SARDS case report #8

Melatonin vs. cortisol replacement — Comparison of two therapies utilized in a case of canine Sudden Acquired Retinal Degeneration

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ABSTRACT

Purpose. To compare the treatments, clinical and laboratory findings of one dog affected with Sudden Acquired Retinal Degeneration (SARD). **Method and Results.** Animal studied: a six-year-old spayed female Brittany Spaniel with clinical signs of PU/PD, PP, obesity, confusion, lethargy, hirsutism, excessive defecation, drooling, and panting in the 16 months surrounding SARD-onset. Diagnostics revealed T4 below normal (Antech Diagnostics). ACTH stimulation test with adrenal sex-hormone panel (University of Tennessee CVM) indicated elevations in two of eight adrenal sex-hormone levels. **Part I.** The general practice veterinarian prescribed melatonin 3mg PO BID. ACTH stimulation test with adrenal sex-hormone panel was repeated after four weeks. Results indicated increases in all adrenal sex-hormone levels with four values above normal limits. The client reported no improvement in clinical signs. **Part II.** Melatonin was discontinued and replaced with low-dose prednisone 3.33mg PO SID and levothyroxine 0.4mg PO BID. ACTH stimulation test with adrenal sex-hormone panel was repeated after 10 weeks. Results indicated all adrenal sex-hormone levels within normal limits. The client reported decreased PU/PD, improved energy and mood. **Conclusion**. In this case, elevated sex-hormone production was exacerbated with melatonin treatment and mitigated with cortisol/thyroid replacement therapy. This pattern is suggestive of adrenal exhaustion — pathological steroidogenesis in which elevated adrenal sex-hormones result from inadequate cortisol production.

Plain English translation

This dog developed signs of excess adrenal gland activity in the 16 months surrounding the SARD diagnoses, including excessive thirst and urination (PU/PD), increased appetite (PP), weight gain, confusion, low energy, thick coat growth, increased BMs at night, and excessive drooling and panting.

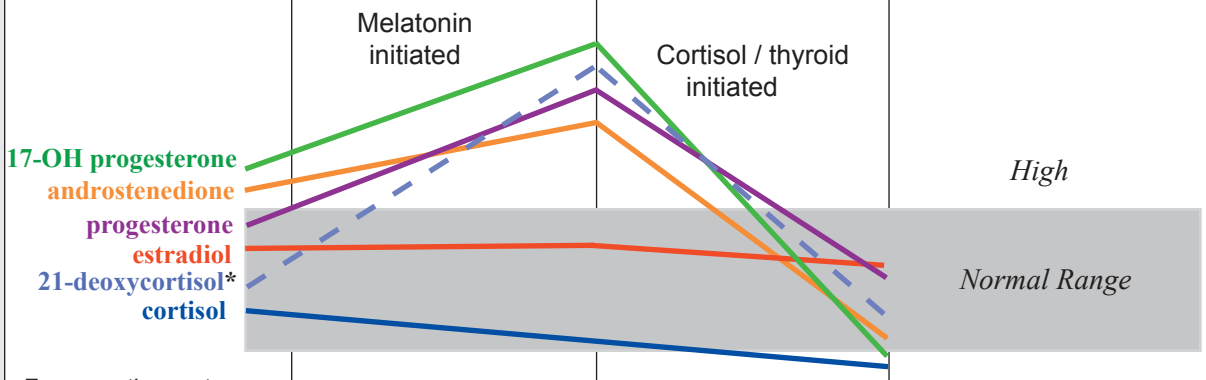
The dog's thyroid test was low. Adrenal sex hormone levels were high. Treatment was started with 3mg of melatonin twice daily. This treatment increased all levels of adrenal sex-hormones. The owner reported no improvment in the dog's condition. The second treatment — cortisol and thyroid hormone replacement therapy — returned all adrenal sex-hormones to normal and improved some of the dogs signs/symptoms.

This pattern supports the concept of adrenal exhaustion as an underlying problem. The author discusses the effects that melatonin and low-dose prednisone therapy have on adrenal gland activity.

