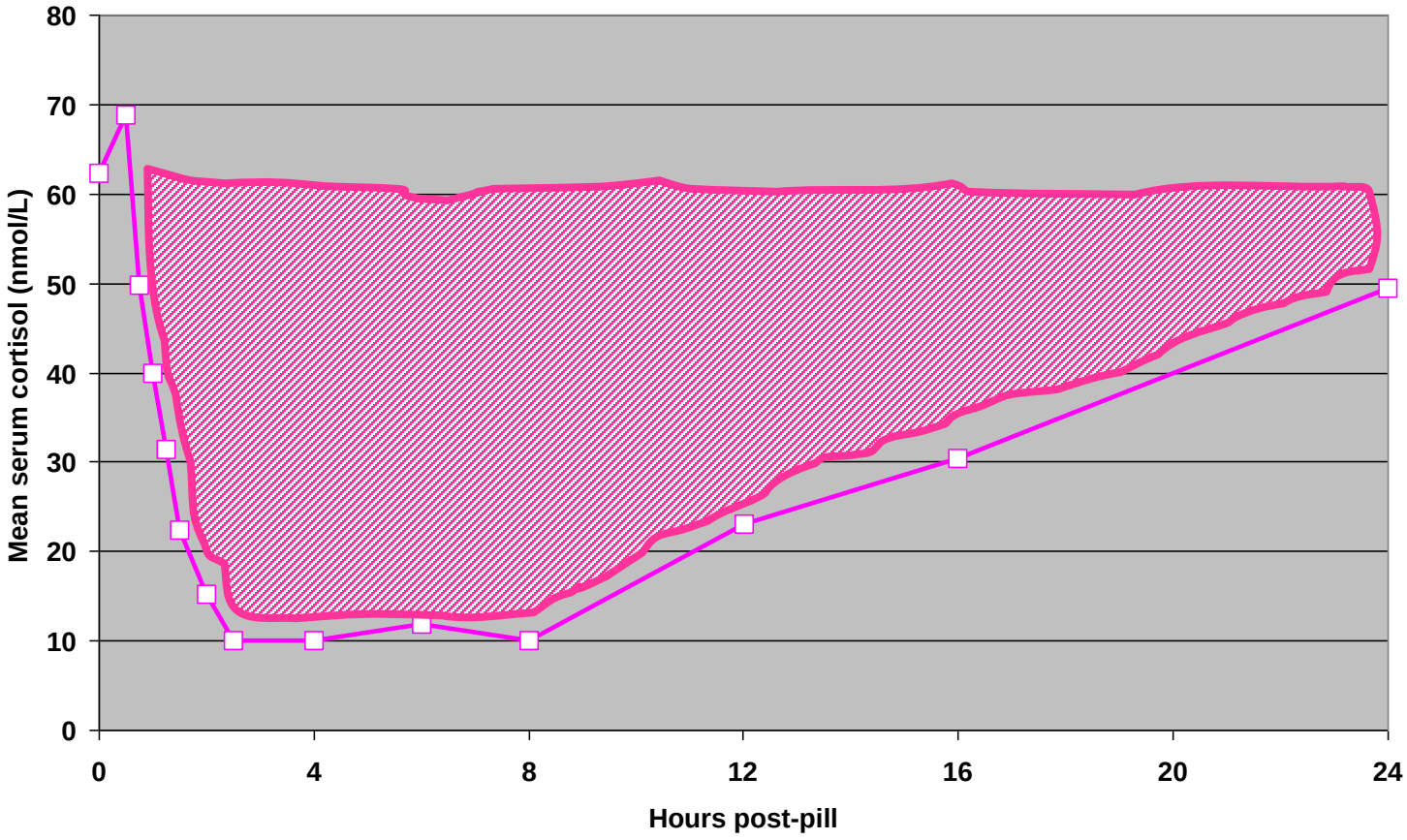
Peak plasma trilostane concentrations at 0.5 – 1.5 hr; ketotrilostane 1-1.5 hr (active metabolite)
Rapidly absorbed from the gastrointestinal tract
Dosing with food significantly ↑ rate & extent of absorption (area under curve significantly larger with fed)

