Old or New? A Comparison of Mitotane and Trilostane for the Management of Hyperadrenocorticism

Joel D Griffies, DVM, DACVD
Animal Dermatology Clinic
Marietta, GA

Abstract: *Hyperadrenocorticism (HAC) is a common endocrinopathy in dogs. With better recognition of the disease, more cases are being presented to clinicians for management. Mitotane, a 3- to 4-decade-old therapy, remains a viable and useful option for management of this disease. Thorough education and understanding of the drug are important, however, as the learning curve of how to manage its effects can be significant. Trilostane, a newer option for management of HAC, offers a simplified protocol and, often, smoother and faster control of the disease. It also requires a comfortable knowledge of expected outcome and possible adverse effects. With either drug, careful monitoring and client communication are crucial.*

Hyperadrenocorticism (HAC) is a common endocrinopathy in dogs. Its most notable clinical features have been well characterized in numerous texts and journals. Classically, clinical presentation includes polyuria/polydipsia (PU/PD) and polyphagia. In fact, some may consider these signs prerequisites for pursuing the diagnosis or performing adrenal function tests. Other dogs, however, may present with prominent dermatologic signs consistent with HAC but have no PU/PD or polyphagia noted by owners. Thorough history and laboratory findings (e.g., low urine specific gravity) may illuminate some of these classic features, but for some owners, it is the skin disease that causes greatest concern.

While often generalized as bilaterally symmetric alopecia, skin-related signs may include chronic recurrent bacterial pyoderma, adult-onset demodicosis, patchy or widespread alopecia, irregular hair regrowth after grooming or clipping for surgery, or coat color or texture changes. Some cases of HAC presented for dermatologic signs may be purely cosmetic and, after careful consideration, may not warrant treatment. Others, however, such as those with chronic recurrent infections or demodicosis, are considered especially worrisome to owners despite the absence of features such as PU/PD and are often treated. Regardless of the clinical manifestations, the treatment goals are the same: to improve the quality of life for the patient and the owner.

Treatments for HAC have been documented in veterinary literature for decades. Reports have included therapies such as mitotane, which continues to be effective, and others with limited or no efficacy. In the past decade, trilostane (Vetoryl, Dechra Veterinary Products) has become another good option for management of HAC. Trilostane was first produced and approved in the United Kingdom, where it has received widespread acceptance for the treatment of HAC. In the past few years, it has been approved by the Food and Drug Administration (FDA) and marketed in the United States. Trilostane and mitotane are both legitimate treatment options for HAC, with pros and cons that should be considered when making a clinical selection for a particular patient.

The diagnosis of HAC should always be confirmed with a combination of clinical signs, laboratory screening tests, and adrenal function tests. Ideally, differentiating tests should also be performed to identify whether the disease is pituitary dependent or caused by an adrenal tumor. "Trial therapies" of either drug should not be considered, as each has the potential for adverse effects, including the death of the patient.

Mitotane

Mitotane (Lysodren, o,p'-DDD) was first described as a tool for management of dogs with HAC in 1973.[1] Over the next 4 decades, it became the most commonly used medication for the management of pituitary-dependent hyperadrenocorticism (PDH). It can also be useful in patients with adrenal tumors for which medical management is chosen over surgery.[2–4] A potent adrenocorticolytic drug, mitotane causes progressive necrosis of the zona fasciculata and zona reticularis and, in some instances, the zona glomerulosa.

Dr. Griffies discloses that he has received honoraria from companies including Dechra Veterinary Products for lectures.

