Low-dose cortisol replacement as a novel treatment for atypical canine Cushing's disease — a retrospective study of five dogs

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ABSTRACT

Purpose. To describe the hormone replacement treatment and laboratory findings of five dogs diagnosed with atypical Cushing's disease. **Method.** Animals studied: Five dogs, four female, one male, all castrated. Age range= 5-9 years (mean age=7 years). ACTH test with adrenal sex-hormone panel (University of Tennessee, Knoxville, TN) confirmed elevated sex hormone/intermediate levels in all dogs (100%) and concurrent elevations in cortisol in 3 dogs (60%). General practice veterinarians administered methylprednisolone 1mg per 10 lbs bodyweight PO SID or prednisone 1.25mg per 10 lbs bodyweight PO SID. ACTH test with adrenal sex-hormone panel was repeated between 3–5.5 months (mean=4.2 months). **Results.** 92% of elevated sex-hormone/ intermediates were reduced, with 64% returning to within normal limits. 100% of estradiol levels were reduced. 88% of cortisol readings were reduced. **Conclusion.** Low-dose, daily cortisol replacement is an effective treatment for dogs with atypical Cushing's disease.

(This column contains a plain English translation of the more complicated terms and concepts,)

SUMMARY OF THE STUDY

When first tested, these five dogs had elevated levels of sex-hormones such as estradiol, androstenedione, progesterone, and 17-OH progesterone. This is referred to as atypical Cushing's disease.

Three of the dogs also *appeared* to have high cortisol levels.

Dogs were given a daily low dose of either methylprednisolone or prednisone. Both of these are man-made versions of the natural cortisol hormone usually produced in the adrenal glands. The dosages where much lower than those typically prescribed for dogs with inflammatory problems.

PO = by mouth, i.e. oral tablets
SID = given once daily

Nearly all of the elevated sex-hormones were reduced with treatment and of those, more than half returned to the normal range. Estradiol (i.e. estrogen) improved in every case. Since estrogen is the cause of many Cushing's-like symptoms, this is a significant result.

OBJECTIVE

Describe the hormone replacement treatment and laboratory findings of five dogs diagnosed with atypical Cushing's disease.

This study examines the effects low-dose cortisol had on elevated sex-hormones levels and evaluates whether these dogs might actually have a cortisol *deficiency*.

PROCEDURE

The charts of five castrated dogs were reviewed: female=4, male=1. Age range=5-9 years (mean age=7 years). Breeds represented: Miniature Dachshund (2), Brittany Spaniel (1), Havanese (1), and Jack Russell Terrier (1).

castrated = spayed or neutered

Atypical Cushing's disease was confirmed by ACTH test with adrenal sex-hormone panel (University of Tennessee, Knoxville, TN). All dogs (100%) demonstrated elevations in a variety of sex-hormone/ intermediate levels such as androstenedione, estradiol, progesterone, and 17-OH progesterone. Three of five dogs (60%) demonstrated concurrent elevations in cortisol. Reference ranges were periodically revised by the laboratory and are reflected in the data.

Each dog was treated by his/her general practice veterinarian with low-dose daily cortisol replacement consisting of either methylprednisolone 1 mg per 10 lbs bodyweight PO SID or prednisone 1.25mg per 10 lbs bodyweight PO SID with no dose exceeding 4mg Medrol SID or 5mg prednisone SID in total. ACTH test with adrenal sex-hormone panels were repeated in 3–5.5 months (mean=4.2 months). One dog (#5) did not have post-ACTH levels re-evaluated. Only baseline data were included from that case.

Most readers are familiar with the high doses of prednisone that are typically prescribed for inflammatory problems or auto-immune diseases. Those doses are called anti-inflammatory or immuno-suppressant level doses. In this study, however, dogs received only low-dose levels. These low levels are basically the same amount the adrenal glands would produce if they are healthy. **This is a key point.**

RESULTS

- 92% of elevated sex-hormones were reduced, with 64% returning to within normal limits.
- 100% of all estradiol levels were reduced.