SID versus BID

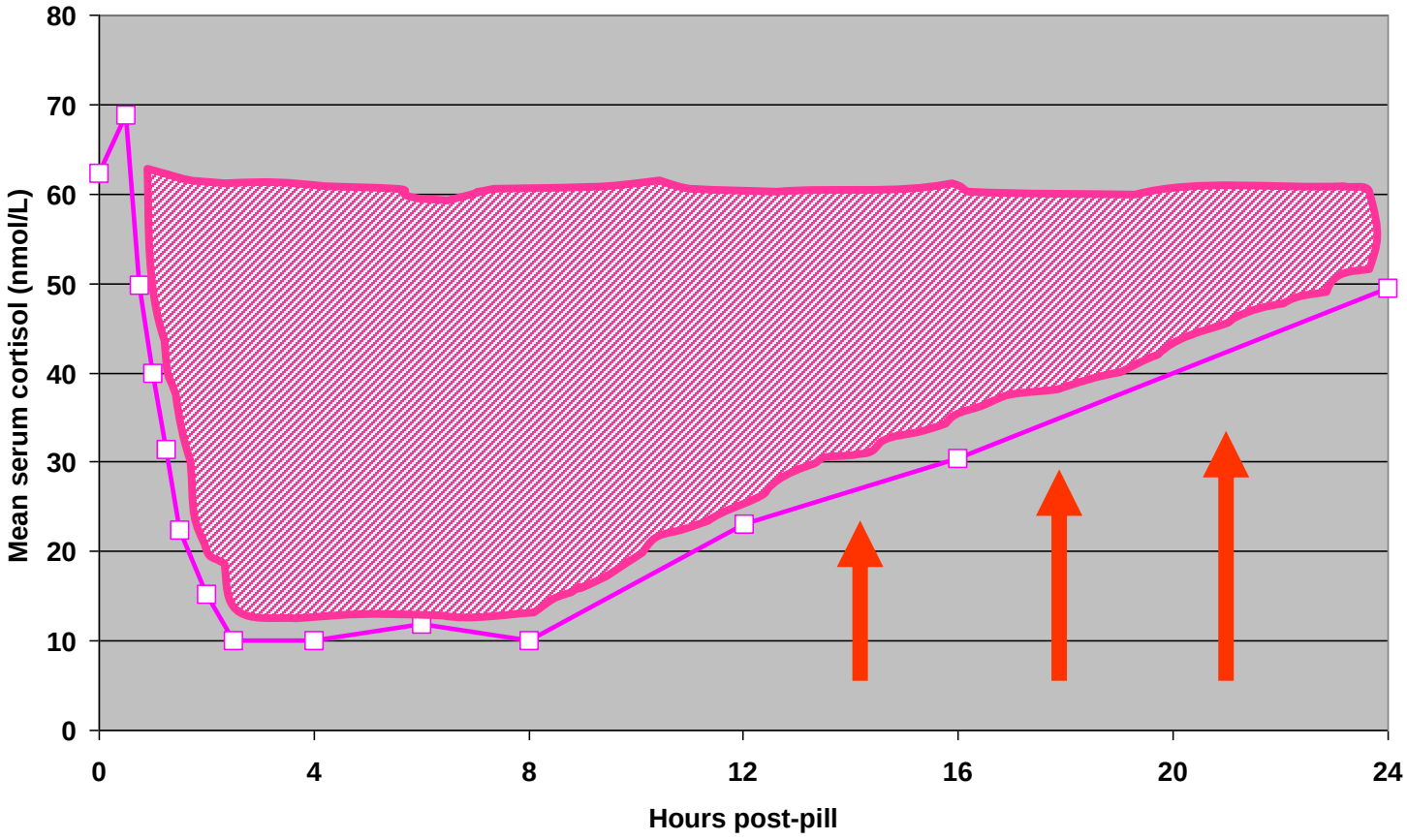
- Basis for SID
- All dogs in US FDA clinical trial started on SID treatment
- 86% completed trial on SID
- **Majority** of dogs without concurrent diabetes do well SID
- There is a real **minority** of dogs without diabetes who do better on BID

- Basis for BID
- Pharmacokinetic curve of trilostane, ketotrilostane and cortisol
- After approximately 18 hr +/- drug is out of system
- If concurrent diabetes, dose BID

VETORYL® CAPSULE- How can SID work?



How might SID fail?



VETORYL® CAPSULES(trilostane)

Dose rate **1-3 mg/lb** (2.2 – 6.7 mg/kg) (see data sheet)

Ideally start at LOWER end – near 1 mg/lb; round DOWN

Start SID (BID if needed) - Dose in morning if SID

There is NO induction period

(10 mg, 30 mg , 60 mg, 120 mg)

Blister packs of 30

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Monitoring

Biochemistry (including **electrolytes**) & **ACTH stimulation test** (monitoring test of choice; 4-6 hours post dosing !!!);

TARGET RANGE = 1.45 ug/dl – 9.1 ug/dl (50-250 nmol/L)

1) 10 -14 days (**Key re-check !**), 4 weeks, 12 weeks after beginning Vetoryl therapy - quite common for cortisol levels to continue to drop from 1st to 2nd ACTH stim.

2) thereafter every 3 months

3) dose adjustment- do ACTH stim 10-14 days after starting new dose

ASSESSMENT OF CLINICAL SIGNS AT EACH RECHECK !!!!!

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Controlling cost of ACTH Stimulation Test

- Determine correct dose for patient – 5 µg/kg IV or IM
- Determine how many tests can be done per vial (each vial contains 250 µg)- ex. 5 tests for 10 kg dog.
- Draw appropriate dose into individual plastic syringes for future testing in that patient.

Remaining Cortrosyn can be aliquoted into 1.0 mL **plastic** syringes. Store syringes frozen (-20ºC) for up to 6 months; thaw to room temp before use

  - No preservative to inhibit bacterial growth

Feldman EC, Nelson RW. *Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, Pa: WB Saunders. 2003:305.*

ACTH Stimulation Test

MONITORING TEST OF CHOICE ONCE THERAPY WITH VETORYL BEGINS!!