DESCRIPTION OF THE CASE

This dog demonstrated clinical signs suggestive of abnormal adrenal activity during a 12-month period prior to, and a four-month period subsequent to SARD diagnosis. (table1)

Table 1. Overview of the case

	4 months post-SARD	Melatonin treatment	Cortisol / thyroid replacement	
Clinical signs	PU/PD PP/obesity confusion lethargy hirsutism excessive defecation excessive drooling excessive panting	PU/PD PP/obesity confusion lethargy: ***increased*** hirsutism defecation drooling panting: ***increased***	PU/PD: ***decreased*** PP/obesity confusion: ***decreased*** lethargy: ***decreased*** hirsutism defecation: ***decreased*** drooling: ***decreased*** panting: ***decreased***	
Diagnostics	**Baseline / Post-ACTH**	**Baseline / Post-ACTH**	**Baseline / Post-ACTH**	**Normal range: Baseline / Post-ACTH**
cortisol	49.7 / 112.4	78.5 **High** / 188.7 **High**	31.8 / 28.0 **Low**	2.1-58.8 / 65.0-174.6 ng/ml
androstendione	6.9 **High** / 22.0	10.0 **High** / 27.3	1.8 / 3.4	0.1-5.7 / 2.7-39.7 ng/ml
estradiol	55.6 / 52.9	57.5 / 54.9	49.0 / 53.7	30.8-69.9 / 27.9-69.2 pg/ml
progesterone	0.31 / 1.41	0.80 **High** / 2.83 **High**	0.25 / 0.44	see tables / 0.10-1.50 ng/ml
17-OH progest.	0.31 / 1.98 **High**	0.70 / 4.83 **High**	0.06 / 0.57	see tables / 0.40-1.62 ng/ml
Adrenal activity				
	Four months post SARD-onset, this dog demonstrated clinical signs and diagnostics consistent with adrenal exhaustion. As the dog became increasingly unable to convert precursors into cortisol, the precursors accumulated. These then "spilled over" into the sex-hormone pathway.	Melatonin *inhibits* cortisol production resulting in continued accumulation of cortisol precursors (progesterones and 21-deoxycortisol.) Melatonin may also inhibit estrogen production, increasing levels of estradiol precursors, such as androstendione and again, the progesterones.	Low-dose prednisone does not register on blood tests. It does, however, register with the brain (hypothalamus). This curbs the excessive stimulation of the adrenal glands and reduces production of precursor hormones. Therapy is required for years in order for glands to recover function, if ever.	

*presumptive

METHODS AND RESULTS

Diagnostic tests performed 2.5 months post SARD-onset revealed T4 below normal and Free T4 via equilibrium dialysis (Antech Diagnostics) within the bottom 10% of normal. (table 2) An ACTH stimulation test with adrenal sex-hormone panel (University of Tennessee CVM) performed three months post SARD-onset indicated elevations in baseline androstenedione as well as post-ACTH 17-OH progesterone. Both pre- and post-ACTH cortisol values were within normal limits. (table 3)

Table 2. Thyroid hormone assay (Antech Diagnostics)

T4	0.9 **Low**	1.0-4.0 ug/dL
Free T4 equilibrium dialysis	11	8-40 pmol/L

Table 3. Initial ACTH stimulation test with sex-hormone panel (University of Tennessee CVM)

	baseline		**post-ACTH**	
cortisol	49.7	21-58.8 ng/l	112.4	65.0-174.6 ng/ml
androstenedione	**6.9 H**	0.1-5.7ng/ml	22.0	2.7-39.7 ng/ml
estradiol	55.6	30.8-69.9 pg/ml	52.9	27.9-69.2 pg/ml
progesterone	0.31	0.01-0.49 ng/ml	1.41	0.10-1.50 ng/ml
17-OH progesterone	0.31	0.01-0.77 ng/ml	**1.98 H**	0.40-1.62 ng/ml

Part I — Melatonin therapy. The general practice veterinarian prescribed melatonin 3mg PO BID. ACTH stimulation test with adrenal sex-hormone panel was repeated after four weeks. (table 4) Results indicated increases in all adrenal sex-hormone levels with four of eight values above normal, including baseline androstendione, baseline progesterone, post-ACTH progesterone, and post-ACTH 17-OH progesterone. Both cortisol values were above normal. (table 1) The client reported no improvement in clinical signs, stating that the dog “was miserable”, “panted heavily,” and “ was going downhill.”

