Too Much Cortisol

https://youtu.be/bmforNx_heE

Monitoring Cushingoid Dogs on Trilostane—What's New?

MISSISSIPPI STATE UNIVERSITY
COLLEGE OF VETERINARY MEDICINE

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Monitoring Cushingoid Dogs on Trilostane

- Trilostane background
- Cases
  - Maya
  - Kismet
  - Rusty
- Monitoring

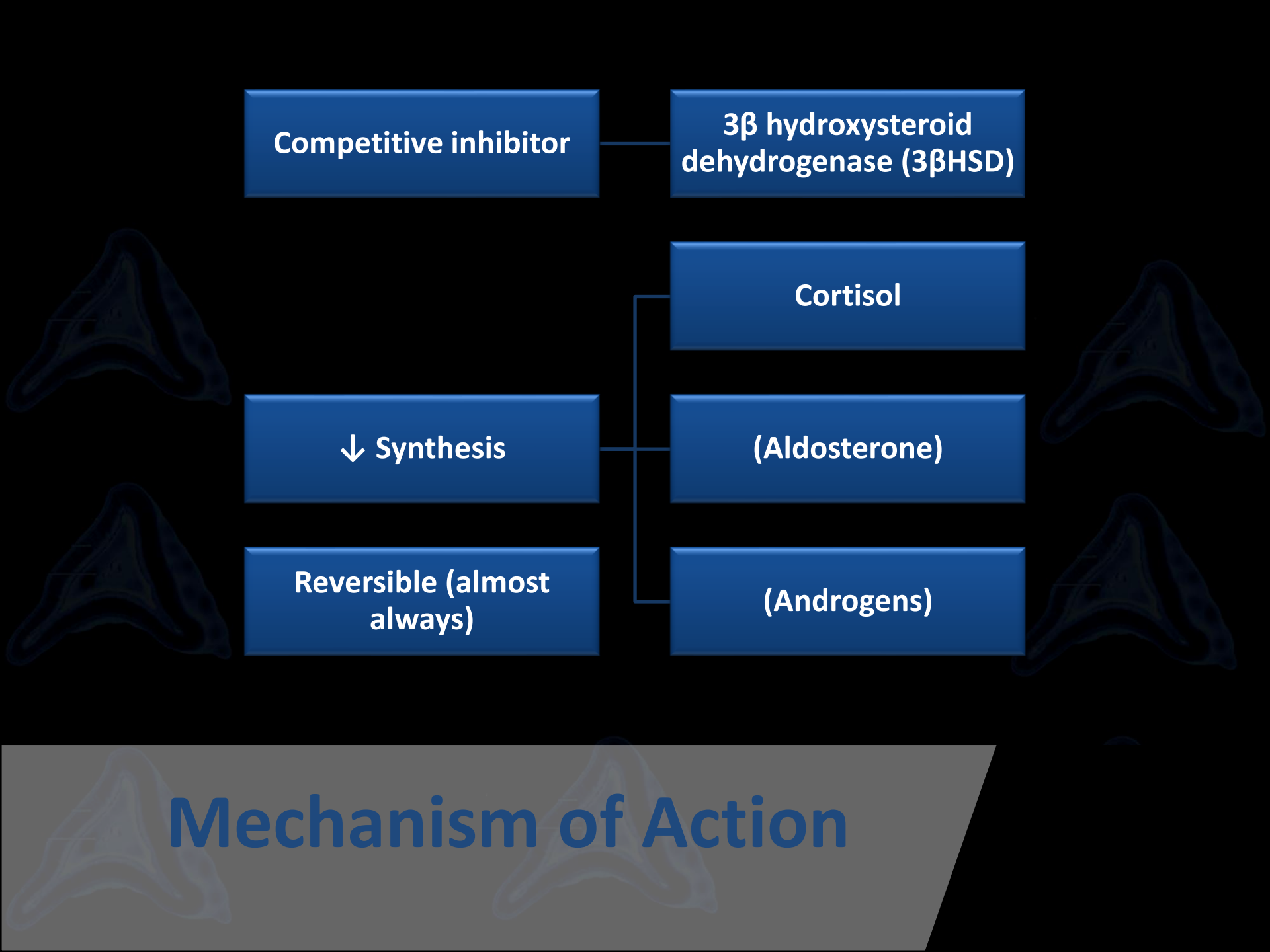
Trilostane

Steroid synthesis inhibitor

Dose titration to effect

- No induction phase necessary

FDA approved for PDH and AT



Mechanism of Action

Trilostane Pharmacokinetics

- Absorption
  - Enhanced with food
- Blood Levels:
  - Peak
    - 1.5 – 2 hours
  - Max effect on cortisol
    - 2-4 hours
  - Duration
    - 10 - 18 hours
      - Varies with individual
      - SID versus BID dosing