- **TARGET RANGE 1.45-9.1 ug/dl**
- **(50-250 nmol/L)**
- **Critical Point - MUST be done in the 4-6 hour period post dosing with Vetoryl!**
- **If done too early or late – possibility to inappropriately raise the dose !!**
- **Galac,S, et al. UCCR cannot be used as an alternative to monitor trilostane dosage**
- **Proceedings ECVIM 2008**

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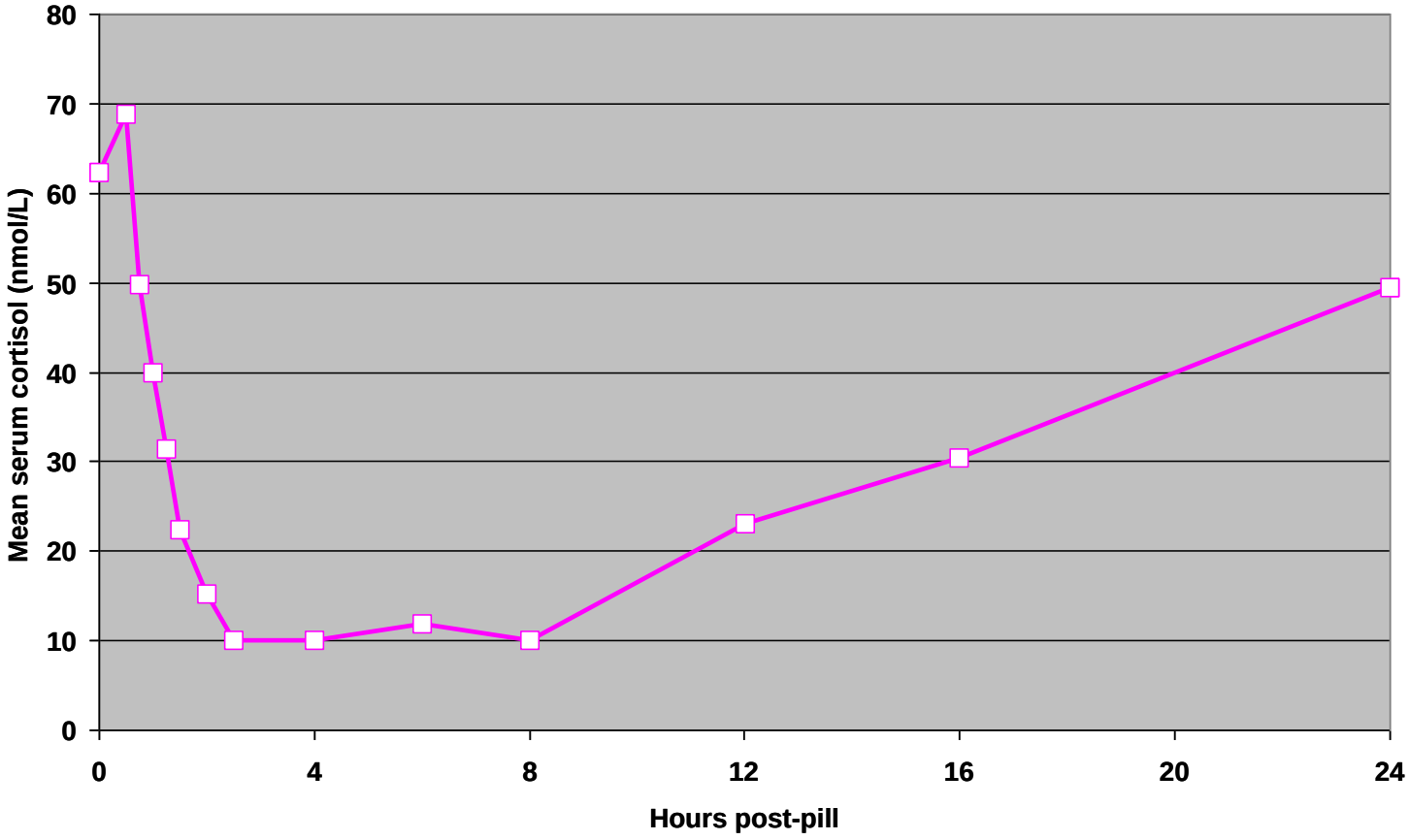
Timing of ACTH stimulation samples 4-6 hr post dosing



How to evaluate clinical progress

POSITIVE response to therapy =

1**) IMPROVEMENT IN CLINICAL SIGNS** – consider noting the time it takes the dog to eat; awareness of signs of over suppression (anorexia, lethargy)

2) **Post-ACTH cortisol 1.45 – 9.1 µg/dl** (50-250 nmol/L)
tested 4-6 hrs after dosing – some prefer max of 4.5 – 5.0 ug/dl

Check monitoring flow chart

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Optimizing VETORYL® CAPSULE treatment

Increase in ONCE daily dose required if:

Clinical signs **not** controlled **AND**

- Post-ACTH cortisol > 9.1 µg/dl (250 nmol/l)
- (performed 4-6 hrs after dosing)
- (most dogs with post-cortisol values between 5.0-9.1 ug/dl respond well – if still symptomatic, increase dose)