The fact that all estrogen levels were reduced in all dogs is **another key point**.

- 88% of all cortisol readings were reduced.
  100% of *elevated* cortisol levels were reduced.
- Follow-up cortisol levels were low in 2 of 5 dogs (40%) and low-normal in 1 of 5 dogs (20%).

#1) Jack Russell Terrier, 7 y/o, F/spayed. Treatment: methylprednisolone1mg PO SID. Retested after 4 months.

	Baseline Initial	Baseline Repeat	Baseline normal range	Post-ACTH Initial	Post-ACTH Repeat	Post-ACTH normal Range
Cortisol ng/ml	23.6	9.9	2.1–58.8	28.5*	79.5	65.0–174.6
Androstenedione ng/ml	12.3*	1.9	0.1–0.5.7	25.1	27.4	2.7–39.7
Estradiol pg/ml	73.5*	44.1	30.8–69.9	67.8	36.4	27.9–69.2
Progesterone ng/ml	1.04*	0.12	0.01–0.49	1.25	2.07*	0.10–1.50
17 OH Progesterone ng/ml	2.03*	0.09	0.01–0.77	3.11*	1.36	0.40–1.62
Testosterone ng/ml	0.11	0.01	3.5–139.9	0.11	0.02	72.9–398.5

#2) Brittany Spaniel, 6 y/o, F/spayed. Treatment: prednisone 3.75mg PO SID. Retested after 3 months.

	Baseline Initial	Baseline Repeat	Baseline normal range	Post-ACTH Initial	Post-ACTH Repeat	Post-ACTH normal Range
Cortisol ng/ml	78.5*	31.8	2.1–58.8	188.7*	28.0*	65.0–174.6
Androstenedione ng/ml	10.0*	1.8	0.1–0.5.7	27.3	3.4	2.7–39.7
Estradiol pg/ml	57.5	49.0	30.8–69.9	64.9	53.7	27.9–69.2
Progesterone ng/ml	0.80*	0.25	0.01–0.49	2.83*	0.44	0.10–1.50
17 OH Progesterone ng/ml	0.70	0.06	0.01–0.77	4.83*	0.57	0.40–1.62
Aldosterone pg/ml	64.8	60.8	3.5–139.9	293.8	106.4	72.9–398.5

#3) Miniature Dachshund, 8 y/o, M/neutered. Treatment: methylprednisolone 1mg PO SID. Retested after 3 months.

	Baseline Initial	Baseline Repeat	Baseline normal range	Post-ACTH Initial	Post-ACTH Repeat	Post-ACTH normal Range
Cortisol ng/ml	47.4	6.9	2.0–56.6	146.1	102.4	70.6–151.2
Androstenedione ng/ml	1.21*	0.81*	0.05–0.36	9.79*	>10*	0.24–2.90
Estradiol pg/ml	105.0*	98.0*	23.1–65.1	95.6*	91.8*	23.3–69.4
Progesterone ng/ml	0.37*	0.06	0.03–0.17	2.88*	0.9	0.22–1.45
17 OH Progesterone ng/ml	0.56*	0.09	0.08–0.22	5.01*	2.11	0.25–2.63
Aldosterone pg/ml	74.6	56.4	11–139.9	295.6	354.8	72.9–398.5

#4) Havanese, 9 y/o, F/spayed, Treatment: prednisone 1.25mg PO SID. Retested after 5.5 months.

