Trilostane Treatment and Monitoring: Is the ACTH Stimulation Test Gone for Good?

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Trilostane

Trilostane (Vetoryl®, Dechra Pharmaceuticals) is licensed for use in dogs for the treatment of pituitary-dependent hyperadrenocorticism as well as for hyperadrenocorticism resulting from a functional adrenocortical tumor. It is an orally active synthetic steroid analog that inhibits 3-beta-hydroxysteroid dehydrogenase (and 11-beta hydroxylase) in the adrenal cortex leading to decreased production of cortisol and to a lesser extent aldosterone. Trilostane is not cytotoxic and does not damage the adrenal cortex so withdrawal of the drug should result in a fairly rapid increase in the cortisol concentration unless adrenal necrosis has occurred. Adrenal necrosis is an uncommon complication that can occur during treatment with trilostane, and is thought to be related to an increased ACTH concentration (endogenous and potentially exogenous from repetitive ACTH stimulation testing associated with therapeutic monitoring). Numerous clinical trials have confirmed the efficacy of trilostane for the treatment of hyperadrenocorticism, and the majority of dogs have good clinical response with minimal side effects/complications.

Dosing Recommendations

- The manufacturer recommends starting trilostane therapy at a dose of 2.2 – 6.7 mg/kg (1 – 3 mg/lb) once daily with food (Vetoryl® package insert).
- The most common starting dose in our hospital is 1 – 2 mg/kg (0.5 – 1 mg/lb) every 12 hours with food. Some authors have recommended administering this dose once daily, but in our experience once daily administration in this dosage range (1 – 2 mg/kg) does not provide adequate cortisol suppression and clinical control in most cases.
- Dosing frequency continues to be a topic of debate. While once daily administration may improve compliance and reduce the cost of treatment, it is our experience that twice daily administration of a lower dose results in superior clinical control and reduces the risk of complications associated with excessive cortisol suppression.
- The commercially available capsule sizes (5 mg, 10 mg, 30 mg, 60 mg, 120 mg) allow the targeted dose to be administered to most dogs without the need for compounding. If an additional size is needed, the commercially available product (Vetoryl®) can be reformulated into the appropriate capsule size by a compounding pharmacy.

Monitoring and Dosage Adjustment

Dechra's European division has recently changed the monitoring recommendations for Vetoryl® because of a shortage of synthetic ACTH in Europe. Research performed at the University of Glasgow and surrounding veterinary practices in the United Kingdom found that the pre-trilostane (before the next

dose) resting cortisol concentration correlated better with clinical control than did the post-pill resting (baseline) and/or post-ACTH cortisol concentrations. It is important to recognize that the pre-trilostane resting cortisol is not the same as the post-trilostane resting cortisol (baseline sample of the ACTH stimulation test performed after trilostane administration), which is not a useful monitoring tool. Although multiple research groups have shown that the post-trilostane ACTH stimulation test (historical monitoring approach) is not a very useful monitoring tool, they have been unable to identify an alternative and superior monitoring option. The pre-trilostane (before the next dose) resting cortisol concentration may be a better alternative to the post-trilostane ACTH stimulation test. In Europe, the manufacturer recommends combining clinical assessment with the pre-trilostane resting cortisol concentration (ideal range: 1.5 – 5 μg/dL [40 nmol/L – 140 nmol/L]) to determine if a dosage change is necessary. It is important to note that clinical assessment and the presence of clinical signs should always be considered when determining if an increase in the trilostane dosage is warranted regardless of the monitoring protocol utilized. It should also be noted that using the pre-trilostane resting cortisol concentration for monitoring should be reserved for dogs that are clinically well. Dogs that are exhibiting signs of cortisol deficiency should have a complete evaluation, including an ACTH stimulation test, performed.

Although the monitoring recommendations have not officially changed in the United States, a number of institutions in the US are evaluating the use of the pre-trilostane resting cortisol concentration for monitoring trilostane therapy. Similar to what has been reported by researchers in the UK, we have found the pre-trilostane cortisol concentration and clinical assessment/response to be an effective and safe way to monitor most dogs that are clinically well. If a single cortisol measurement is to be used for monitoring purposes (synthetic ACTH is not available or an ACTH stimulation test cannot be performed because of financial limitations), the pre-trilostane cortisol concentration will likely provide the most clinically useful information.