Dogs with PDH have an increased sensitivity to the effects of the drug compared with normal dogs and often respond with decreased cortisol secretion in 5 to 9 days.[5]

Use of mitotane involves a two-phase approach with an initial induction period of daily dosing followed by a reduced-dose maintenance regimen. Because monitoring of progress includes observing decreases in post-ACTH stimulation cortisol levels, a baseline ACTH stimulation test is essential before starting therapy regardless of whether this test is used for the initial diagnosis. Initiation of mitotane therapy includes a starting dose of 25 to 50 mg/kg/day, administered PO divided q12h for 5 to 10 days.[3] Determination of exact dose, duration, and follow-up testing vary in published studies.[1–3,6] In my cases, the starting dose is influenced by the overall status and health of the dog, concurrent medications, and degree of clinical signs. Owner factors are also important and may include tolerance for adverse effects and ability to note changes in appetite or other subtleties. For example, an otherwise healthy, middle-aged dog with prominent PU/PD and significant dermatologic abnormalities may receive a starting dose of mitotane closer to 50 mg/kg/day, while a more geriatric dog in less optimal health may receive a starting dose of 30 mg/kg/day. Thorough explanation of the effects of lowering cortisol levels and appropriate at-home vigilance are crucial in the early stages of therapy.

Because of the potency of this drug and potential for harm if instructions are not strictly followed, it has also been suggested that an owner should not be provided with more than 7 to 8 days' worth of medication at a time during this phase. Some authors have suggested that appetite is the single most important factor in determining when to conclude a loading-dose regimen with mitotane.[5] In my group, however, because this feature is not always as prominent as other clinical signs, we routinely plan to reevaluate an ACTH stimulation test at a predetermined, often conservative, time after starting the loading-dose therapy (i.e., 5 to 7 days). The exact timing of this reevaluation may depend on multiple factors, including exact drug dose selected, age and overall condition of the dog, and, of course, the owner. Again, it important to stress that regular owner contact during this period is a vital monitoring tool. Some authors have suggested concurrent low-dose prednisone during induction therapy. Others provide a small supply of prednisone to the owner for use under the advice of the managing clinician if needed, based on reports by phone. The latter is my typical choice.

Once an appropriate post-ACTH stimulation cortisol level is achieved (1 to 5 µg/dL), the mitotane dosing schedule is changed to a maintenance protocol. This has been described as a regimen of 50 mg/kg/week divided over a number of once-daily doses, or a protocol whereby the loading dose is divided over a week.[5] In my cases, best control with fewest adverse effects is achieved by dividing the total weekly dose over 5 to 7 days. This tends to provide more even control and minimize adverse effects. Appropriate actions if a dog becomes ill or has a post-ACTH plasma cortisol level <1 µg/dL have been described and essentially involve a break from the medication until the adrenal cortex has recovered and post-ACTH levels have increased.[5] If a dog is clinically ill or if post-ACTH cortisol levels are <1 µg/dL, glucocorticoids are indicated. Electrolytes should also be evaluated in these patients and mineralocorticoid supplementation pursued if needed. Long-term maintenance doses of mitotane may vary considerably, with huge potential for individual patient sensitivity.

Many consider mitotane the "tried and true" drug for HAC management, but it is important to remember the significant potential for adverse effects. In fact, drug-related adverse effects are common in the loading-dose phase. In one study of 200 dogs, 25% exhibited one or more adverse effects during induction, including weakness, vomiting, anorexia, diarrhea, and ataxia.[6] None of these dogs died during this phase. However, in another study, mitotane was responsible for the deaths of five dogs, which were attributed to mineralocorticoid and/or glucocorticoid deficiency.[1] In that study, of the 184 dogs that continued on a maintenance regimen of mitotane, 107 had one or more relapses of HAC during treatment, indicated by recurrence of clinical signs and increased post-ACTH cortisol concentrations. Feldman et al reported that in their cohort of 1500 dogs with PDH, 35% had at least one period of relapse requiring dose adjustment.[5] In this population, death from overdose of mitotane was seen in less than 1% of patients. Adverse effects are dose-related, but because individual patient sensitivity can vary dramatically, they may be difficult to predict.

