

# Hypoadrenocorticism – A New Approach to a Familiar Disease

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# Outline

- **Description of hypoadrenocorticism**
  - **Types**
  - **Signalment/prevalence**
  - **Diagnosis (in brief)**
- **Current treatment strategies (including review of previous research)**
- **Importance of mineralocorticoid excess**
- **Newly published treatment strategy**
- **Questions**

# Types of hypoadrenocorticism (HA)

- Primary
  - 90% loss of adrenocortical function
  - Immune mediated adrenalitis is most common etiology
  - Accounts for >95% of canine hypoadrenocorticism
- Secondary
  - Reduced secretion of ACTH from pituitary gland
  - Spares zona glomerulosa
- Atypical
  - Up to 30% of dogs with primary HA have normal electrolytes at time of diagnosis
  - Not commonly measuring aldosterone

# Signalment/prevalence

- Prevalence in general population: 0.06% - 0.28%
  - Prevalence rate at MSU VMC estimated between 12.5-21% (among dogs that undergo testing for HA)
- Age range: 4 months\* to 14 years
- Younger to middle aged females
- Heritable in some breeds



# Sequela of HA

- Hyponatremia
- Hypochloremia
- Hyperkalemia
- Hypoglycemia
- Metabolic acidosis
- Pre-renal azotemia
- Hypovolemic shock
- Hypotension
- Anorexia
- Vomiting/diarrhea
- Weight loss
- Lethargy
- Polyuria/polydipsia
- Muscle weakness
- Seizures
- Death

# Diagnosis of HA

- Gold standard = ACTH stimulation test
- Screening test
  - Baseline cortisol ( $< 2 \text{ ug/dL}$  or  $< 55 \text{ nmol/L}$ )
    - Sensitivity = 99%
  - In-house SNAP cortisol? Interpret with caution

Journal of Veterinary Internal Medicine

ACVIM  
American College of Veterinary Internal Medicine

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*Standard Article*

*J Vet Intern Med* 2016;30:1798–1805

## Evaluation of Basal Serum or Plasma Cortisol Concentrations for the Diagnosis of Hypoadrenocorticism in Dogs

A.J. Gold, D.K. Langlois, and K.R. Refsal

# Diagnosis of HA

- Role of measuring aldosterone??



**\*\*Ensure patient has not seen any recent steroid use (ocular, aural, shampoos, etc.)**

- Falsely low cortisol leading to misinterpretation

# Treatment of HA

## Glucocorticoid supplementation

- Prednisone
- Fludrocortisone (Florinef®)
- Hydrocortisone

## Mineralocorticoid supplementation

- Fludrocortisone
- Desoxycorticosterone pivalate (DOCP)
  - Percorten®
  - Zycortal®



# Glucocorticoid supplementation

- Prednisone
  - Most common
  - Range from  $< 0.05 - 0.4$  mg/kg/day
- Fludrocortisone (Florinef<sup>®</sup>)
  - 50% may need supplementation with prednisone
  - Refractory over time
- Hydrocortisone
  - Excessive glucocorticoid dose to get adequate mineralocorticoid effect → Hyperadrenocorticism
  - Not recommended

# Mineralocorticoid supplementation (DOCP)

- Percorten<sup>®</sup>
  - Elanco
  - 2.2 mg/kg IM q25days starting dose
- Zycortal<sup>®</sup>
  - Dechra
  - 2.2 mg/kg SQ on individual dosing interval




# Limitations of mineralocorticoid supplementation

- Cost
- Dosing
- Monitoring

# Cost to treat per year - mineralocorticoids



		
<b>Zycortal<sup>®</sup></b>	<b>\$475</b>	<b>\$2,851</b>
<b>Percorten<sup>®</sup></b>	<b>\$528</b>	<b>\$3,168</b>
<b>Florinef<sup>®</sup></b>	<b>\$504</b>	<b>\$3,024</b>