Maya

- 11 yo FS Mini Poodle
- History x 2 years
  - PU/PD
  - Panting
  - Previous UTI
- Diagnosed with PDH at MSU-CVM
  - LDDS, eACTH, U/S

Maya

- PE, CBC/Chem/UA: Consistent with Cushing's
- Urine culture: negative
- ACTH stimulation test
  - Pre-ACTH cortisol: 6.2 µg/dL
  - Post-ACTH: 17.6 µg/dL
- Referred to MSU-CVM
- U/S: enlarged adrenals
- LDDS:
  - 0h: 4.1 µg/dL
  - 4h: 1.2 µg/dL
  - 8h: 1.9 µg/dL
  - PDH
- eACTH: 51 pg/mL
  - PDH

PLAN

- Trilostane, 1 mg/kg PO BID with food
- Dexamethasone for rescue
  - (~0.1 mg/kg in case of signs of Addison's but stable)
- Monitor
  - PU/PD, polyphagia, panting
  - GI signs (v, d), lethargy
- Recheck in 2 wks

Two Week Recheck

- Clinically normal per owners
  - No more accidents
  - “Normal urination”
- Diagnostics
  - (Ideally a renal profile/elytes)
  - Pre-Pill cortisol: 7 µg/dL
  - 3h Post-Pill cortisol: 3.8 µg/dL
  - Post-ACTH stim cortisol: 5.0 µg/dL

A Pre-Pill Cortisol???

Trilostane monitoring

- Goals of treatment
  - Control clinical signs/improve QOL
    - (avoid complications of HAC)
  - Don’t make them Addisonian
- Traditional monitoring
  - ACTH stimulation test
    - “Controlled” with post-stimulation cortisol between 2 µg/dL and 6 µg/dL (or 9…)
  - May not be the best way to monitor

Lack of association between clinical signs and laboratory parameters in dogs with hyperadrenocorticism before and during trilostane treatment

F. S. Boretti[1], J. Holzthüm[1], C. E. Reusch[1], N. S. Sieber-Ruckstuhl[1]

[1]Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich

- ***Schweiz Arch Tierheilkd*, 2016**
- **Clinical scores based on questionnaire**
  - **Did not correlate with post-ACTH stimulation cortisol**

Journal of Veterinary Internal Medicine
ACVIM
Open Access
J Vet Intern Med 2015;29:1529–1533

Cortisol Concentrations in Well-Regulated Dogs with Hyperadrenocorticism Treated with Trilostane

J.N. Midence, K.J. Drobatz, and R.S. Hess

- 13 dogs on trilostane with clinically well-regulated HAC
  - 3-6h post-stim cortisol <2 µg/dL (1-1.9 µg/dL)
  - 9-12h post-stim cortisol (2.8-9.2 µg/dL)
- 12 remained on same dose for 2 mos to 2 years; 1 required a dose reduction
- *Not all dogs with a low stim at 4-6 h need a dose reduction.

OPEN ACCESS

Pre-trilostane and three-hour post-trilostane cortisol to monitor trilostane therapy in dogs

L. Macfarlane, T. Parkin, I. Ramsey

- (ACTH became unavailable in Europe!)
- Pre-pill cortisol correlates with clinical signs “better” than the post-ACTH stimulation cortisol
- Less expensive and time consuming
- ACTH stim still necessary sometimes!

Pre-pill Cortisol

Client Consent Form for Clinical Study

Study: *Pre-Pill Cortisol for Evaluation of Trilostane Therapy*

Purpose of Study: To evaluate the use of a pre-pill cortisol sample for monitoring trilostane therapy.