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Optimizing VETORYL® CAPSULE treatment

<u>TWICE daily dosing may be required if</u>

Clinical signs **not** controlled **BUT**

- Post-ACTH cortisol < 9.1 µg/dl (< 250 nmol/L)

(performed 4-6 hours after dosing) –

- **If owners do not note clinical signs apparent in evening – then consider increasing SID dosing.**
- **If owners DO note clinical signs are apparent in evening or during night, but controlled during day, then consider changing to BID dosing.**

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Change from SID to BID dosing

Use combination of capsule to slowly increase the dose and divide

Ex: 60 mg SID to 30 mg BID

or 60 mg am, 10 mg pm

Ex: patient on 30 mg SID – options

a) 30 mg am, 10 mg pm

b) 20 mg am, 20 mg pm

Importance of Monitoring

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

Corticosteroid deficiencies

Glucocorticoid deficiency

'cortisol withdrawal syndrome' – small % of dogs may develop these signs within 7-10 days of starting treatment

abdominal"cramping", hypoglycemia, weakness, lethargy, vomiting, anorexia, weight loss, poor response to stress

Tx: stop Vetoryl for ~ 7 days; restart lower dose

Mineralocorticoid deficiency

weakness, lethargy, anorexia, v+/d+, collapse, shock, hypothermia, hyponatremia, hyperkalemia, Na+:K+ <27

Tx: stop Vetoryl; symptomatic therapy needed – IV fluids (0.9% NaCl), glucocorticoid , mineralocorticoid if needed – IV fluids may be enough

Wait until clinical signs return – restart lower dose

IMPORTANT TO DIFFERENTIATE !! – clinical signs maybe similar - perform electrolytes and ACTH stimulation

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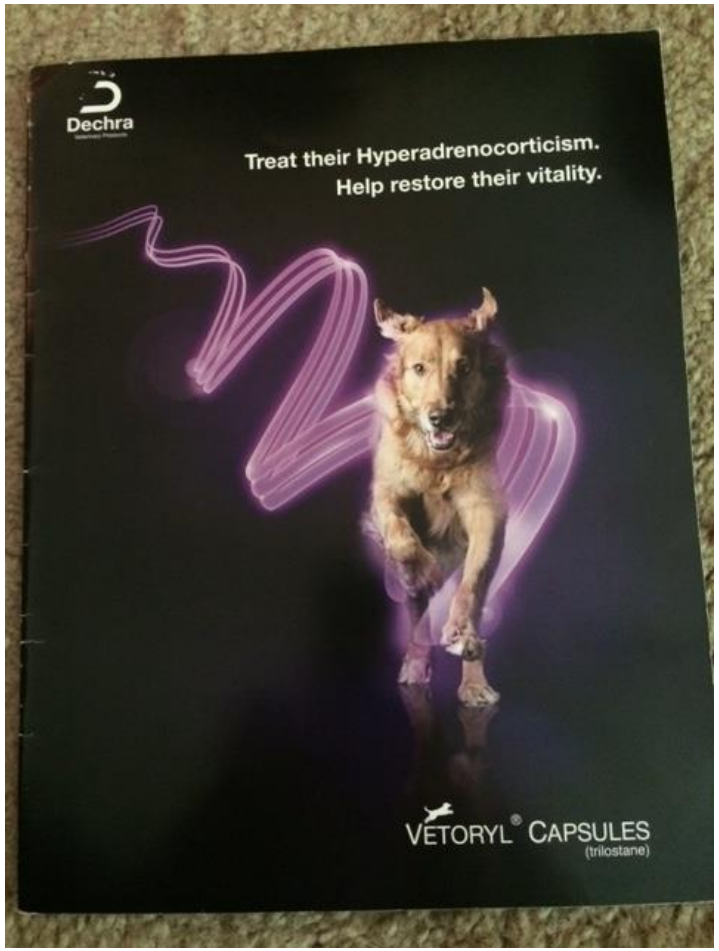
Clinic Aids



Treatment and Monitoring Brochure (great flowchart)