# Estimated cost over lifetime

	Cost
Zycortal <sup>®</sup>	\$15,585
Percorten <sup>®</sup>	\$17,075
Florinef <sup>®</sup>	\$16,397



# Treatment and Long-Term Follow-up of 205 Dogs With Hypoadrenocorticism

Peter P. Kintzer and Mark E. Peterson

- 200 dogs with primary HA, 5 with secondary
  - 190 dogs started on fludrocortisone
  - 6 started on DOCP and pred
  - 4 started on just prednisone
- No difference in response to treatment between fludrocortisone and DOCP but...
  - Daily dose of fludrocortisone increased significantly during treatment from initial median dose (13.1 ug/kg to 22.6 ug/kg)
  - 27 dogs were switched from fludrocortisone to DOCP
    - Adverse effects (10)
    - Drug resistance or poor response (7)
    - Owner convenience (7)
    - Financial concerns (3)

**Use of Plasma Renin Activity to Monitor Mineralocorticoid Treatment in Dogs with Primary Hypoadrenocorticism: Desoxycorticosterone Versus Fludrocortisone**

M.E. Baumstark, J. Nussberger, F.S. Boretti, M.W. Baumstark, B. Riond, C.E. Rensch, and N.S. Sieber-Ruckstuhl

- Take away points
  - DOCP is more effective than fludrocortisone?
    - PRA of dogs on fludrocortisone remained very high and unchanged
    - PRA of dogs on DOCP decreased into reference range or lower
    - More dogs on DOCP had normal electrolytes
    - Electrolyte abnormalities normalized when dogs switched from fludrocortisone to DOCP

## **Use of Plasma Renin Activity to Monitor Mineralocorticoid Treatment in Dogs with Primary Hypoadrenocorticism: Desoxycorticosterone Versus Fludrocortisone**

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- Take away points continued
  - Are we overdosing with DOCP?
    - PRA completely suppressed in dogs within this study = mineralocorticoid excess?
    - Some dogs on DOCP suppressed PRA lower than reference range
    - Another study in primary HA dogs found, overdosing DOCP 15x normal dose for 6 months lead to
      - PU/PD
      - Decreased potassium concentrations
      - Increased sodium concentrations



# Dose and monitoring - Zycortal<sup>®</sup>

Table 1: Day 25: Administering the Second Dose of ZYCORTAL Suspension

If the Day 10 Na <sup>+</sup> /K <sup>+</sup> ratio is:	Do not administer Dose 2 on Day 10.	25 days after the first dose, administer ZYCORTAL Suspension, as follows:
> 34		Decrease dose to: 2.0 mg/kg
> 32 to 34		Decrease dose to: 2.1 mg/kg
27 to 32		Continue 2.2 mg/kg
24 to < 27		Increase dose to: 2.3 mg/kg
< 24		Increase dose to: 2.4 mg/kg

## Prolonging the dosing interval:

If the dog is clinically normal and the Day 25 Na<sup>+</sup>/K<sup>+</sup> ratio is > 32, it is possible to prolong the dosing interval instead of adjusting the dose as described in Table 1. Evaluate the electrolytes every 3-7 days until the Na<sup>+</sup>/K<sup>+</sup> ratio is < 32, and then administer 2.2 mg/kg of ZYCORTAL Suspension.

# Dose and monitoring key points - Zycortal<sup>®</sup>

- Recheck electrolytes 10 and 25 days post-injection
- Dose and interval change recommendations based on electrolytes
  - Hyperkalemia, hyponatremia, or Na:K < 27
    - → Decrease dosing interval by 2-3 days
  - Hypokalemia or hypernatremia
    - → Decrease Zycortal<sup>®</sup> dose

# Dose and monitoring - Percorten<sup>®</sup>

- If all electrolyte values are normal at day 14 and normal at day 25, change to 30-day dosing frequency.
- If all electrolyte values are normal at day 14 but abnormal at day 25, change to 21-day dosing frequency.
- Once stable, check electrolytes every 3 to 4 months.