Table 4. ACTH stimulation test with sex-hormone panel four weeks post-melatonin treatment

	baseline		**post-ACTH**	
cortisol	**78.5 H**	21-58.8 ng/l	**188.7 H**	65.0-174.6 ng/ml
androstenedione	**10.0 H**	0.1-5.7ng/ml	27.3	2.7-39.7 ng/ml
estradiol	57.5	30.8-69.9 pg/ml	54.9	27.9-69.2 pg/ml
progesterone	**0.80 H**	0.01-0.49 ng/ml	**4.83 H**	0.10-1.50 ng/ml
17-OH progesterone	0.70	0.01-0.77 ng/ml	**1.98 H**	0.40-1.62 ng/ml

Part II — Cortisol / thyroid replacement therapy. Melatonin was discontinued and replaced with low-dose prednisone (cortisol replacement) 3.33mg PO SID and levothyroxine (thyroid replacement) 0.4mg PO BID. ACTH stimulation test with adrenal sex-hormone panel was repeated after 10 weeks. (table 5) Results indicated all adrenal sex-hormone levels within normal limits. The pre-ACTH cortisol value returned to normal. The post-ACTH cortisol value was below normal. The client reported decreased PU/PD, improved energy, and stated that the dog's "personality was back to normal."

Table 5. ACTH-stimulation test with sex-hormone panel ten weeks post cortisol/thyroid replacement

	baseline		**post-ACTH**	
cortisol	31.8	21-58.8 ng/l	**28.0 L**	65.0-174.6 ng/ml
androstenedione	1.8	0.1-5.7ng/ml	3.4	2.7-39.7 ng/ml
estradiol	49.0	30.8-69.9 pg/ml	53.7	27.9-69.2 pg/ml
progesterone	0.25	0.03-0.49 ng/ml	0.44	0.10-1.50 ng/ml
17-OH progesterone	0.06	0.08-0.77 ng/ml	0.57	0.40-1.62 ng/ml

DISCUSSION

Dogs affected with SARD routinely present with signs suggestive of hypercortisolism (1,2,3,4,5) but only a minority are diagnosed with Cushing's disease. (2,6) Early on, researchers speculated that this hypercortisolism was the physiological response to some unidentified stress (5). SARD-affected dogs also demonstrate elevated levels of adrenal sex-hormones (androstenedione, estradiol, progesterones, and testosterone) within the first year of blindness. (7,8) One explanation for this pattern of events is Selye's model of stress adaptation, which describes the progression from adrenal gland hyperactivity (hypercortisolism) to adrenal gland exhaustion (cortisol insufficiency). In Selye's model, adrenal activity is marked by three phases: alarm, resistance, and exhaustion. (9)