- Ideal for posting in pharmacy/lab
- Quick reference for vets and techs

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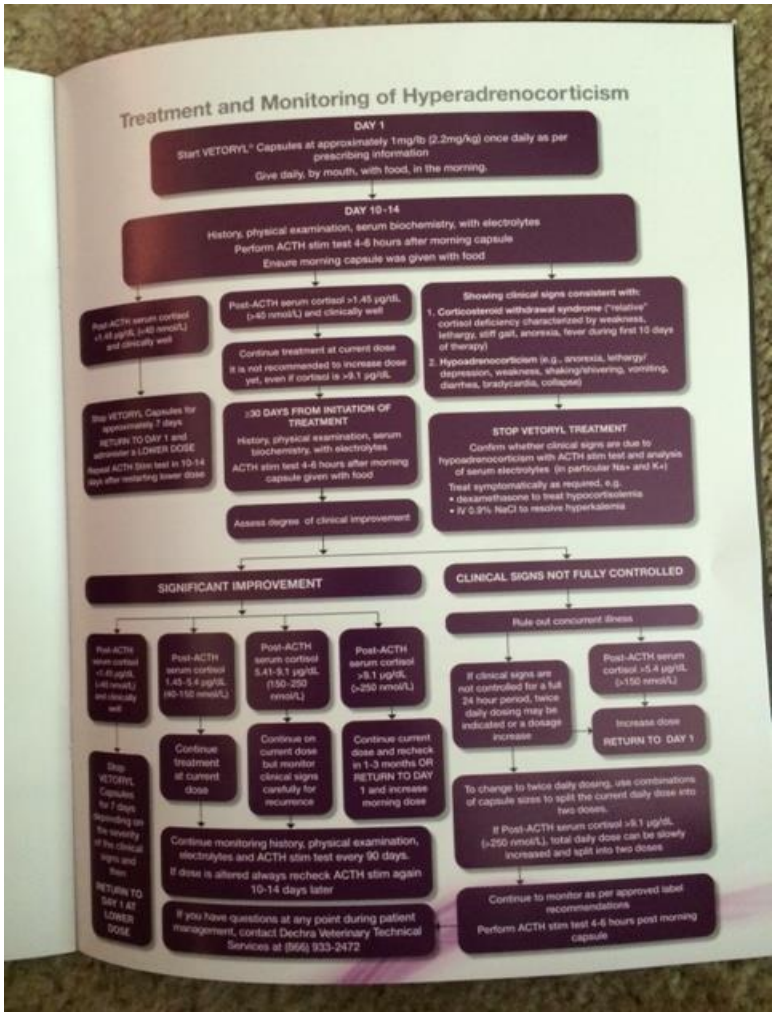
Treatment and Monitoring of Hyperadrenocorticism
DAY 1
Start VETORYL® Capsules at approximately 1mg/lb (2.2mg/kg) once daily as per prescribing information
Give daily, by mouth, with food, in the morning.
DAY 10-14
History, physical examination, serum biochemistry, with electrolytes
Perform ACTH stim test 4-6 hours after morning capsule
Ensure morning capsule was given with food
Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well
Post-ACTH serum cortisol >1.45 µg/dL (>40 nmol/L) and clinically well
Continue treatment at current dose
It is not recommended to increase dose yet, even if cortisol is >9.1 µg/dL
Showing clinical signs consistent with:
1. Corticosteroid withdrawal syndrome ("relative" cortisol deficiency characterized by weakness, lethargy, stiff gait, anorexia, fever during first 10 days of therapy)
2. Hypoadrenocorticism (e.g., anorexia, lethargy/depression, weakness, shaking/shivering, vomiting, diarrhea, bradycardia, collapse)
Stop VETORYL Capsules for approximately 7 days
RETURN TO DAY 1 and administer a LOWER DOSE
Repeat ACTH Stim test in 10-14 days after restarting lower dose
≥30 DAYS FROM INITIATION OF TREATMENT
History, physical examination, serum biochemistry, with electrolytes
ACTH stim test 4-6 hours after morning capsule given with food
STOP VETORYL TREATMENT
Confirm whether clinical signs are due to hypoadrenocorticism with ACTH stim test and analysis of serum electrolytes (in particular Na+ and K+)
Treat symptomatically as required, e.g.,
• dexamethasone to treat hypocortisolemia
• IV 0.9% NaCl to resolve hyperkalemia
Assess degree of clinical improvement
SIGNIFICANT IMPROVEMENT
CLINICAL SIGNS NOT FULLY CONTROLLED
Post-ACTH serum cortisol <1.45 µg/dL (<40 nmol/L) and clinically well
Post-ACTH serum cortisol 1.45-5.4 µg/dL (40-150 nmol/L)
Post-ACTH serum cortisol 5.41-9.1 µg/dL (150-250 nmol/L)
Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L)
Rule out concurrent illness
If clinical signs are not controlled for a full 24 hour period, twice daily dosing may be indicated or a dosage increase
Post-ACTH serum cortisol >5.4 µg/dL (>150 nmol/L)
Increase dose
RETURN TO DAY 1
Stop VETORYL Capsules for 7 days depending on the severity of the clinical signs and then:
RETURN TO DAY 1 AT LOWER DOSE
Continue treatment at current dose
Continue on current dose but monitor clinical signs carefully for recurrence
Continue current dose and recheck in 1-3 months OR RETURN TO DAY 1 and increase morning dose
To change to twice daily dosing, use combinations of capsule sizes to split the current daily dose into two doses.
If Post-ACTH serum cortisol >9.1 µg/dL (>250 nmol/L), total daily dose can be slowly increased and split into two doses
Continue monitoring history, physical examination, electrolytes and ACTH stim test every 90 days.
If dose is altered always recheck ACTH stim again 10-14 days later
Continue to monitor as per approved label recommendations
Perform ACTH stim test 4-6 hours post morning capsule
If you have questions at any point during patient management, contact Dechra Veterinary Technical Services at (866) 933-2472