# Dose and monitoring key points - Zycortal<sup>®</sup>

- Check electrolytes at day 14 and 25 for the first 3 months of treatment
- 1.65 mg/kg to 2.2 mg/kg given q 21-30 days is effective for most patients

# Mineralocorticoid Excess - Humans

- Overdose of DOCP is associated with
  - Excessive weight gain
  - Edema →
    - Moderate, transient edema in some patients within 10-14 days of receiving a moderately excessive dose
  - Hypertension
  - Hypokalemia
  - Potential eventual cardiac failure
- Clinical signs directly related to
  - Excessive water and salt retention
  - Excessive potassium elimination

# Mineralocorticoid Excess - Humans

- Dose adjustments
  - Increase dose to prolong period of efficacy? →
    - Appearance of signs of overtreatment
  - Decrease dosing interval →
    - Better choice
    - Provided sufficient overlap of metabolic effect to avert signs of inadequate hormonal control

# Mineralocorticoid Excess - Dogs

## **Corticosterone- and aldosterone-secreting adrenocortical tumor in a dog**

Ellen N. Behrend, VMD, PhD, DACVIM; Claire M. Weigand, DVM, DACVIM; Elizabeth M. Whitley, DVM, PhD, DACVP;  
Kent R. Refsal, DVM, PhD; Diane W. Young, PhD; Robert J. Kemppainen, DVM, PhD

- Severe weakness
- Hypernatremia
- Hypokalemia
- Polyuria
- Nocturia

# Mineralocorticoid Excess - Dogs

J Am Vet Med Assoc. 1995 Feb 1;206(3):327-31.

**Effects of desoxycorticosterone pivalate administration on blood pressure in dogs with primary hypoadrenocorticism.**

Kaplan AJ<sup>1</sup>, Peterson ME.

- 8 dogs administered DOCP at 2.2 mg/kg IM q30d
- Blood pressure measured with doppler
- Conclusion: DOCP given at labeled dose does not appear to cause hypertension in dogs with HA
- BUT...



# Mineralocorticoid Excess - Dogs

- BUT significant weight gain within study patients
- DOCP when administered in excess of what is needed to control electrolytes may result in extracellular volume retention in some dogs →
  - Weight gain

# Mineralocorticoid Excess - Dogs

- Percorten<sup>®</sup> safety study – DOCP given at 1x, 3x, and 5x labeled dose
- Results
  - No mortality or significant effect on body weight, food consumption, or ophthalmic observations at any dose level
  - Decreased creatinine noted in all groups
  - Renal changes on histopath in the 6.6 mg/kg (3x) dose group and higher
    - → could lead to renal damage long-term

# Can HA be well managed with a lower DOCP dose?

**Lower initial dose desoxycorticosterone pivalate for treatment of canine primary hypoadrenocorticism**

JA Bates,<sup>a</sup> S Shott<sup>b\*</sup> and WD Schall<sup>a</sup>



- Retrospective study out of MSU
- 49 dogs total - 4 Groups
  - Substantially lower (0.36-0.96 mg/kg)
  - Moderately lower (1.0-1.47 mg/kg)
  - Slightly lower (1.76-2.19 mg/kg)
  - Recommended or higher (2.2-3.82 mg/kg)


# Results of the Bates et al. study

- Regardless of initial DOCP dose no dogs had an Addisonian crisis after treatment
- No dogs needed an increased DOCP dose
- No relationship between DOCP dose and
  - Survival
  - Post-treatment Na<sup>+</sup>, K<sup>+</sup>, or Na:K ratio

# Limitations of the Bates et al. study

- Retrospective
- Widely varied DOCP starting dose
- Dosing interval not standardized
- Prednisone dosing not standardized
- Inconsistent owner compliance for rechecks
- Plasma renin activity, blood pressure, UPC not measured

