SARDS Case Report #6

Trilostane and Mitotane treatment
in a dog with Sudden Acquired Retinal Degeneration

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ABSTRACT

Purpose. To describe the clinical and laboratory findings, treatment, and outcome of one dog affected with Sudden Acquired Retinal Degeneration (SARD). **Methods.** Data was collected retrospectively from the general practice chart of a thirteen-year-old neutered male Miniature Schnauzer. **Case description.** The dog was diagnosed with SARD September 2007 and developed escalating signs of PU/PD, PP, lethargy, confusion, ataxia, and GI distress during the four months post SARD-onset. Diagnostic tests (urine cortisol creatinine ratio, low-dose dexamethasone suppression test and ACTH-suppression test) were inconclusive for Cushing's disease. Two months post-onset ACTH-suppression test results were again normal. Three months post-onset ACTH-suppression test results were equivocal. The general practice veterinarian initially prescribed Trilostane 20mg PO BID. After 18 days Trilostane treatment was discontinued and Mitotane 125mg PO BID was prescribed along with Prednisone 1.25mg PO SID. **Results**. After 18 days of Trilostane treatment the ACTH-suppression test was normal but the client reported no improvement in clinical signs. Treatment with Mitotane resulted in escalating clinical signs and rapid physical deterioration. The dog was euthanized after 10 days of Mitotane treatment. **Conclusion**. The dog described here demonstrated clinical signs suggestive of hypercortisolism but diagnostic test results were inconclusive for Cushing's disease. Treatment with Trilostane and Mitotane exacerbated clinical presentation. This pattern suggests clinical presentation may have been the result of hyperestrogenism (adrenal exhaustion) rather than hypercortisolism. Effects of Trilostane and Mitotane treatment are discussed.

Plain English translation

This dog developed signs of excess adrenal gland activity in the four months after SARD diagnoses, including excessive thirst and urination (PU/PD), increased appetite (PP), lack of energy, confusion, difficulty walking, and digestive upset.

A variety of tests were done to evaluate the dog for Cushing's disease (a tumor). Some of the test results suggested Cushing's disease, others (the ACTH tests) did not. After three months, and worsening signs/symptoms, the ACTH test results were finally "borderline" for Cushing's disease and treatment was started. The first medication—Trilostane—resulted in a normal ACTH test but did not improve any of the dog's signs/symptoms. Mitotane (Lysodren®) actually caused signs/symptoms to escalate. The dog deteriorated rapidly and was euthanized 10 days later.

The author suggests this was a case of adrenal exhaustion (*low* cortisol / high *estrogen)* rather than Cushing's disease. The author discusses the unfavorable effects these Cushing's treatments have during adrenal exhaustion.

DESCRIPTION OF THE CASE

A thirteen-year-old, neutered male Miniature Schnauzer demonstrated persistent clinical signs suggestive of abnormal adrenal activity during the four-month period following SARD diagnosis. Severity of clinical signs escalated over time. (table 1)

Table 1. Clinical signs of elevated adrenal activity

	September 2006	October 2006	November 2006	December 2006	January 2007
Clinical presentation *(Bold text indicates increasing severity)*	polyphagia PU/PD confusion	polyphagia PU/PD confusion pneumonia	polyphagia **PU/PD** confusion	polyphagia **PU/PD** **confusion** lethargy ataxia GI distress	polyphagia **PU/PD** **confusion** **lethargy** ataxia GI distress

A battery of adrenal function tests yielded equivocal results. A urine cortisol creatinine ratio (UCCR) was suggestive of hypercortisolism. (table 2) A low-dose dexamethasone suppression test (LDDST) supported a diagnosis of pituitary-dependant hyperadrenocorticism. (table 3) The ACTH-stimulation test was negative for Cushing's disease. (table 4)

Table 2. Urine cortisol/creatinine ratio (Idexx Laboratories, Inc.)

	9-18-06	Normal range
UCCR	29	<13.5

Table 3. Low-dose dexamethasone suppression test (Idexx Laboratories, Inc.)

LDDST	9-21-06	Normal range
baseline cortisol	6.1	1.0-6.0 ug/dL
post 4 hr dex	0.6	Less than 1.5
post 8 hr dex	1.8	Less than 1.5

No treatment was initiated based on inconclusive results. The ACTH test was repeated two months post-SARD onset (results normal). (table 4) Three months post-SARD onset ACTH test results were equivocal at which time the general practice veterinarian prescribed Trilostane 20mg PO BID. Trilostane treatment was discontinued after 18 days and Mitotane (Lysodren®) 125mg PO BID was prescribed along with Prednisone 1.25mg PO SID.