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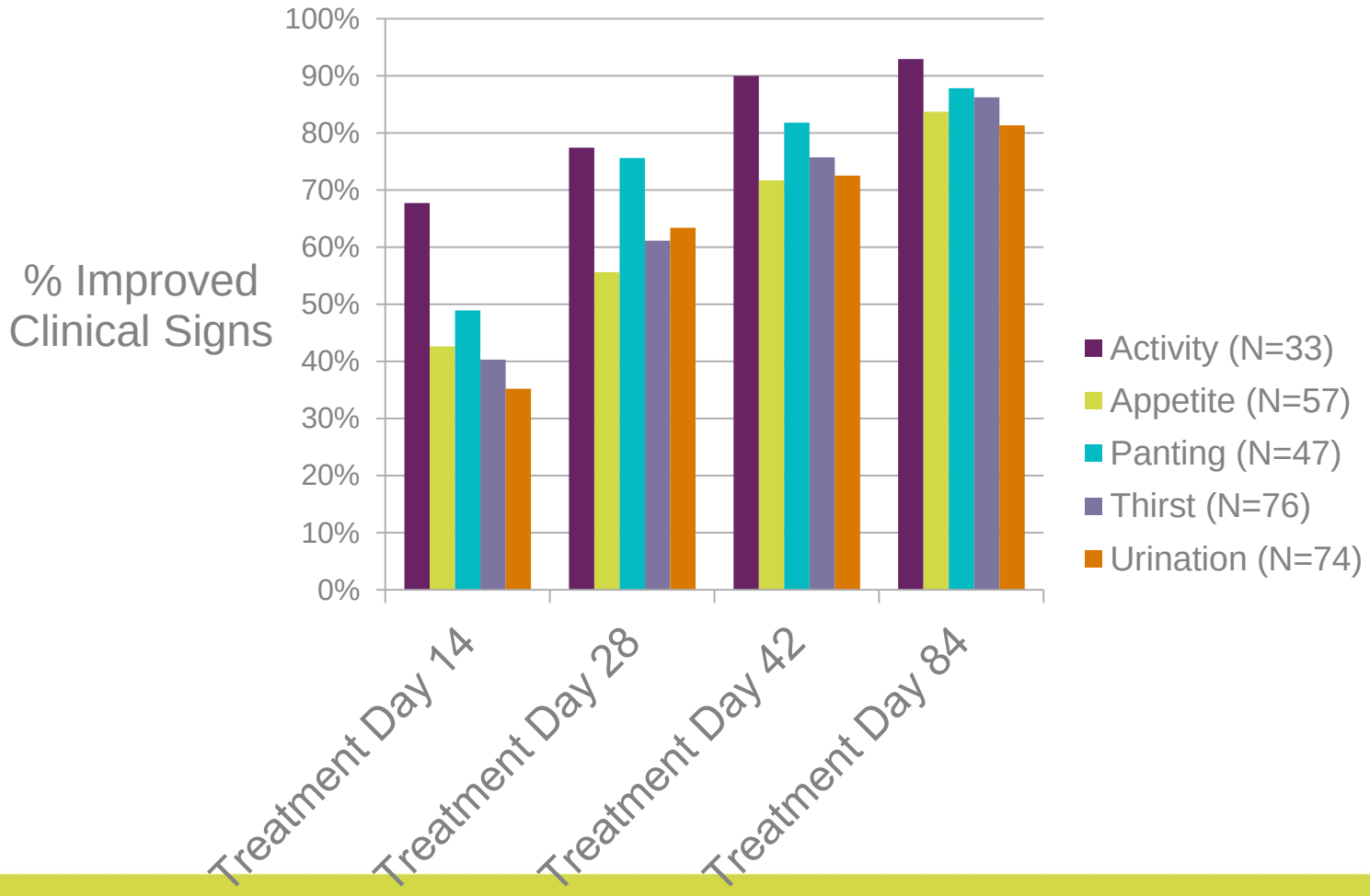
VETORYL® CAPSULE - Changes in Clinical Signs



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Pre-treatment

3 months of treatment

9 months of treatment

Pre-treatment

3 months of treatment

9 months of treatment

Pre-treatment

3 months of treatment

9 months of treatment

Photographs courtesy of Carlos Melian DVM PhD

Contraindications

- Demonstrated hypersensitivity to trilostane
- Not to be used in animals suffering from primary hepatic disease and/or renal insufficiency – not hepatotoxic or nephrotoxic; based on metabolism and excretion patterns – risk/benefit assessment
- Do not use in pregnant or nursing bitches, or in any animals intended for breeding
- Do not use in animals weighing less than 3kg – caution – originally too few dogs recruited for clin trial. Now, USE 5 mg!!
- Do not divide or open capsules

Special warnings/considerations

VETORYL® CAPSULES: has anti-aldosterone action (inhibits production); this effect MAY be additive with concommittant use of:

- K+-sparing diuretics /K+ supplements – risk of hyperkalemia
- ACE inhibitors – risk of hyperkalemia – risk/benefit and closely monitor

Concurrent diabetes mellitus – monitor insulin dosages closely ; likely to see insulin dose decrease as cortisol levels are controlled - Key Opinion Leaders prefer BID dosing