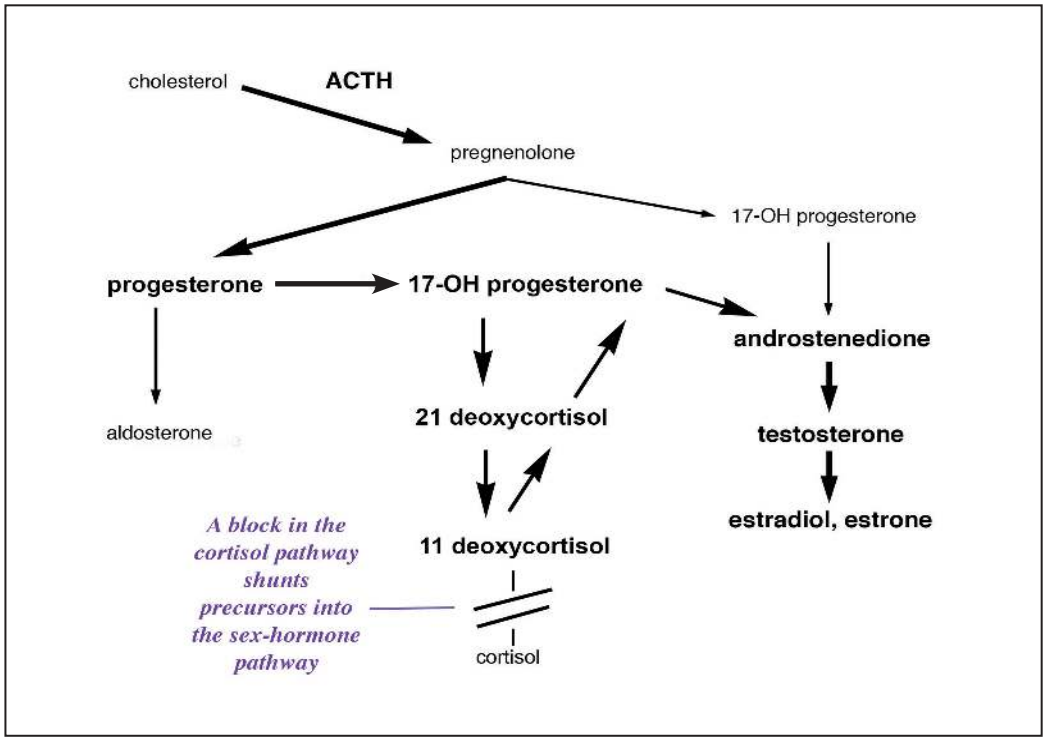
Phases of adrenal activity

During the alarm phase the body responds to stressors with increased hypothalamic-pituitary-adrenal (HPA) activity and cortisol secretion. Cortisol production returns to normal when the stressor is resolved. This is the normal, healthy response to psychological and physical stressors (irritation).

The resistance phase occurs following a prolonged period of stress. Elevated cortisol production continues but falls to a level only slightly above normal. The HPA feedback loop fails. Cortisol production continues unabated. (10)

In the final phase—exhaustion—the adrenal glands are unable to sustain elevated cortisol production. The enzyme 11β-hydroxylase fails to convert deoxycortisol to cortisol. Consequently, precursor hormones such as 11-deoxycortisol, 21-deoxycortisol, progesterone, and 17-OH-progesterone accumulate. These precursors are then shunted into the adjacent the sex-hormone pathway increasing production of androstenedione and estradiol. (figure 1) In dogs, this scenario has also been described as: hyperestrogenism, adrenal hyperplasia-like syndrome, atypical Cushing's disease (when sex-hormones are assayed) or atypical Addison's (when cortisol/aldosterone are assayed). Humans born with a similar group of conditions are described as having congental adrenal hyperplasia (CAH).

Figure 1. Sex-hormone accumulation during adreno-cortical exhaustion



Bold text indicates elevated hormone levels

Clinical signs of adrenal exhaustion

Hyperestrogenism produces effects similar to hypercortisolism including, confusion, fatigue, depression, agitation, pancreatitis, and seizures in humans, (13-19) renal disease, and bone marrow depression in dogs (20,21); immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, and thyroid binding in both species. (12,16,22,23) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (24,25)

Increases in related sex-hormones, such as progesterone and **androstenedione** result in heat intolerance (panting), polyphagia, obesity, lethargy, acne, and hirsutism. (26, 27)

Inadequate cortisol production may cause anorexia, abdominal pain, weight loss, vomiting, diarrhea or increased defecation, and weakness. Without treatment, severe hypocortisolism is fatal. (28,29)

Interpretation of cortisol values

The dog described here demonstrated "normal" cortisol values upon initial screening, "elevated" cortisol values during melatonin treatment, and a *low* cortisol value during low-dose prednisone treatment. This seems counterintuitive but can be explained with a brief review of molecular biology and steroidogenesis.