The scenario of waxing and waning disease has been reported numerous times, illustrating that HAC is often a dynamic disease, and making regular monitoring an integral part of long-term management. In my experience, when adjusting a maintenance regimen of mitotane, it is important to allow adequate time for progress in clinical signs and decrease in cortisol levels as measured by the ACTH stimulation test. This lag phase can sometimes result in delayed therapeutic response and, if cases are not monitored appropriately, may allow dogs to stray outside of good control ranges or below recommended cortisol levels over time. It is this feature of mitotane, I believe, that makes it a sometimes frustrating

Key Points

- Diagnosis of hyperadrenocorticism should always be confirmed with a combination of clinical signs, laboratory screening tests, and adrenal function tests.
- Thorough explanation of the effects of lowering cortisol levels and appropriate at-home vigilance are crucial, especially in the early stages of therapy.
- Mitotane continues to be a reasonable and reliable medication for management of hyperadrenocorticism.
- Starting trilostane therapy at the low end of the recommended dosing protocol may be wise.
- I find trilostane to be a successful drug for managing HAC. It has a very smooth and frequently short period to accomplish good control of the disease compared with mitotane.
- With proper drug therapy, patient follow-up, and client communication, successful management of hyperadrenocorticism can result in significantly improved quality of life for the patient and the owner.

drug for both pet owners and veterinarians. However, with careful patient evaluation and a comfortable knowledge of expected effects, mitotane continues to be a reasonable and reliable medication for management of HAC.

Trilostane

Trilostane is the newest drug approved for treatment of HAC in dogs and has been a hot topic in the past few years in managing this disease. Many have embraced this drug and now use it exclusively, while others have avoided it in favor of other methods. Trilostane selectively inhibits 3-β-hydroxysteroid dehydrogenase in the adrenal cortex, thereby inhibiting the conversion of pregnenolone to progesterone (**FIGURE 1**). This inhibition blocks production of glucocorticoids and, to a lesser extent, mineralocorticoids and sex hormones.[7] Although the FDA approved this drug for use in dogs in the United States fairly recently (2008), trilostane has been studied in a variety of species over the past 30 years.[8–11] European studies demonstrating trilostane's efficacy in HAC in dogs were first published in 1998.[12] Since then, a variety of papers and texts have verified its usefulness in the disease.

The manufacturer-recommended protocol for trilostane includes a dosage regimen of 2.2 to 6.7 mg/kg PO q24h, with a chart provided to recommend capsule size based on the patient's weight range. Follow-up monitoring using the ACTH stimulation test is recommended 10 to 14 days after starting therapy, and dosage adjustment is recommended depending on results.[7] A review of trilostane use in dogs compared six studies (2002 to 2008) in which starting doses ranged from 0.5 mg/mg q12h to 20 mg/kg q24h.[13] Each of these studies found clinical efficacy in management of HAC, with success rates ranging from 67% to 95%. The final maintenance dose of trilostane varied greatly in these studies, with a finishing mean/median dose of 2.8 to 7.3 mg/kg/day in five of the studies (divided into twice-daily dosing in two studies).

No studies have directly compared efficacy of trilostane in once-daily versus twice-daily protocols. However, it has been demonstrated that trilostane's ability to decrease cortisol levels often lasts less than 24 hours.[14,15] The magnitude of fluctuation varies by individual and may not always affect clinical outcome. In my practice, both successes and failures have been observed based on this phenomenon. Some cases show a variation in ACTH-stimulated cortisol results that stays within a reasonable reference range over 24 hours; these patients tend to be successfully managed with once-daily dosing. Other cases illustrate the limited time of control, with ACTH-stimulated cortisol levels well outside the reference range at 24 hours; these patients often require twice-daily dosing.

Perhaps the most useful and interesting information published in the past few years is that significantly lower doses of trilostane may be successful in managing HAC. In a group of dogs with HAC treated with trilostane at a starting dose of 0.21 to 1.1 mg/kg q12h, 15 of 38 (39%) had a good response to the initial dose or had it decreased further.[16] Other dogs required an increase in