Changing from mitotane to VETORYL® CAPSULES

- Different modes of action – cytolytic versus enzyme inhibition
- Step 1: Stop mitotane.
- Step 2: Wait until return of clinical signs – plasma ½ life of mitotane in humans is 18-159 days !
- Step 3: Do ACTH stimulation to prove adrenal reserve present. Post cortisol > 9.1 ug/dl (250 nmol/L) or higher
- Step 4: Start Vetoryl at LOW dose
- MONITOR

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“Unmasking” underlying disease

- Corticosteroid-responsive problems can be “masked” prior to controlling cortisol
- Osteoarthritis
- Allergic skin disease
- With control of cortisol levels, clinical signs may appear, i.e., limping, scratching

Clinical Trials

- Vetoryl® Capsules: well researched with proven effectiveness
- Six premarketing clinical trials in Europe
  - carefully controlled research
- Field use in Europe since 2005
  - approved in UK 2005, Europe 2006
  - typical use in practice
  - pharmacovigilance data

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Clinical Trials vs Field Use

Clinical Trials	Field Use
Inclusion/exclusion criteria	Real world
Strict protocol directives	Possible interaction with concurrent Dx and meds
Small number of patients	Larger number of patients
Thorough evaluation and follow up	Variable ages/ conditions
Committed pet owners and clinical investigators	Variable environments and owner compliance
Owners tend to be different than real world – overly committed.	Post-approval pharmacovigilance

US Clinical Trial

107 dogs enrolled/223 dogs screened

- Various breeds
- Age range 6-16 years
- Body weight 3-53.5 kg
- Causes of HAC

  - 95 (89%) PDH
  - 5 dogs (5%) ADH
  - 1 dog (1%) PDH + ADH
  - 6 dogs inconclusive localization

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US Clinical Trial

- Treatment dosages
  - Targeted **start** 2.2-6.7 mg/kg/day (1-3 mg/lb)
  - Actual range **start** 2.5-6.2 mg/kg/day (1.1 – 2.8 mg/lb)
  - Actual range **end** 1.2-15.6 mg/kg/day (0.5 - 7.1 mg/lb)
  - Mean actual dose at **end** 4.81 mg/kg/day (2.2 mg/lb)
- Dose adjustments based on clinical response & lab results
  - increase - ACTH stim cortisol levels > 9.1 µg/dL and/or no clinical improvement
  - decrease - ACTH stim cortisol <1.45 µg/dL @ 4-6 hrs. or if signs of over suppression (anorexia, vomiting, diarrhea, lethargy, depression)

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US Clinical Trials

- Pre- and post- clinical trials chemistries

- Significant decreases in ALT, AST, alkaline phosphatase, Na:K ratio, cholesterol ($p < 0.0001$)- indicative of improvements in hyperadrenocorticism
- ↑ eosinophils, ↑ lymphocytes(counts and %),↓ segmented neutrophils (counts and %) – represents improvement in stress leukogram associated with hyperadrenocorticism.

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US Clinical Trial

80.0% cases remaining at Day 84 were treatment successes

- Success criteria post-ACTH stim <9.1 ug/dL + clinical improvement

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US Clinical Trial

Safety assessment (all 107 dogs included)

- Most severe adverse reactions

  - Adrenal necrosis (rupture) 2 dogs – 1 dog died; 1 responded to discontinuation and supportive care

  - Hypoadrenocorticism 2 dogs – both responded to discontinuation; 1 needed further Tx

- Five dogs died or euthanized

  - Adrenal necrosis 1 dog

  - Progressive CHF 2 dogs (pre-existing)

  - Progressive CNS signs

  - Cognitive decline – inappropriate elimination

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Re: Fear of adrenal necrosis

- " would you withhold insulin from a diabetic because you were afraid of hypoglycemia?" A Cook, TAMU
- "would you prefer to use a drug that had <2% of dogs develop adrenal necrosis, or a drug where 100% developed adrenal necrosis?"
- Importance of monitoring. D Bruyette, VCA West LA

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Recent reference on adrenal necrosis

- Burkhardt, WA, et al. Domestic Animal Endocrinology 40 (2011) pp. 155-164
- “Supports the hypothesis that adrenal lesions seen in trilostane-treated dogs with PDHAC are caused by elevated ACTH levels and not be trilostane per se.”

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US Clinical Trial

% Dogs Improved Clinical Signs Relative to Day 0
Owner's perception

Day	% Improved	Confidence Interval Lower Limit
14	85	77
28	92	86
42	93	87
84	93	86

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Survival Times

- JVIM vol 25; pp 251-260; Mar/Apr 2011. Helm, JR, et al
- 37 animals with ADHAC
- 22/37 trilostane; 13/37 mitotane; 2 both
- Median survival time trilostane 353 days (95-528)
- Median survival time mitotane 102 days (43-277 days)

Survival Times

- Neiger R., et al. Trilostane treatment of 78 dogs with pituitary-dependent hyperadrenocorticism. Vet Record. June 29, 2002. p. 799-804
- 26 dogs who died median survival time – 549 days
- 51 dogs alive at end of 3 year study
- 1 dog lost to follow up after 241 days

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Survival Times

- Barker EN, Campbell AJ, et al. A Comparison of the Survival Times of Dogs Treated with Mitotane or Trilostane for Pituitary-dependent Hyperadrenocorticism. JVIM 2005 19: 810-815
- Median survival Trilostane 662 days
- Median survival Mitotane 708 days