Principal Investigators: Drs. Patty Lathan and Todd Archer

- Collaboration with European VTHs
- Dogs on BID trilostane
- Pre-pill, 3h post-pill, and 1h post-ACTH cortisol
  - Compared to clinical signs
- Questions
  - Me: "Would I make the same tx decision?"
  - Miss any Addisonians?
  - Appears promising

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Pre-pill Cortisol: When?

- Clinically well
  - No signs of Addison's (need a stim!)
- No concurrent disease that causes PU/PD(?)
  - Diabetes, renal disease, etc.
- Attentive owner AND vet
  - MUST notice and report clinical signs!
    - Measuring water intake and/or USG helpful if unclear
  - Everything interpreted in light of clinical signs!

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Date: _____ Owner's Last Name: _____ Dog's Name: _____

What size Vetoryl capsules does your dog receive? _____mg How many times per day? _____

1) When your dog was diagnosed with Cushing's, how much was he/she drinking compared to 1 year ago?

Less About the same
A little more A LOT more

2) How much is your dog drinking compared to when he/she started taking Vetoryl/trilostane?

A lot less A little less
Same More

3) How much is your dog urinating compared to when he/she started taking Vetoryl/trilostane?

A lot less A little less
Same More

4) Has your dog had any urinary accidents/leakage within the past month?

No Yes, but less than before
Yes, same as before

5) How active is your dog compared to when he/she started taking Vetoryl/trilostane?

Less active The same
A little more active
A lot more active/back to normal

6) Rate your dog's appetite change since the beginning of treatment?

A lot less A little less
Same Increased

7) How does your dog's haircoat look?

Less Hair Slight improvement
No change Hair improved/Normal

8) Overall, how do you think your dog is responding to treatment for Cushing's?

Now worse No difference
Some improvement Nearly normal now
Completely normal

Have you had to use the Dexamethasone tablets provided at previous visit : Yes No

Has your dog had any vomiting/diarrhea/trembling/other signs of illness? Please explain if yes.

Pre-pill Cortisol

(I will have a better slide for pictures later)

- Most useful in clinically controlled dogs
  - If pre-pill cortisol >1.4-2 µg/dL, probably safe to continue current dose
  - Stim if <1.4-2 µg/dL (at 3h or at 9h?)
    - Or ↓ dose
  - What if…>7 µg/dL?
- If NOT clinically controlled
  - When is it safe to increase dose?
    - >5 µg/dL? Stim if <3-5 µg/dL before increasing dose…

Timing of Rechecks

- Pre-pill cortisol is same as ACTH stims
- 2 weeks into treatment
- Then at 1 month
- Then q3-6 months
- Clock starts over when dose is adjusted
- Pre-pill cortisol: Prior to morning pill
  - Afternoon has not been studied. More to come…

Back to Maya…

- Clinically normal
- Pre-Pill cortisol: 7 µg/dL
- 3h Post-Pill cortisol: 3.8 µg/dL
- Post-ACTH stim cortisol: 5.0 µg/dL
- Recheck in 2 weeks, also check electrolytes

Recheck 2 weeks later

- Clinically great
- 3h post-trilostane: 3.1 µg/dL
- 1h post-stim 5.9 µg/dL
- Pre-pill cortisol: 3.7 µg/dL
- Dose maintained

2 months later

- Clinically controlled
- 3h post-pill: 3.2 µg/dL
- 1h post-ACTH: 5.5 µg/dL
- Electrolytes wnl
- Pre-pill: 5.2 µg/dL
- Dose maintained

Maya

- Pre-pill monitoring worked great
- Ideal patient—clinically controlled

Kismet

- Born March 2000
- FS Rat terrier/beagle
- 9/2016
  - Hair loss (significant owner concern)
  - Lethargy (in hindsight)
  - Mild PU/PD

Kismet

- CBC/Chem/UA/culture
  - Increased ALP
  - USG 1.020
  - Negative culture
- U/S: Bilateral adrenomegaly
- ACTH Stim post cortisol: 23.7 µg/dL
- Trilostane, 1 mg/kg PO BID (10 mg)

Kismet, 2 weeks later

- Clinically great, 10 mg PO BID
  - More energy, more pep during walks
  - No more PU/PD, but no hair growth (for at least 6 months in her!)
- Pre-pill cortisol: <1 µg/dL
- 3h post-pill 1.8 µg/dL, 1 h post-stim 5.1 µg/dL
- Maintained dose

