THE ENDGAME The primary goals of trilostane therapy are resolving clinical signs of hyperadrenocorticism and avoiding oversuppression of the adrenal axis.

FOCUS ON

Trilostane for Dogs With Hyperadrenocorticism

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Trilostane (Vetoryl; Dechra, dechra.com) is approved by the U.S. Food and Drug Administration (FDA) for the medical management of dogs with pituitary-dependent hyperadrenocorticism (PDH) as well as adrenal-dependent hyperadrenocorticism (ADH). It is supplied as a capsule to be given orally, with the dosage adjusted based on the individual patient response, including monitoring of clinical signs and results of laboratory testing. Treatment should be reserved for those patients with a definitive diagnosis of hyperadrenocorticism established by appropriate testing and compatible clinical signs.

The author's 2 main goals of trilostane treatment are to improve quality of life/resolution of clinical signs and to avoid oversuppression of the adrenal axis. Although the FDA label for trilostane is for once-daily dosing, the author has better success using a lower, twice-daily dosing regimen.

MECHANISM OF ACTION

Trilostane is an orally active synthetic steroid analogue that competitively inhibits the enzyme 3-β-hydroxysteroid dehydrogenase within the adrenal cortex. Inhibition of this enzyme reduces synthesis of cortisol and, to a lesser extent, aldosterone and adrenal androgens (sex hormones). Inhibition is dosage dependent and reversible, although adrenal necrosis is possible.[1,2]

PHARMACOKINETICS

Trilostane is administered orally. Absorption is enhanced when administered with food, and thus it is recommended to give with food, including on days when rechecks are scheduled.[1,3] Plasma trilostane levels peak approximately 1.5 to 2 hours after drug administration and return to baseline within 12 hours.[1]

Caution should be used when considering compounded trilostane. One study evaluated compounded trilostane products from 8 compounding pharmacies, as well as capsules compounded from the licensed product.[4] Results showed that 38% of the batches from compounding pharmacies failed to meet an acceptance criterion for trilostane content of 90% to 105% of label claim (or amount claimed to be in the capsule), and that the trilostane content of batches from compounding pharmacies ranged from 39% to 152.6% of label claim.[4] All batches compounded from the licensed product met acceptance criteria for content. The author prefers to prescribe Vetoryl capsules when possible, and if compounded trilostane is absolutely needed for an individual patient, only trilostane compounded from Vetoryl is used.

CLINICAL APPLICATIONS

Once hyperadrenocorticism is diagnosed and medical management is chosen, oral dosing with trilostane can be initiated. The FDA label for trilostane describes a starting dose range of 2.2 to 6.7 mg/kg q24h and recommends starting with the lowest possible dose based on body weight and available combination of capsule sizes.[1] Based on the literature and extensive clinical experience, the author instead uses a lower-dosage, twice-daily dosing strategy of 0.8 to 1 mg/kg PO q12h (with food).[2,5,6] The author also recommends twice-daily trilostane dosing in diabetic dogs, as breaks in control of hyperadrenocorticism could be detrimental.[7] The author concurrently dispenses oral dexamethasone at a dosage of 0.15 mg/kg, for use only in a possible addisonian crisis.

MONITORING THERAPY

The author evaluates patients at each recheck with 2 main goals of therapy in mind: improve quality of life/resolve clinical signs and avoid oversuppression of the adrenal axis (hypocortisolism).

Quality of Life and Clinical Signs

Owners present dogs for evaluation due to the development of clinical signs seen at home. Treatment is aimed at resolving these clinical signs to bring a good quality of life to the patient as well as the owner. The most common clinical signs in dogs with hyperadrenocorticism include polyuria, polydipsia, polyphagia, weight gain, pot-bellied appearance, and alopecia.[8] Owners may also describe dogs as "slowing down" and having less energy.

It is vital to identify the clinical signs the owners are seeing at home and quantify the severity of each, both before therapy and at each recheck, to help decide if there is room for improvement with therapy. The author uses a questionnaire at each recheck to help assess improvement over time.

Suppression of the Adrenal Axis

The author uses cortisol testing to ensure it is safe to continue therapy, or to increase the dose if the patient is not well controlled, in an effort to avoid oversuppression. He does not use cortisol testing to decide whether a patient is well controlled; rather, this assessment is based on clinical signs and the owner's perception of how the patient is doing at home.