	Baseline Initial	Baseline Repeat	Baseline normal range	Post-ACTH Initial	Post-ACTH Repeat	Post-ACTH normal Range
Cortisol ng/ml	69.2*	6.0	2.1–58.8	144.2	41.7*	65.0–174.6
Androstenedione ng/ml	1.40*	0.31	0.05–0.57	3.90	3.20	0.27–3.97
Estradiol pg/ml	87.1*	71.7*	30.8–69.9	88.9*	82.5*	27.9–69.2
Progesterone ng/ml	0.20	0.03	0.03–0.49	1.00	0.26	0.10–1.50
17 OH Progesterone ng/ml	0.55	0.05	0.08–0.77	2.11*	0.72	0.40–1.62
Aldosterone pg/ml	17.1	42.0	11–139.9	160.7	277.3	72.9–398.5

#5) Miniature Dachshund, 5 y/o F/spayed. Treatment: methylprednisolone1mg PO SID. Retested after 5.5 months.

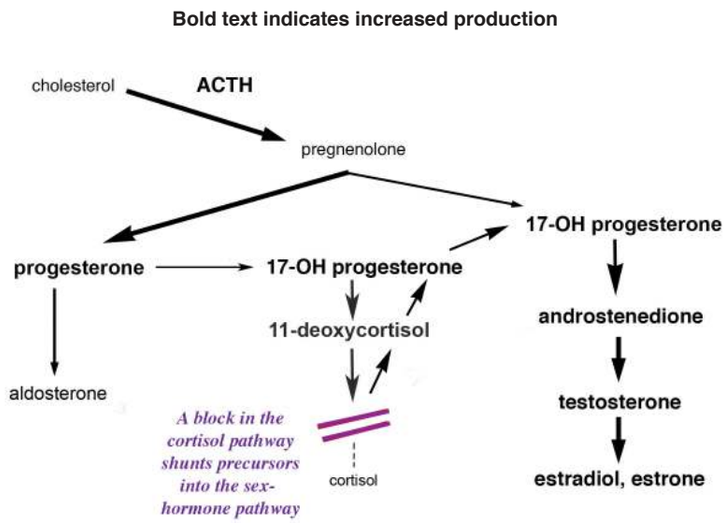
	Baseline Initial	Baseline Repeat	Baseline normal range	Post-ACTH Initial	Post-ACTH Repeat	Post-ACTH normal Range
Cortisol ng/ml	130.0*	4.5	2.1–58.8	188.1*	not tested	65.0–174.6
Androstenedione ng/ml	2.24*	0.54	0.05–0.57	3.53	not tested	0.27–3.97
Estradiol pg/ml	100.0*	78.7*	30.8–69.9	88.9*	not tested	27.9–69.2
Progesterone ng/ml	0.79*	0.55*	0.03–0.49	1.47	not tested	0.10–1.50
17 OH Progesterone ng/ml	1.56*	0.05	0.08–0.77	4.96*	not tested	0.40–1.62
Aldosterone pg/ml	59.7	31.4	11–139.9	200.7	not tested	72.9–398.5

DISCUSSION

Atypical Cushing's disease is the most recent moniker used to describe elevated adrenal sex-hormone production with or without elevated cortisol readings. This condition has previously been described as adreno-hyperplasia-like syndrome or hyperestrinism in the veterinary literature. Standard treatment options include melatonin, mitotane, and trilostane. Melatonin is reported to reduce estradiol only variably. Mitotane is reportedly ineffective in reducing estradiol. Trilostane use increases levels of estradiol, androstenedione, 11-deoxycortisol, progesterone, and 17-OH progesterone. (1)

Similar conditions in humans (congental adrenal hyperplasia and adult onset adrenal exhaustion) result from a disruption in enzyme activity. Failure of 11β-hydroxylase to convert deoxycortisol to cortisol causes precursor hormones (11-deoxycortisol, progesterone, and 17-OH-progesterone) to accumulate. Precursor hormones are shunted into the sex-hormone pathway increasing production of sex hormones such as estradiol (figure 1).

Figure 1. Disruption in 11β-hydroxylase enzyme activity and resulting steroidogenesis.