Cross-reactivity

During adrenal exhaustion, 11-deoxycortisol levels accumulate due to the impasse in the cortisol pathway. (figure 1) 11-deoxycortisol demonstrates significant cross-reactivity with cortisol on a number of diagnostic assays. Consequently, 11-deoxycortisol may be erroneously read as part of the "cortisol" value. (30-34)

Stereoisomers or "mirror image molecules"

Chronic activation of the HPA axis acts to increase production of hormone stereoisomers—molecules possessing identical constituents, but differing in their three-dimensional arrangement of atoms. Production of stereoisomers is suspected to occur in peripheral tissues during the cortisone-cortisol shuttle when cortisone is converted to cortisol. (35-37) The stereoisomer of cortisol most often described in the literature is 11-epicortisol. This isomer is less potent and does not exert activity equivalent to cortisol, including regulatory activity on the HPA axis. (38-40)

Few diagnostics differentiate cortisol from cortisol stereoisomers. Therefore, a "cortisol" value may be an amalgamation of active cortisol plus less active stereoisomers. Patients in adrenal exhaustion, producing increased levels of 11-epicortisol, increased levels of 11-deoxycortisol; and *decreased* levels of active cortisol may demonstrate a normal "cortisol" value on diagnostics. (table 3)

Effects of melatonin

In dogs treated with melatonin, estradiol production is occasionally reduced (due to inhibition of aromatase enzyme activity) and cortisol production is consistently reduced (due to inhibition of 21-hydroxylase activity). (41) (figure 2) Inhibition of 21-hyrdoxylase enzyme activity consistently raises levels of **21-deoxycortisol**. (42-44) Like 11-deoxycortisol, 21-deoxycortisol demonstrates significant cross reactivity on many diagnostic assays. (31,32,44) Increased levels of

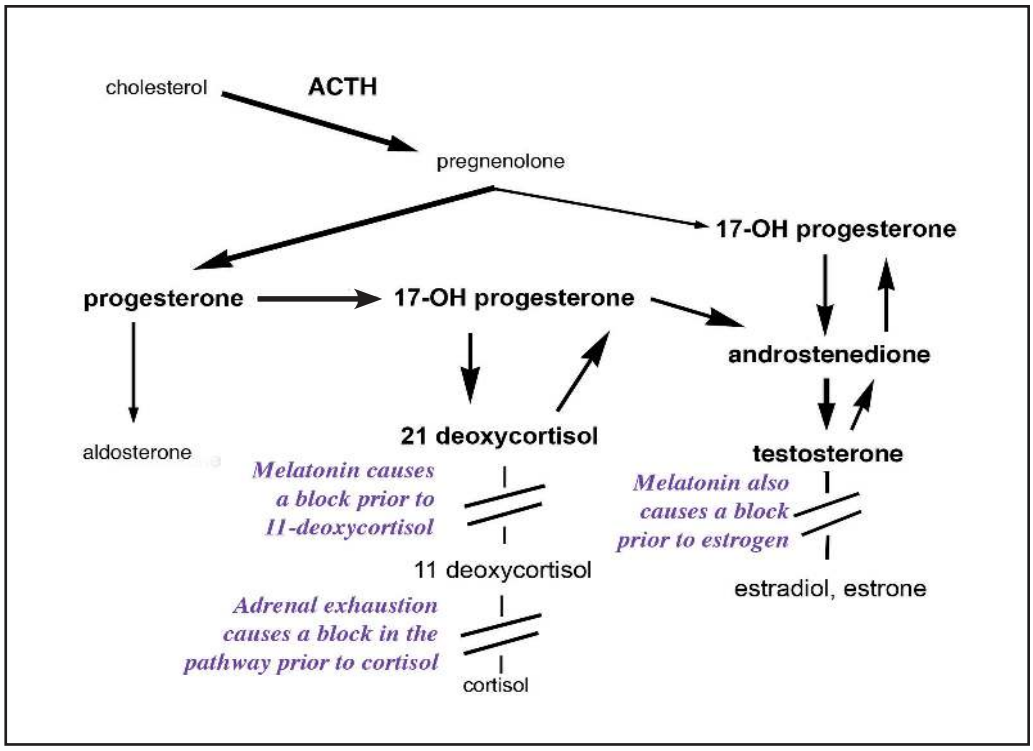
During adrenal exhaustion, when the body craves cortisol, the brain tells the adrenal glands, "Work harder! Make cortisol!". But since the adrenals simply can't create any more, the precursors (the building blocks) just accumulate.