Table 4. ACTH suppression tests post SARD (Idexx Laboratories, Inc.)

ACTH tests	9-25-06 *SARD onset*	11-13-06	12-21-06	1-06-07 *After 18 days of Trilostane treatment*	Interpretation
baseline cortisol	3.1	4.3	5.9	6.6	2 - 6 ug/dL normal
post ACTH cortisol	8.7	7.2		9.4	6 - 18 ug/dL normal
			20.9		18 - 22 ug/dL equivocal
					>22 ug/dL consistent with hyperadrenocorticism
					<0.5 ug/dL consistent with hypoadrenocorticism

RESULTS

The 18-day course of Trilostane resulted in a normal ACTH-suppression test (table 4) but the client reported "no improvement whatsoever" in clinical signs. Additionally, the dog developed ataxia and GI distress (loose stools and flatulence).

During a 10-day course of Mitotane, the owner reported further exacerbation of PU/PD. Polydipsia was described as "insatiable—all he wanted to do was drink." Lethargy and confusion "increased dramatically". The dog was euthanized after 10 days due to rapidly deteriorating physical condition.

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 stages: alarm, resistance, and exhaustion. (9)

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. When cortisol production falls (i.e., precursors are insufficiently converted to cortisol) levels of these precursors (11-deoxycortisol and 17-OH-progesterone) accumulate prior to the block and are shunted into the sex-hormone pathway. (figure 1) Levels of androstenedione, and later, estradiol and estrone rise. (11) This pattern of adrenal exhaustion and elevated sex-hormone production has been identifed in SARD-affected dogs. (12,13)