Current Monitoring Options

- Pre-trilostane resting cortisol concentration (attractive because inexpensive and convenient)
- Post-trilostane ACTH stimulation test (remains most common monitoring protocol in US)
- Pre-trilostane cortisol + post-trilostane ACTH stimulation test (recommended for any dog exhibiting signs of cortisol deficiency)

It is very important that clinical control and/or persistence of clinical signs associated with hypercortisolemia be considered when interpreting the results of any monitoring test/protocol and determining if a trilostane dosage increase is necessary.

Author's recommendations based on the post-ACTH cortisol concentration 2-4 hours after trilostane administration.

Post-ACTH Cortisol Concentration	Recommendation

< 1 μg/dL (< 28 nmol/L)	Stop treatment. Evaluate electrolytes; ACTH stimulation test (off of trilostane) in 2 weeks and/or re-start trilostane at a lower dose if/when clinical signs reoccur.
< 1.8 μg/dL (< 50 nmol/L)	Temporarily stop treatment. Re-start at a lower dose
1.8 – 9.1 μg/dL (50 – 250 nmol/L)	Either: Continue current dose if clinical signs are well controlled Or: Dosage increase based on clinical assessment and persistence of clinical signs
> 9.1 – 16.3 μg/dL (> 250 – 450 nmol/L)	Either: Continue current dose if clinical signs are well controlled Or: Dosage increase based on clinical assessment and persistence of clinical signs
> 16.3 μg/dL (> 450 nmol/L)	Dosage increase based on clinical assessment and persistence of clinical signs

Author's Recommendations Based on the Pre-trilostane Cortisol Concentration (modified from the Pre-Vetoryl® Cortisol monitoring guidelines; Dechra Europe)

Pre-trilostane Cortisol Concentration	Recommendation
< 1 – 1.5 μg/dL (< 28 – 40 nmol/L)	Consider a lower dose
1.5 – 5 μg/dL (40 – 140 nmol/L)	No clinical signs of HAC- continue current dose Or: Increase dosage or dosing frequency (once to twice daily) if inadequate clinical control/persistent clinical signs
3 – 5 μg/dL (80 – 140 nmol/L)	No clinical signs of HAC- continue current dose Or: Increase dosage or dosing frequency (once to twice daily) if inadequate clinical control/persistent clinical signs
> 5 μg/dL (> 140 nmol/L)	No clinical signs of HAC- continue current dose Or: Increase dosage or dosing frequency (once to twice daily) if inadequate clinical control/persistent clinical signs

Monitoring Frequency and Recommended Testing

- 10 – 14 days after initiating therapy or a dosage change: confirm that the dog is clinically well; no hormone testing necessary if no signs of cortisol deficiency

- 4 – 6 weeks: cortisol monitoring (see Current Monitoring Options)
- 2 – 3 months: cortisol monitoring (see Current Monitoring Options)
- 4 – 6 months: cortisol monitoring (see Current Monitoring Options), electrolytes
- Recommend re-evaluation 2 – 3 times per year as long as the dose is stable, clinical signs are well-controlled, and the dog is doing well.

Dosage Adjustment

- Dosage adjustments should be based on a combination of clinical assessment (persistence of clinical signs) and serum cortisol concentrations.

- The trilostane dose should be increased by 5 – 10 mg/dose depending on the cortisol concentrations, severity of clinical signs, size of the dog, current dose, and frequency of administration.

- If the dog is receiving once daily trilostane and the cortisol concentrations are within the recommended/acceptable ranges but clinical signs are not well-controlled (persistent polyuria, polydipsia, polyphagia, and/or other signs), divide the dose and administer twice daily. If the cortisol concentration(s) are above the recommended range(s), divide the dose for twice daily administration and increase by 10-25%.

References

References available upon request.