Hyperestrogenism produces effects similar to hypercortisolism including confusion, fatigue, depression, agitation, pancreatitis, and seizures in humans, (2-8) renal disease, and bone marrow depression in dogs (9,10); immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, and thyroid binding in both species. (5,11-13) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (14,15) Increases in related

To date, treatment for atypical Cushing's disease has not been very effective. Melatonin reduces estradiol levels only some of the time, mitotane doesn't reduce estradiol levels much at all, and trilostane actually increases levels of sex-hormones.

For many years practitioners in human health care have been familiar with diseases that produce excessive adrenal sex-hormones. These include congenital adrenal hyperplasia (CAH) and adrenal exhaustion. These conditions result when the body can not produce sufficient cortisol.

When the adrenal glands are unable to produce sufficient cortisol, it's like building a dam across a river. (See figure 1) The precursor hormones pile up behind the dam and eventually spill over into the adjacent pathway — the sex-hormone pathway. The result is increased levels of sex-hormones such as androstenedione (similar to testosterone) and estradiol (a type of estrogen).

As two molecules go, estradiol and cortisol are very similar. Estradiol is a potent steroid, too. Consequently, they cause nearly the same signs/symptoms in the body. So, when estradiol levels are elevated it can mimic Cushing's disease in many ways.

renal disease = kidney disease
bone marrow depression = immune system problems
immunoglobulin suppression = allergy and intestinal problems
hepatic dysfunction = liver disease
mast cell activity = histamine release, itchiness and stuffiness

hormones, such as progesterone and androstenedione result in heat intolerance (panting), polyphagia, obesity, lethargy, acne, and hirsutism. (16, 17)

Normal or elevated cortisol readings in these cases are deceptive and may represent false positive readings resulting from cross-reactivity. 11-deoxycortisol demonstrates significant cross-reactivity with cortisol on a number of diagnostic tests and may be erroneously read as part of the "cortisol" value. (18-22) The practitioner must be suspect in cases when both sex-hormones and cortisol levels appear elevated because it is inadequate cortisol production that has long been reported as a primary cause of elevated adrenal sex-hormones in both man and dog. (11,23-28)

Low-dose daily oral cortisol replacement exerted regulatory control over the HPA axis in these cases. Levels of sex-hormones and intermediates were reduced along with seemingly elevated cortisol readings. Upon retest, true cortisol levels were low or low-normal in 60% of dogs. (Oral prednisone is molecularly distinct from endogenous cortisol and will not register as cortisol on repeat diagnostics.)

CONCLUSION

Elevations in adrenal sex-hormone/intermediate hormone production was significantly improved in all five cases. Reductions in estradiol levels were comprehensive. Elevated cortisol readings were reduced by low-dose cortisol replacement, demonstrating that initial cortisol readings were false positives. Low-dose, daily cortisol replacement is an effective treatment for dogs with atypical Cushing's disease.

PU/PD = increased drinking and urination
polyphagia = increased appetite
hirsutism = changes in hair growth patterns

The high cortisol readings in these cases are misleading. Most lab tests are not sensitive enough to distinguish between true cortisol and the precursor hormone 11-deoxycortisol. So if 11-deoxycortisol piles up "behind the dam" (see figure 1) most lab tests pick it up and lump it together with true cortisol levels. So even if cortisol levels are quite low, the patient will have a normal or even high "cortisol" reading if the two values are combined on the test.

Giving the dogs low-dose cortisol caused a *drop* in every elevated cortisol reading. This seems really backwards until one understands the way the feedback loop works in the body. When the brain realizes there is cortisol replacement circulating in the body (the oral tablets) it stops over-stimulating the adrenal glands.

When the adrenal glands calm down, levels of precursors and sex-hormones decline toward the normal range. One of those precursors is 11-deoxycortisol. Once it declines, we're able to see the true level of cortisol production — in these cases, low or low-normal.

Atypical Cushing's is a disease in which cortisol levels are actually low. Treatment with low-dose cortisol replacement consistently reduced sex-hormone levels, especially estrogen, which is something not achieved by any other treatment to date.

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