Figure 1. Steroidogenesis during adreno-cortical exhaustion

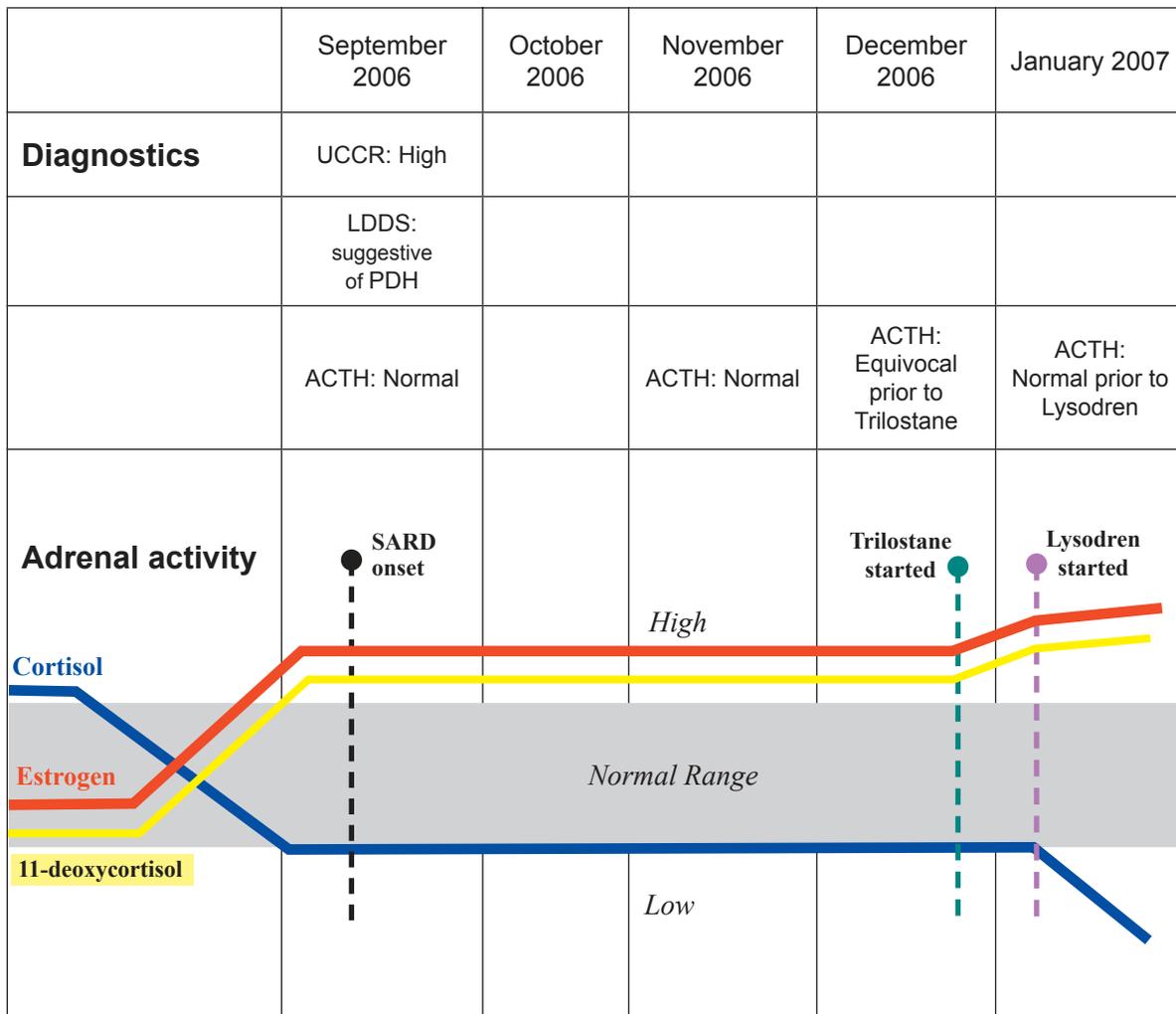Bold text indicates elevated hormone levels
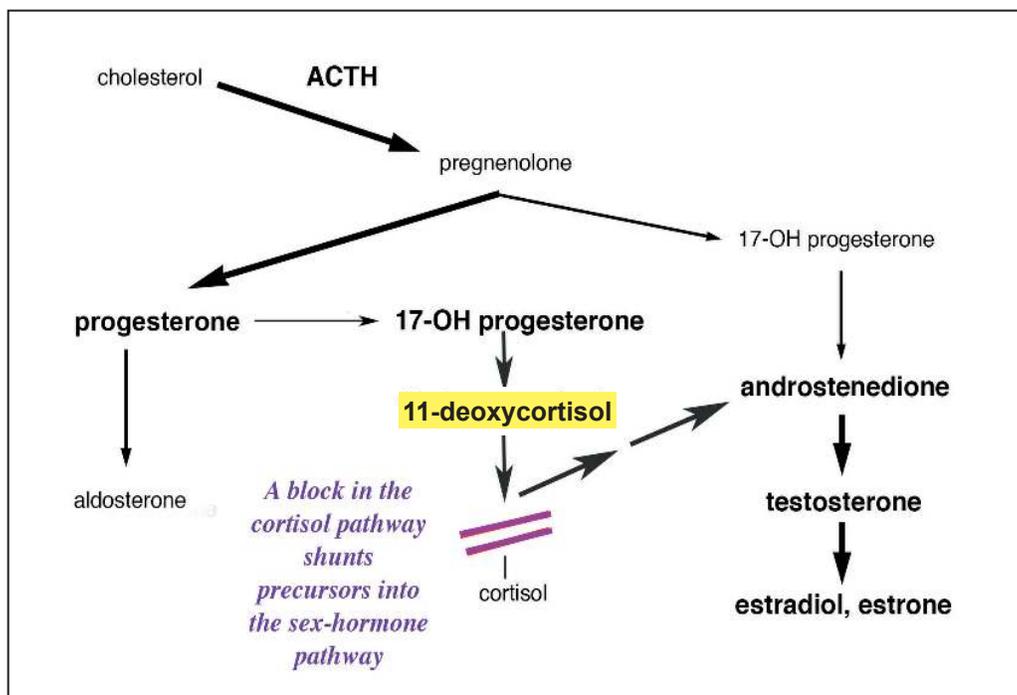
Clinical presentation of adrenal exhaustion —

Hyperestrogenism produces effects similar to hypercortisolism including, confusion, fatigue, depression, agitation, pancreatitis, and seizures in humans, (16-22) renal disease, and bone marrow depression in dogs (23,24); immunoglobulin suppression, hepatic dysfunction, increased mast cell activity, and thyroid binding in both species. (15,19,25,26) Estrogen-treated rats experience PU/PD and an inability to concentrate urine. (27,28)

Increases in related sex-hormones, such as progesterone, androstenedione, and testosterone cause polyphagia, heat intolerance, acne, obesity, and alterations in coat growth. (29, 30,31)

Severely depleted cortisol results in anorexia, weakness, abdominal pain, weight loss, vomiting, and diarrhea. Without treatment, severe hypocortisolism is fatal. (32,33)

Table 5. Diagnostic tests and related adrenal activity

	September 2006	October 2006	November 2006	December 2006	January 2007
Diagnostics	UCCR: High				
	LDDS: suggestive of PDH				
	ACTH: Normal		ACTH: Normal	ACTH: Equivocal prior to Trilostane	ACTH: Normal prior to Lysodren

Interpretation of Diagnostics —

High levels of hormone precursors contribute to false positive results in conventional diagnostic tests. Cortisol precursors such as 11-deoxycortisol and 21-deoxycortisol demonstrate high cross-reactivity on the Urine Cortisol Creatinine Ratio (UCCR) test. (34) During adrenal exhaustion, elevated levels of these precursors erroneously contribute to high "cortisol" readings in dogs.