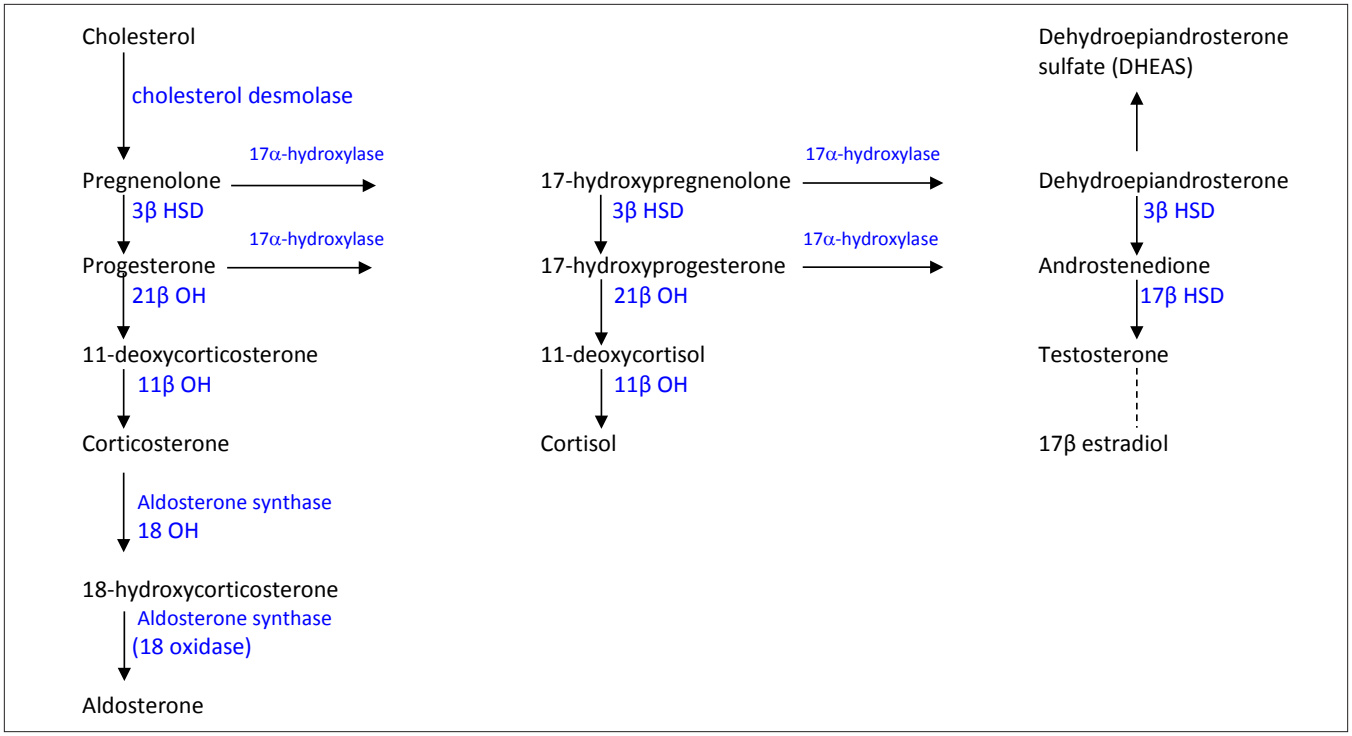

Figure 1. Corticosteroid hormone synthesis pathways. 3β HSD = 3 β hydroxysteroid dehydrogenase; 21β OH = 21 β hydroxylase; 17β HSD = 17β hydroxysteroid dehydrogenase; 11β OH = 11β hydroxylase; 18 OH = 18 hydroxylase *Adapted from: Sieber-Ruckstuhl NS, Boretti FS, Wenger M, et al. Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane.* Domest Anim Endocrinol *2006;31:63-75.*

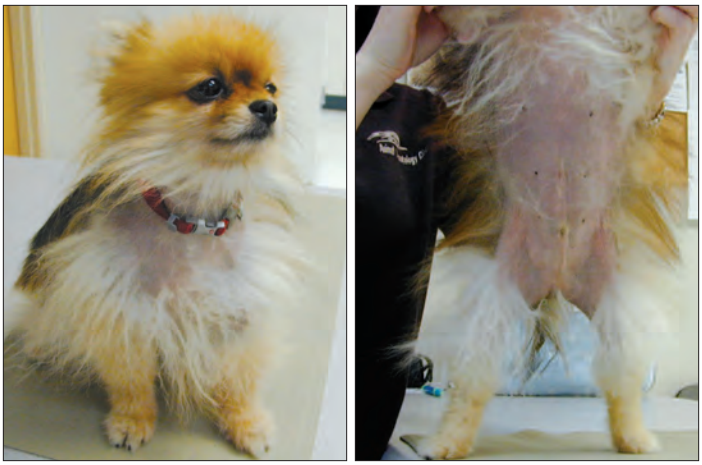

Figure 2. A 3-year-old male neutered Pomeranian that was successfully managed with oral trilostane. These images were taken before treatment with trilostane.

dose to obtain proper control; however, this study illustrates that much lower doses of trilostane than those initially used may be successful in managing HAC in some cases. This report suggests it may be wise to start trilostane therapy at the low end of the recommended dosing protocol.