# Evaluation of a low-dose desoxycorticosterone pivalate treatment protocol for long-term management of dogs with primary hypoadrenocorticism

Nadia S. Sieber-Ruckstuhl<sup>1</sup>  | Claudia E. Reusch<sup>1</sup> | Nathalie Hofer-Inteeworn<sup>1</sup> |  
Claudia Kuemmerle-Fraune<sup>1</sup> | Claudia Müller<sup>1</sup> | Regina Hofmann-Lehmann<sup>2</sup>  |  
Felicitas S. Boretti<sup>1</sup> 

- 12 newly diagnosed HA, 5 previously treated with fludrocortisone
- Initial DOCP doses
  - Newly diagnosed = 1.5 mg/kg DOCP
  - Fludrocortisone group = 1.0-1.8 mg/kg DOCP
    - Dosing was based on serum electrolytes and owner financial concerns

## Sieber-Rucksthul et al. continued

- DOCP dosing was adjusted to maintain injection interval of 28-30 days based on normal serum electrolytes
- Goal for prednisone dose was to be  $< \text{or} = 0.1 \text{ mg/kg/day}$  with no signs of glucocorticoid excess
- Study dogs had electrolyte concentrations checked monthly

# Results of Sieber-Rucksthul et al. study

- Starting dose of 1.5 mg/kg DOCP was effective for the majority\* of dogs with HA
- Additional dose reductions may be needed to maintain a dose interval of 28-30 days
- Young and growing animals may need higher doses of DOCP
  - Initial Zycortal<sup>®</sup> studies used research Beagles (5-6 months of age) and may be why label starting dose is higher
- Even at doses of 1.5 mg/kg DOCP, hypokalemia seems to be common at 28 days after 1st dose →
  - Potential sign of mineralocorticoid excess



# Limitations of Sieber-Rucksthul et al. study

- No measurement of blood pressure
- No measurement of plasma renin activity (how can you truly predict mineralocorticoid excess without it?)
- Small sample size (only 17 dogs)

# Hot off the press...


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## Low-dose desoxycorticosterone pivalate treatment of hypoadrenocorticism in dogs: A randomized controlled clinical trial

Alysha M. Vincent, Linda K. Okonkowski, Jean M. Brudvig, Kent R. Refsal, Nora Berghoff, N. Bari Olivier, Daniel K. Langlois 



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 MEDVET

# Objectives & Hypothesis

- **Objective:** prospectively investigate efficacy and adverse effect profile in a standard dose (2.2 mg/kg) and low-dose (1.1 mg/kg) DOCP protocol in dogs with primary HA
- **Hypothesis:** Both DOCP protocols will prevent evidence of mineralocorticoid deficiency, but evidence of mineralocorticoid excess would be more likely to occur in the standard-dose population

# Study Design

- Randomized controlled double-blinded clinical trial
- 3 dogs assigned randomly into
  - Standard-dose (control group) = 2.2 mg/kg
  - Low-dose (test group) = 1.1 mg/kg
- Recheck q10-14 days for 3 months (6 rechecks total)
- Dosing interval of Zycortal® 25-35 days
  - Na:K 28-32 = continue at q30 days
  - Na:K >32 = increase to q35 days
  - Na:K < 28 = decrease to q25 days
- Prednisone dosing standardized between 0.05 - 0.3 mg/kg PO q24

# Inclusion/Exclusion Criteria

## Inclusion Criteria

- Confirmed HA based on pre and post-ACTH stimulated cortisol concentration  $\leq 55$  nmol/L (2.0 ug/dL)
- Presence of mineralocorticoid deficiency
  - Na:K  $\leq 27$
  - HypoNa<sup>+</sup> w/ concurrent K<sup>+</sup> in upper-half of RI
  - HyperK<sup>+</sup> w/ concurrent Na<sup>+</sup> in lower-half of RI
  - (+/- decreased post-ACTH stimulated aldosterone)