Humans with secondary adrenal insufficiency have demonstrated normal cortisol responses to corticotropin injection (ACTH stimulation). (35) Researchers have postulated that the normal ACTH dose overstimulates the adrenals, producing falsely adequate responses. Low dose ACTH tests are more sensitive in identifying mild adrenal deficits in humans. (36)

False positive results are also well described in the low-dose dexamethasone suppression test. Since this test is not routinely performed on patients with adrenal insufficiency or adrenal hyperplasia (elevated sex-hormone production) little data exists as to expected outcomes in such cases.

Effects of Treatment —

Trilotstane is a competitive inhibitor of 3β-hydroxysteroid dehydrogenase (3β-HSD) the enzyme that mediates the conversion of pregnenolone to progesterone. Trilostane also inhibits the action of 11β-hydroxylase, the enzyme that converts 11-deoxycortisol to cortisol. (figure 2) Consequently, levels of 11-deoxycortisol, 17-OH progesterone, androstenedione, and estradiol rise in dogs treated with Trilostane. (37)

Trilostane is highly effective in treating classic cases of hyperadrenocorticism. However, in cases of *adrenal exhaustion*—in which cortisol production wanes and clinical signs result from elevated sex hormones—Trilostane treatment merely duplicates the underlying pathogenesis, further suppressing cortisol synthesis and increasing sex-hormone production.

The UCCR test picks up several other hormones and can falsely include them in the cortisol "total" — hormones that are elevated during adrenal exhaustion. This may be true for other Cushing's tests as well.

Research in humans suggests that the standard ACTH test is not good at identifying *mild* failure of the adrenal glands.

During adrenal exhaustion, when the body is having trouble producing cortisol and precursor hormones are piling up, adding Trilostane only compounds the problem.

Figure 2.

Steroidogenesis with Trilostane use

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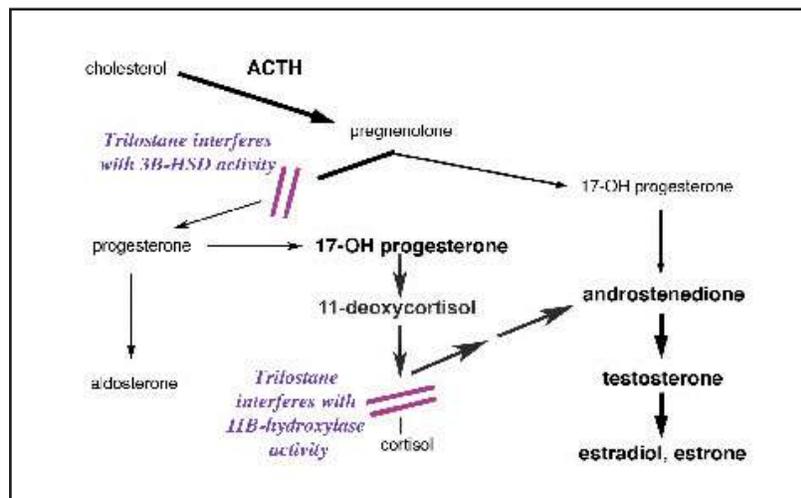
Mitotane (Lysodren®) is also an effective treatment of hyperadrenocorticism. By binding to the mitochondria, Mitotane treatment results in progressive necrosis of the zona fasciculate and with prolonged use, the zona reticularis (38) resulting in a therapeutic decline in cortisol levels.

However, in cases of *adrenal exhaustion*, Mitotane-induced destruction of the adrenal cortex has the clear potential to induce iatrogenic hypoadrenocorticism by suppressing what little cortisol production exists. As with Trilostane use, Mitotane treatment would compound the underlying pathogenesis in these cases (i.e., reduce cortisol production further) ultimately resulting in an Addisonian-type crisis. Weakness, ataxia, and GI upset would follow, as reported in this case.