As with mitotane, trilostane use may result in adverse events, including anorexia, lethargy, vomiting, diarrhea, and other events typical of a hypoadrenal state. In rare cases, true hypoadrenocorticism has been seen with both glucocorticoid and mineralocorticoid deficiency. While most cases rebound from this effect when trilostane is discontinued, rarely, it is persistent. In some initial investigations, deaths were also reported, with documented adrenal rupture and adrenal necrosis.[17] However, in more recent studies using much lower doses, the incidence of adverse effects decreased significantly and no deaths were reported.[15,16] Overall, I find trilostane to be a successful drug for managing HAC. It has a very smooth and frequently short period to accomplish good control of the disease compared with mitotane.

Manufacturer monitoring recommendations include ACTH stimulation testing 10 to 14 days after starting trilostane, with the test being started 4 to 6 hours after morning administration of the medication. This time frame is estimated to be within trilostane's peak activity in suppressing cortisol production. If a post-ACTH stimulated cortisol level is within the suggested target range (1.45 to 5.4 µg/dL) and the dog is doing well clinically, the same dose is continued. If the cortisol level is above the reference range, dose or frequency adjustments are recommended.[7]

Most investigators perform follow-up ACTH stimulation tests every 3 to 6 months after cortisol target levels are reached. In my practice, I tend to monitor more frequently and then taper to this interval if results remain within the reference range. This often includes monitoring 10 to 14 days after starting therapy, 3 to 4 weeks later, and then after another 2 to 3 months, as long as cortisol levels remain within range.

Recommendations regarding once-daily versus twice-daily initial dosing of trilostane vary among clinicians. Twice-daily dosing for more even control throughout the day is prudent in patients with concurrent disease such as diabetes mellitus and, especially with lower doses, has been associated with fewer adverse effects. However, many patients with primarily dermatologic clinical manifestations can be well controlled with once-daily dosing. In my practice, once-daily dosing is most common at the outset of therapy. A common recommendation is to increase to twice-daily dosing if clinical disease is not well controlled but 4- to 6-hour post-ACTH stimulated cortisol levels are within the target range. Manufacturer recommendations are to increase the total daily dose by one-half to one-third and to divide the dose into equal amounts given 12 hours apart.

In my practice, dosing is often increased to twice daily, but I prefer to document the degree of variation of cortisol levels before this adjustment. For example, if clinical signs (including hair regrowth, recurrent infections, and PU/PD or polyphagia) are not well controlled, but ACTH-stimulated cortisol levels are within the target range, I ask the owners to bring the dog back for a follow-up ACTH stimulation test 1 to 3 weeks later. The test starts at the hour at which the dog would typically receive trilostane, but without giving the medication. By beginning the test at this time, we are able to document the highest level of cortisol possible for the patient during the day. This level documents the significant variation between patients: some stay within or just outside the cortisol target range, and others are well outside a level of reasonable control (i.e., >5.4 µg/dL). Clinical decisions on how much to alter the trilostane dose are based largely on these results. Some patients, like the Pomeranian shown in **FIGURE 2A**, **FIGURE 2B**, **FIGURE 3A**,

Figure 3. Same dog as in Figure 2. These images were taken after 6 months of twice-daily therapy.

FIGURE 3B, and **FIGURE 3C**, have ACTH stimulation test results within range 4 to 6 hours after trilostane administration but cortisol levels well above the reference range for this test when it is performed just before the medication is administered again (in this case, >14 µg/dL). Other patients, with good control on once-daily therapy, may vary only slightly over 24 hours, with test results that remain within the reference range throughout the day. Although each case must be considered individually with regard to the patient and the treatment goals of the clinician and the owner, an ACTH stimulation test at 24 hours with results >7 µg/dL typically prompts me to consider twice-daily dosing.