Kismet

- 2 weeks later
  - Clinically great
  - Pre-pill: 1.5 µg/dL
  - 3 hr post pill: 2.3 µg/dL
  - Post-stim: 5.8 µg/dL
  - Maintained
- 1 month later, Nov 2016
  - Clinically well
  - Pre-pill: <1 µg/dL
  - 3h post-pill: 2.2 µg/dL
  - Post-stim: 7.8 µg/dL
  - Maintained
- 2 mos later, Jan 2017
  - Clinically well
  - 1.8, <1, 3.8

Kismet

- 2 mos later, Mar 2017
  - Clinically well
  - Pre-pill: 2.8 µg/dL
  - 3h post-pill: 2.0 µg/dL
  - 1h post-stim: 2.7 µg/dL
  - Maintained dose
  - Finished study
  - All other testing decisions are made clinically
- 6 mos later, Sept 2017
  - Clinically great
  - Pre-pill—4.8 µg/dL
  - Didn't stim
  - Maintained dose

Kismet

- 7 mos later, May 2018
  - Clinically well
    - Pre-pill: 1.3 µg/dL
    - 3h post pill: <1 µg/dL
    - Post-stim 2.1 µg/dL
  - Maintained
  - Rec return in 1 month…
  - Did not…
    - CKD cat died ☹

Kismet

- June 29, 2018
  - Idiopathic vestibular disease
  - Resolved w/ supportive therapy, otherwise okay
  - Seen by another service, no pre-pill cortisol performed

Kismet

- June 29, 2018
  - Idiopathic vestibular disease
  - Resolved w/ supportive therapy, otherwise okay
- Returned August 7, after nagging
  - Clinically great
  - Pre-pill cortisol: 1.1 µg/dL
  - 3 hour post-pill cortisol: 1.2 µg/dL
  - 1 hour post-stim cortisol: 1.6 µg/dL

Kismet

- Owner thought was more active after dose decrease (10 mg → 8 mg)
- 8 Total Rechecks
  - Stim required 5/8 times
- Logistics of returning
  - Easy for us, not as easy in private practice
  - Options: ↓ dose or start with stim
  - EU protocol probably would have decreased dose
- Kismet is NOT typical
  - VERY patient/understanding owner
- Update
  - Bronchoalveolar carcinoma—euthanized 12/2019, 19 yo

What We've Learned

- 1 mg/kg BID is a great starting dose
  - Maintained in 8/12 initial study dogs, prob more
- Increased the dose in one dog
  - "Accidents" may have been behavioral
  - USG helped settle that (concentrated)
- Decreased in two others
  - One owner not observant
  - USG helped sometimes (concentrated or not?)

Clinically Well, Controlled Dogs

(Useful picture slide)

- Pre-pill cortisol <1.4-2 µg/dL
  - ↓ dose by 10% OR ACTH stim
- Pre-pill cortisol >1.4-2 µg/dL
  - Continue current dose
- Pre-pill cortisol >5 µg/dL
  - Re-evaluate history and CONSIDER splitting the dose (if SID) or small dose increase, based on CS

Clinically Uncontrolled Dogs

(Useful picture slide)

- Pre-pill cortisol <1.4-2 µg/dL
  - Re-evaluate history, perform ACTH stim, +/- other diagnostics, consult with an internist
- Pre-pill cortisol 1.4-5 µg/dL
  - Grey zone
  - Maybe increase or split dose if >….3 µg/dL?
  - Stim if <3 µg/dL ?
- Pre-pill cortisol >5 µg/dL
  - Increase dose or split

Beginners Tips for Pre-Pill Cortisol

- Start in dogs that have been on a stable dose for several months
- Individual dogs tend to have patterns in the relationship between pp cortisol and post-stim cortisol.
  - Check the pp cortisol with the stim initially in each dog, and then use the pp cortisol when you feel comfortable that it will be useful.

Treating Cushing's

- Trilostane, 1 mg/kg PO BID with food
- CLINICAL SIGNS. CLINICAL SIGNS.
- Increase dose based on clinical signs.
- Use stim and/or pre-pill cortisol to make sure it's safe.
  - MUST use stim to diagnose Addison's!
    - ANY SICK DOG
- Pre-pill cortisol won't work in all patients.
  - Optimize for patient, client, clinic