Trilostane Dosing and Monitoring in Dogs

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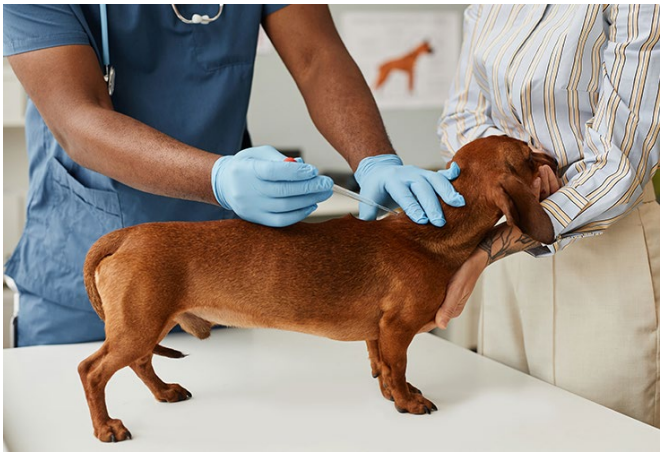
Canine hyperadrenocorticism (Cushing's disease) is one of the most common endocrine disorders that veterinarians treat. For many years, trilostane has been the treatment of choice for most veterinarians' medical management of the condition. Trilostane is a competitive inhibitor of 3β-hydroxysteroid dehydrogenase, the enzyme required to synthesize cortisol. This inhibition blocks the conversion of pregnenolone to progesterone, which inhibits the production of glucocorticoids and, to some extent, mineralocorticoids and sex hormones. As an aside, it is not uncommon for dogs receiving trilostane to be mild to moderately hyperkalemic due to these effects on mineralocorticoids.

Trilostane has an extensive dose range, and the starting doses can vary significantly. The manufacturer's (Dechra) recommendation is a starting dose of 2.2 to 6.7 mg/kg once daily. Recent studies have shown, however, that lower initial doses are equally effective and may be safer. Generally speaking, the Angell Animal Medical Center Internal Medicine service uses starting doses of 1 to 2 mg/kg twice daily (usually closer to 1mg/kg twice daily). Larger dogs generally require a lower mg/kg dose than smaller dogs. Although trilostane may be given either once or twice a day, twice-a-day treatment is preferred by most clinicians due to the short half-life of the drug and a more consistent clinical response. Trilostane should always be given with food to improve absorption.

Historically, Monitoring treatment includes assessing response to therapy with improvement of clinical signs and an ACTH stimulation test. In recent years, synthetic ACTH shortages and increasing prices have made it more challenging to routinely do the ACTH stimulation test. Additionally, the test requires two blood samples taken an hour apart, resulting in more clinical space and staff utilization. Due to the increased price and time needed for this test, other monitoring diagnostics have been proposed.

Most recently, monitoring Cushing's just based on a "pre-trilostane" (just before the morning dose was to be given) baseline cortisol level alone has been proposed. If used appropriately, this can be a much more practical and less labor intense method of monitoring the response to trilostane. Initial studies at the University of Glasgow showed that the pre-trilostane cortisol levels correlated better with clinical signs than the two-hour post-cortisol level with classical ACTH stimulation testing.



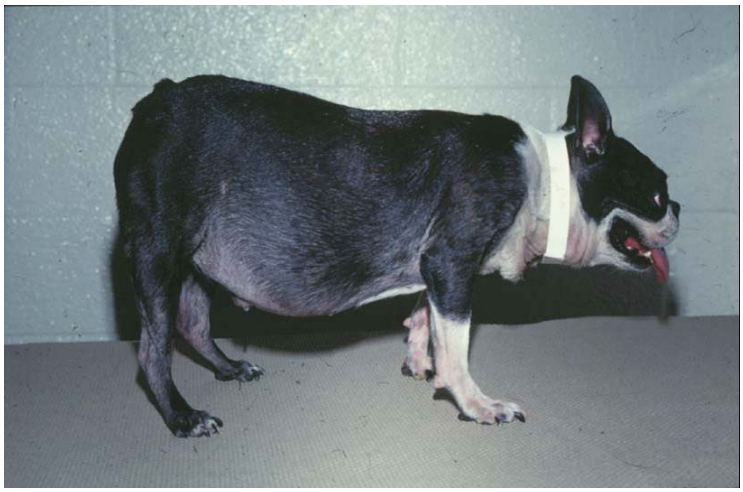
The ACTH stimulation test still has an appropriate place in monitoring. Deciding which test to use is the key to proper assessment and is based on the clinical condition of each patient. Pre-trilostane basal cortisol monitoring should be reserved for dogs clinically doing well. For a dog on trilostane that is feeling well or even still showing signs of Cushing's disease (PU, PD, PP, etc.), it is very reasonable to do a pre-trilostane cortisol level rather than a full stimulation test.