Few diagnostic tests distinguish between cortisol and its precursor, 11-deoxycortisol. Therefore any 11-deoxycortisol can mistakenly be added into the cortisol value on the test. This is called cross-reactivity.

Furthermore, during chronic stress or irritation, the body increases production of isomers (mirror image molecules) called epi-cortisol. Epi-cortisol is so similar to real cortisol that most laboratory tests count it as part of the "cortisol" level.

Melatonin causes *two more blockages* in the adrenal pathway. The first blockage increase in a hormone called 21-deoxycortisol.

Figure 2. Accumulation of precursors with Melatonin use



Bold text indicates elevated hormone levels

21-deoxycortisol may be erroneously read as part of increased "cortisol", as well. (34,44) Consequently, in this case, "cortisol" levels that were elevated during melatonin treatment may well have been elevated levels of **21-deoxycortisol** instead. (table 4)

In cases of adrenal exhaustion, such further disruption of the cortisol pathway is not without risk. While melatonin may reduce estrogen levels in some cases, it routinely interferes with any residual production of active cortisol. In this dog, such a scenario exacerbated clinical complaints.

Effects of low-dose prednisone

Oral prednisone therapy is well known to exert regulatory control over the HPA axis. In cases of adrenal exhaustion, cortisol replacement normalizes ACTH secretion, which reduces excessive levels of deoxycortisols and perhaps 11-epicortisol. As a result of low-dose prednisone supplementation, the erroneously elevated "cortisol" reading falls to its true value. (45) 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 dogs. (11,12,46-49)

Just like 11-deoxycortisol, 21-deoxycortisol is read as "cortisol" by many lab tests. As this "pile-up" of 21-deoxycortisol increased, so did the dog's "cortisol" value. Hence, the high "cortisol" reading during melatonin treatment.

When a patient develops adrenal exhaustion the Cushing's-like symptoms are the result of increased production of sex-hormones, including estrogen. Melatonin may or may not reduce levels of estrogen, but it *consistently* reduces levels of cortisol. This is not an ideal goal for patients with underlying adrenal exhaustion.

When a patient is given low-dose prednisone, the brain says, "Thank goodness! Finally, some cortisol!" The brain

Cortisol replacement therapy resolved excessive ACTH stimulation as evidenced by normalizing levels of cortisol precursors such as progesterone and 17-OH progesterone. As a result, levels of adrenal sex-hormone (androstenedione and estradiol) and deoxycortisols declined. Declining deoxycortisol levels no longer contributed to the "cortisol" value, and the dog's true cortisol production became apparent (pre-ACTH = normal; post-ACTH = low). (table 5)

Oral prednisone is molecularly distinct from endogenous cortisol and does not register as cortisol on diagnostics. Low-dose prednisone therapy replaces the cortisol deficit, providing the adrenal gland with a necessary rest period. The body may not restore 11β-hydroxylase enzyme activity for some time, if at all. Consequently, the true activity of cortisol production may continue to freefall. (table 1)

CONCLUSION

In the case of this dog, elevated sex-hormone production was exacerbated with melatonin treatment and mitigated with cortisol/thyroid replacement therapy. This pattern is indicative of adrenal exhaustion — pathological steroidogenesis in which elevated adrenal sex-hormones result from inadequate production of true cortisol.

then tells the adrenals to relax. When they do, the high levels of precursor hormones fall back to normal. (Production of epicortisol—the mirror image molecule—declines as well.)

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