Figure 3. Steroidogenesis with Mitotane use
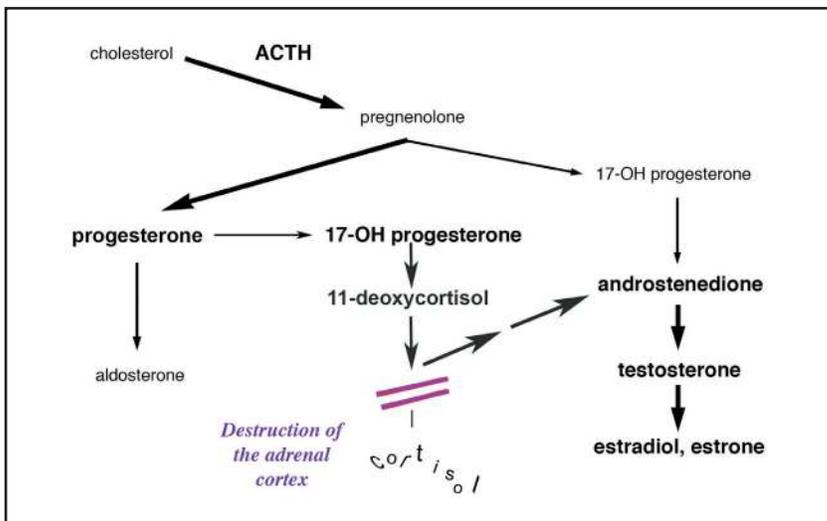
In humans, low-level glucocorticoid replacement therapy successfully modulates elevated sex hormone levels. Glucocorticoid replacement reduces chronic ACTH secretion via the hypothalamic-pituitary-adrenal feedback mechanism, thereby reducing activity in the sex-hormone pathway. (39,40,41,42,43) This pattern has also been demonstrated in SARD-affected dogs. (12,13,44)

CONCLUSION

The dog described here demonstrated diagnostic test results inconclusive for Cushing's disease and clinical signs exacerbated by conventional Cushing's treatments. The author suggests that clinical presentation was the result of hyperestrogenism rather than hypercortisolism—as recently reported in other SARD-affected dogs.

Differential diagnosis of adrenal disease in SARD-affected dogs is crucial. In cases of elevated sex-hormone production, therapies that further disrupt cortisol pathways may be detrimental. Owners of SARD-affected dogs should be encouraged to pursue *adrenal estrogen testing* for signs of elevated adrenal activity.

Lysodren destroys the portion of the adrenal gland that produces cortisol. In cases of adrenal exhaustion when the body already has difficulty producing cortisol, Lysodren treatment can be unsafe.

Adrenal exhaustion *easily gives the impression of Cushing's* disease. That's why these medications have been used in the past. However, any treatment that interferes with cortisol production will simply compound the problem.

It's crucial to determine whether a dog has Cushing's disease or, in fact, has adrenal exhaustion. This is done by testing levels of adrenal estrogen and/or other sex hormones. Cortisol replacement therapy has been beneficial for a number of SARD dogs with adrenal exhaustion.

Overview of case

	September 2006	October 2006	November 2006	December 2006	January 2007
Clinical presentation	polyphagia PU/PD confusion	polyphagia PU/PD confusion pneumonia	polyphagia **PU/PD** confusion	polyphagia **PU/PD confusion** lethargy ataxia	polyphagia **PU/PD confusion lethargy** ataxia GI distress
Diagnostics	UCCR: High				
	LDDS: suggestive of PDH				
	ACTH: Normal		ACTH: Normal	ACTH: Equivocal prior to Trilostane	ACTH: Normal prior to Lysodren

Adrenal activity

Cortisol

High

Normal Range

Estrogen

Low

● **SARD onset**

● **Trilostane started**

● **Lysodren started**

ACTH test

Adrenal exhaustion

— initial —

Following a prolonged period of stress or irritation, adrenal gland function becomes exhausted. Cortisol production begins to fail. Previously elevated levels of cortisol temporarily drop within the normal range.

Adrenal exhaustion

— advanced —

As adrenal exhaustion progresses, cortisol levels drop below normal. The brain attempts to increase cortisol production (via continual ACTH secretion). This only increases levels of precursors and sex-hormones (estrogen, progesterone, and androgens). Elevated sex-hormones cause clinical signs that mimic Cushing's disease.

During this phase, adrenal glands may still be able to "rise to the challenge" of an ACTH test, but they produce insufficient cortisol for daily needs.

Trilostane is used to treat *Cushing's disease* because it interferes with –and reduces– cortisol production. When used in cases of adrenal exhaustion (i.e., cases when cortisol production is not elevated), sex-hormone levels rise further and clinical signs do not improve.

Lysodren is used to treat *Cushing's disease* because it destroys the portion of the gland that produces cortisol. When used in cases of adrenal exhaustion, Lysodren will destroy what little cortisol *is* being produced and clinical signs will escalate.

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