## Exclusion Criteria

- Iatrogenic HA
- Exogenous steroids  $<45$  days prior to diagnosis of HA
- Concurrent therapy with ACE inhibitors, diuretics, fludrocortisone, or aldosterone antagonists
- Previous or current congestive heart failure or kidney disease

# Methodology

- **Recheck q10-14 days**
  - PE and history
  - Doppler blood pressure
  - PCV/TS
  - Renal profile
  - Urinalysis
  - UPC
  - Plasma Renin Activity (PRA)
- **Study conclusion on day 90**
  - 6<sup>th</sup> recheck; 4<sup>th</sup> DOCP injection day
  - Clinicians and owners un-blinded

# Patient Demographics

Variable	Test (n = 19)	Control (n = 18)	P value
Age (years)	4.3 ± 2.1	4.5 ± 2.5	.78
Sex (male/female)	11/8	10/8	.99
Weight (kg)	25.0 (16.2-33.6)	24.0 (18.5-36.0)	.99
Na:K ratio	18.8 ± 4.7	18.8 ± 4.9	.99
Prednisone (mg/kg)	0.12 (0.10-0.15)	0.11 (0.07-0.2)	.43

# Patient Demographics

- Control population (n = 18)
  - 17 = hypoNa+
  - 17 = hyperK+
  - 17 = Na:K < or = 27
  - 2 = decreased post-ACTH stimulation aldosterone concentration
- Test population (n = 19)
  - 17 = hypoNa+
  - 18 = hyperK+
  - 19 = Na:K
  - 1 = decreased post-ACTH stimulation aldosterone concentration
- Median (IQR) final daily prednisone maintenance dosage = 0.07 – 0.2 mg/kg



## Results – Clinical effects

- No dogs developed critical illness during the course of the study
- No dogs required increases in DOCP dosing
- DOCP dosing interval was not different between groups
- 88.2% of dogs gained weight during the study, but no significant difference in the amount of weight gain (or BCS) between groups
- No difference in blood pressure measurements between groups at any time point during study

## Results – Clinical effects

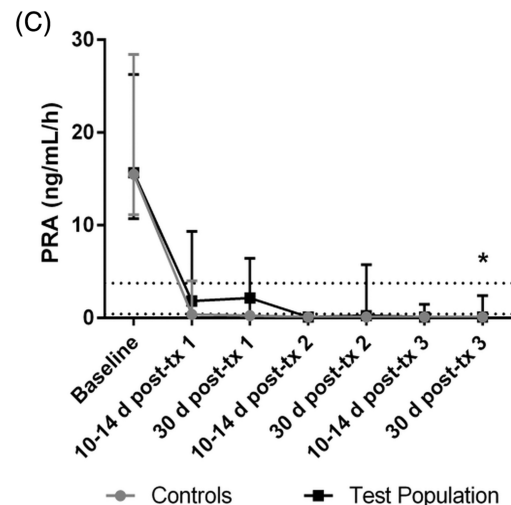
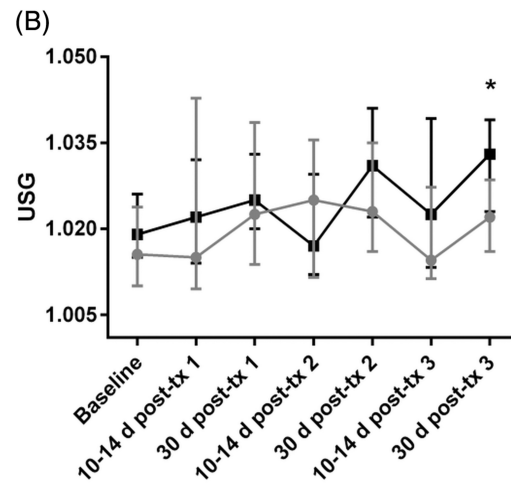
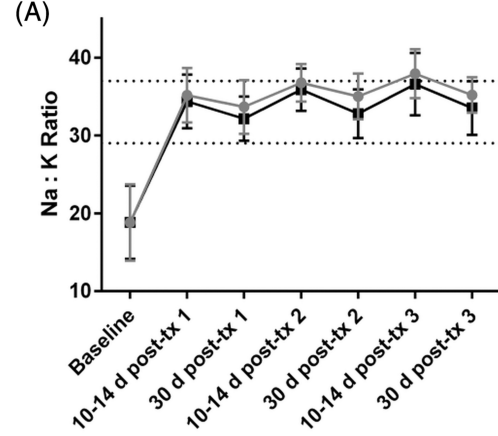
- Adverse clinical effects were uncommon
- All dogs were reported to be clinically healthy >6 months after study completion
  - No test population dogs had an increase in DOCP post-study
  - 3 test population dogs had further dosage decreases