A single cortisol level in dogs feeling ill would probably not be the best choice. For these cases, an ACTH stimulation should always be done. A sick dog's cortisol level may be low but raised to adequate levels with the stimulation test. If just the single cortisol level was used for evaluation, the wrong diagnosis of a cortisol deficiency might be made. The dog may be ill due to a different condition. Dogs not doing well on trilostane therapy should always have an ACTH stimulation test, a more comprehensive evaluation, and possibly additional labwork or diagnostics.

When evaluating the results of a single basal cortisol level in a dog on trilostane, the most important diagnostic criterion, once again, is clinical signs. Is the dog feeling well? Does the dog still have clinical signs of Cushing's? Is the dog showing any new symptoms? What is considered "normal" cortisol levels in a dog on trilostane therapy are controversial, and the values must be considered in relation to clinical signs? If a specific trilostane dose controls a dog's clinical signs and his cortisol levels are above the normal range, keeping the dog on that same trilostane dose is reasonable.

Conversely, if the dogs clinical signs have not improved significantly, and the cortisol levels are within the normal range, increasing the trilostane dose should be considered. Dosage adjustments should always be made based on the dog's clinical signs (particularly resolution of polyuria/polydipsia, polyphagia, etc.) and the cortisol blood levels. It should be noted that if the clinical signs of Cushing's have not improved within a couple of weeks of an increased trilostane dose, it may also be prudent to wait a couple more weeks before increasing the amount of medication as the effects of the given dose of trilostane can often

continue to increase even after the first two weeks of therapy. Thus if a 14-day cortisol level is 9 mg/dl, two weeks later, it could be 5 mg/dl.



As a general guideline for using single pre-trilostane cortisol levels in dogs that are not ill:

If **pre-trilostane cortisol levels are <`-1.5 mg/dl,** then: 1) consider a lower dose, especially if the dose was just increased; 2) If no clinical signs of Cushing's, then consider continuing the same dose. 3) If clinical signs of Cushing's persist, consider increasing to twice daily treatment (if given once daily at the time of testing), or increase the total trilostane dose if already given twice daily. An ACTH stimulation test should be considered if the dosage is to be increased.

If **pre-trilostane cortisol levels are 1.5 mg/dl to 6 mg/dl,** then: 1) if there are no clinical signs of Cushing's, stay on the current dose. 2) If clinical signs of Cushing's, increase the frequency or dosage of trilostane.

If **pre-trilostane cortisol levels are> 6 mg/dl,** then: 1) if there are no clinical signs of Cushing's, stay at the same dose even though the cortisol level is above the normal range. 2) if clinical signs of Cushing's, increase the trilostane dose.

Most all dogs with **cortisol levels above 10 mg/dl** will be clinical for Cushing's and need increased trilostane doses.

Generally, the trilostane dose can be increased by 5 to 10 mg (or 10 to 25%) depending on the cortisol levels, clinical signs, and the patient's size.

Eliminating the need for doing an ACTH stimulation test to monitor dogs on trilostane therapy due to Cushing's disease can significantly affect the chronic care of these patients. Clients may be more compliant in treatment due to the decreased cost and time spent at the clinic. The veterinary practice may benefit from the relative ease of performing a single blood test (lower technician time; able to continue caring for these patients instead of having to refer to specialty practices to do an ACTH stimulation test). Finally, when monitoring dogs on trilostane therapy, the decision to do a stimulation test or just a basal cortisol level needs to be based on each patient's clinical signs and physical exam. The clinical assessment and presence of clinical signs should always be considered when determining if an increase in the trilostane dosage is appropriate, regardless of the monitoring protocol used.

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