Survival Times

- Alenza DP, Arenas C, et. al. Long Term Efficacy of Trilostane Administered Twice Daily in Dogs with Pituitary-dependent Hyperadrenocorticism. JAAHA Jul/Aug 2006, Vol 42. p. 269-276.
- Mean survival time was 930 days

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Survival time

- Survival data for dogs treated for HAC in a first opinion practice. Fahy KL, Johnson J, Herrtage, ME WSAVA Oral Presentations 2012
- 53 dogs included
- Median age at Dx: 11 yr
- Mean age at Dx: 11 yr, 1 mo. (7-17)
- Median survival time- 304 days
- Mean survival time – 422 days (12-1680)
- 1 year survival fraction – 58%
- 2 year survival fraction – 28%

Prognostic factors for survival

- PDH – 85 dogs treated with trilostane/Vetoryl at one referral center
- Median survival = 852 days
- Clinical signs, liver enzymes, serum cortisol values from testing, proteinuria, systolic hypertension or frequency of trilostane were NOT associated with survival times.
- Hyperphosphatemia was a negative prognosic factor
- Fracassi, Corradini, et al…Vet Record 2014

What if VETORYL® CAPSULE therapy is not going as expected?

- Questions to ask?
- Why might this happen?
- Key information to determine
- What information do you need to obtain from the owner?

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Vetoryl “logistics”

- Is the owner able to medicate the dog?
- Is the dog spitting out the capsule?
- How are the owners medicating the dog? As recommended? Something weird, such as mixing weekly dose in water and dosing with a syringe! Or sprinkling on food; dog not eating?
- Is Vetoryl being given with food?

Questions related to ACTH stimulation results

- When was the test performed relative to dosing with Vetoryl – MUST be 4-6 hr after.
- On day of ACTH monitoring, someone in practice must ask a) did dog receive Vetoryl that morning, and b) when? If not given, reschedule ACTH stimulation testing.
- Make sure dog is not being dosed at night

? Re: ACTH stim results (cont.)

- Was testing done in-house or sent out (Antech, Idexx, Marshfield, etc). If in-house, might suggest sending it out. (Equipment maintainance or calibration might be issue)
- Is the vet using Cortrosyn or ACTH gel? If gel, should probably repeat with Cortrosyn

ACTH stim results (cont.)

- Are symptoms still present? Is there any improvement? How long has the dog been on Vetoryl? Perhaps a dosage adjustment is needed (CALL TECH SERVICES!)
- Is concurrent disease present, such as diabetes, kidney disease, etc. All clinical signs of Cushing's but *maybe* one can be caused by something else – (calcinosis cutis may be the exception.)
- Does the dog have Cushing's?

How do you know the dose is too high?

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

Example 1 of actual calls to Tech Services

- 25 pound Beagle; 30 mg Vetoryl SID for 2 wks
- ACTH stim: pre 6.7 post 18.0 (1.45-9.1)
- Why this result?
- 1) was Vetoryl given the morning of test
- 2) is dog being dosed at night?
- 3) are owners giving with food?
- 4) are clinical signs improving?

Example 2

- 50 pound dog; 60 mg once a day.
- After 2 weeks therapy;

ACTH post- 1.5 ug/dl (1.45-9.1) – this result is near the bottom of our range.

Is this a concern and if so, why?

Case 3

- 35 pound mix breed; 30 mg Vetoryl SID for 8 weeks. Dosed in morning
- ACTH pre 2.5, post 7.0
- Clinical signs improving, but owners mention pu/pd, panting in the evening.
- Rec: 30 mg am, 10 mg pm

Baseline cortisol vs ACTH stim

- 50 lb dog; 60 mg SID. Doing well clinically, on Vetoryl for 10 months.
- ACTH stimulation pre 0.7; post 3.0
- What would you do if you only had baseline?
- What would you do if you have full ACTH stim?

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!

- Ref: AK Cook, et al. Pharmaceutical Evaluation of Compounded Trilostane Products. JAAHA: 48:4. Jul/Aug 2012. pp. 228-233

Learnings from the “field”…

- Get the diagnosis RIGHT- don’t treat if not symptomatic
- There is NO induction period
- Start low end of dose guidance – SID adequate for vast majority
- If BID - start low, determine total daily dose and divide THAT dose in half.
- Never miss early monitoring (10d)
- Don’t dose increase at initial monitor (10d) unless patient is extremely symptomatic and high ACTH post-cortisol
- Over-suppression and glucocorticoid withdrawal most common avoidable consequences
- Beware of long-term decrease in dose requirements

Beau (left) and Cody Pre Tx

Beau(left) and Cody After TX

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US Clinical Trial

Conclusion – Vetoryl highly effective for HAC and generally well-tolerated.
Serious adverse events can occur, but appear to be rare.
Monitoring very important.

Question? I’m all ears !

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Questions?

Please feel free to contact:

Dechra Veterinary Technical Services

1-866-933-2472

Fax: 913-327-0016

Website: www.dechra-us.com

Email : support@dechra.com