## Results – Biochemical effects (highlights)

- Na:K ratios were not significantly different between test and control populations at any time point, but...
  - Na:K ratios were numerically higher in control population dogs
  - More instances of hypokalemia documented in the control group
- USG was significantly decreased in control population compared to test population

## Results – Biochemical effects (highlights)

- PRA was significantly decreased in control population compared to test population
- Other hematologic and biochemical parameters were not different between groups
  - Hct, albumin, creatinine, TCO<sub>2</sub>, UPC



# Discussion

- DOCP starting and maintenance doses of 1.1 mg/kg were safe and effective in our study population
  - Mild hyperK<sup>+</sup> in only 2 dogs
  - \*This may not be appropriate starting point for juvenile patients or patients <10 kg
  - Comorbidities such as kidney disease and heart disease excluded

## Discussion – Mineralocorticoid excess

- Most dogs receiving 2.2 mg/kg DOCP were likely overtreated
  - Mean Na:K ratios were either in upper-end of RI or increased throughout the study
  - Mean K<sup>+</sup> concentrations consistently in lower-end of RI
  - Decreased USG speculated to be due to mineralocorticoid excess
  - PRA commonly suppressed below the RI in control dogs
  - Subtle differences may not be appreciated by owners

# Limitations

- Larger sample size required to detect more subtle biochemical differences between groups
- DOCP duration of action (i.e. dosing interval) not addressed
- Need to establish canine specific reference ranges for PRA
  - Inferred from human medicine
  - MSU VDL has this in the works



## Study conclusion

- 1.1 mg/kg starting and maintenance dosages of DOCP appear to be safe and effective (in our study population)
- Based on serum electrolyte and PRA concentrations, dosages of 2.2 mg/kg were unlikely to be necessary for most dogs
- Additional studies needed to further refine DOCP treatment protocols and determine the long-term outcomes of these different approaches

# Cost comparison for Zycortal® treatment



	Annual Cost	Annual Cost	Lifetime Cost	Lifetime Cost
Standard dose (2.2 mg/kg)	\$475	\$2851	\$2232	\$13400
Low dose (1.1 mg/kg)	\$237	\$1425	\$1114	\$6698

# Summary

- “Great pretender of all diseases”
- ACTH stimulation test needed to confirm diagnosis +/- aldosterone
- Consider importance of mineralocorticoid excess
- What dose should I use?
  - Honestly, I usually go between 1.1 and 2.2 mg/kg and aim for 1.5 mg/kg
  - Follow-up 30 days later
  - Continue q30d dosing interval at 1.5 mg/kg
  - Recheck q6 months
  - \*Exception – young growing dog, any co-morbidities affecting electrolytes

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- MedVet Dayton
- Hill's Pet Nutrition
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  - Dr. Alysha Vincent
  - Dr. Daniel Langlois
  - Vet tech support (Judy Eastman, Cait O'Reilly, Heather DeFore)
  - MSU VDL Endocrinology



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# Questions?



“Finn” – study  
participant at his  
final visit

(used with owner  
permission)