Conclusion

Both mitotane and trilostane are useful tools in the management of an often insidious chronic disease. While both have pros and cons, the clinician's comfort level, experience, and understanding of each drug are probably the most important features in deciding which to choose. With proper drug therapy, patient follow-up, and client communication, successful management of HAC can result in significantly improved quality of life for the patient and the owner.

References

1. Schechter RD, Stabenfeldt GH, Gribble DH, et al. Treatment of Cushing's syndrome in the dog with an adrenocorticolytic agent (o,p'DDD). *J Am Vet Med Assoc* 1973;162:629-639.
2. Kintzer PP, Peterson ME. Mitotane treatment of 32 dogs with cortisol-secreting adrenocortical neoplasms. *J Am Vet Med Assoc* 1994;205:54-61.
3. Feldman EC, Nelson RW, Feldman MS, et al. Comparison of mitotane treatment for adrenal tumor versus pituitary-dependent hyperadrenocorticism in dogs. *J Am Vet Med Assoc* 1992;200:1642-1647.
4. Helm JR, McLauchlan G, Boden LA, et al. A comparison of factors that influence survival in dogs with adrenal-dependent hyperadrenocorticism treated with mitotane or trilostane. *J Vet Intern Med* 2011;25:251-260.
5. Feldman EC, Nelson RW. Canine hyperadrenocorticism (Cushing's syndrome). *Canine and Feline Endocrinology and Reproduction*. 3rd ed. Philadelphia: WB Saunders Co., 2004;252-357.
6. Kintzer PP, Peterson ME. Mitotane (o,p'-DDD) treatment of 200 dogs with pituitary-dependent hyperadrenocorticism. *J Vet Intern Med* 1991;5:182-190.
7. Vetoryl. [package insert]. Overland Park, Kansas: Dechra Veterinary Products, 2008.
8. Lambert F, Corcelle-Cerf F, Lammerant J, et al. On the specificity of the inhibitory effect of trilostane and aminoglutethimide on adrenocortical steroidogenesis in guinea pig. *Mol Cell Endocrinol* 1984;37:115-120.
9. Komanicky P, Spark RF, Melby JC. Treatment of Cushing's syndrome with trilostane (WIN 24,540), an inhibitor of adrenal steroid biosynthesis. *J Clin Endocrinol Metab* 1978;47:1042-1051.
10. Semple CG, Beastall GH, Gray CE, et al. Trilostane in the management of Cushing's syndrome. *Acta Endocrinol (Copenh)* 1983;102:107-110.
11. Vierhapper H, Nowotny P, Waldhausl W. Effect of trilostan on steroid excretion in man: compensated inhibition of 3 beta-hydroxysteroid dehydrogenase. *J Steroid Biochem* 1986;24:577-580.
12. Hurley A, Sturgess K, Cauvin A, Kuipers R. The use of trilostane for the treatment of hyperadrenocorticism in dogs. *J Vet Intern Med* 1998;12:210.
13. Ramsey IK. Trilostane in dogs. *Vet Clin North Am Small Anim Pract* 2010;40:269-283.
14. Bell R, Neiger R, McGrotty Y, et al. Study of the effects of once daily doses of trilostane on cortisol concentrations and responsiveness to adrenocorticotrophic hormone in hyperadrenocorticoid dogs. *Vet Rec* 2006;159:277-281.
15. Vaughan MA, Feldman EC, Hoar BR, et al. Evaluation of twice-daily, low-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. *J Am Vet Med Assoc* 2008;232:1321-1328.
16. Feldman EC. Evaluation of twice-daily lower-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. *J Am Vet Med Assoc* 2011;238:1441-1451.
17. Neiger R, Ramsey I, O'Connor J, et al. Trilostane treatment of 78 dogs with pituitary-dependent hyperadrenocorticism. *Vet Rec* 2002;150:799-804.