For example, if cortisol test results fall in the "ideal range" (see **Adjusting Therapy**) but the patient still displays clinical signs, the patient is not receiving the correct dosage/frequency and additional strategies need to be employed to better control the clinical signs. If the patient is well controlled (no clinical signs of hyperadrenocorticism) but measured cortisol is too low, recommendations are to stop or decrease the trilostane dosage until cortisol testing determines the axis has recovered. If the patient is exhibiting clinical signs of hypocortisolism (e.g., lethargy, vomiting, diarrhea, anorexia, collapse) and measured cortisol is too low, recommendations are to stop trilostane therapy and treat for hypoadrenocorticism accordingly.

The traditional way to monitor cortisol values during therapy is with an adrenocorticotropic hormone (ACTH) stimulation test. Alternatively, the pre-pill cortisol concentration may be useful for monitoring some patients. One study showed that this measure correlated better with clinical signs than the post-ACTH cortisol value.[9]

ACTH Stimulation Testing

This is the traditional method of monitoring cortisol values during treatment with trilostane. The ACTH stimulation test is performed 4 to 6 hours after administration of trilostane and ideally at the same time for all rechecks for an individual patient. The dosage of cosyntropin for the ACTH stimulation test used during trilostane therapy has traditionally been 5 µg/kg, but a recent study showed that a dosage of 1 µg/kg can also be used for monitoring during trilostane therapy (but not for the diagnosis of hyperadrenocorticism).[10]

Pre-Pill Cortisol Testing

Pre-pill cortisol testing is a new method the author uses to monitor therapy in certain patients. The best way to utilize this test has not been determined. The author uses it only in clinically well dogs that do not show signs of possible hypoadrenocorticism. Testing involves collecting a serum sample at the end of the dosing interval, just before the next dose of trilostane. Again, the author uses this test, with its single value, to demonstrate the adrenal axis is not being oversuppressed.

Pre-pill cortisol testing may help offset the cost of the ACTH stimulation test, as only a single cortisol

measurement is needed. However, it must be coordinated with the owner's dosing schedule so the patient can be tested at the end of the dosing interval. Also, if the result is low (see **Adjusting Therapy**), an ACTH stimulation test must then be performed, which can be frustrating for some owners.

Schedule

The first recheck should be scheduled for 10 to 14 days after starting therapy or adjusting dosage (or sooner if the dog becomes unwell for any reason). The author does not increase the trilostane dose at the first recheck, but instead uses this recheck to ensure the adrenal axis is not oversuppressed (cortisol <2). The dosage is not adjusted at this time because additional suppression may be seen over a full month at the same dose. The next recheck is then at 1 month.

Once an optimal dosage of trilostane is achieved, the patient is rechecked at 3 months and then every 3 to 6 months thereafter. If the dosage needs to be increased due to ongoing clinical signs, increments are often in the range of 10% to 50%, depending on the severity of clinical signs and measured cortisol values. Alternatively, the dosing frequency can be adjusted (e.g., from once daily to twice daily, or even from twice daily to 3 times daily). If trilostane therapy needs to be stopped owing to oversuppression/iatrogenic hypoadrenocorticism and then restarted based on recurrence of clinical signs and appropriate cortisol testing, the author restarts therapy at a dose reduced by at least 50%.

At each recheck, time should be spent with the owner to evaluate how well therapy is controlling the clinical signs. Use of a standard questionnaire can help keep this evaluation consistent. Tests performed at these visits should include cortisol testing (ACTH stimulation or pre-pill cortisol testing, based on preference and comfort of veterinarian) and a serum chemistry panel, with particular attention to electrolytes as well as renal and hepatic function.

ADJUSTING THERAPY

As mentioned above, cortisol testing is used to ensure it is safe to continue a certain dosage if the patient is doing well clinically or safe to increase a dosage if the patient still has clinical signs, or to determine if the adrenal axis is oversuppressed.

FDA Label Recommendations

The following are used to guide decisions based on the post-ACTH stimulation cortisol values.[1]

- **Cortisol <1.45 µg/dL:** Stop treatment. Restart at a decreased dose.
- **Cortisol between 1.45 and 5.4 µg/dL:** Continue on the same dose.
- **Cortisol between 5.4 and 9.1 µg/dL:** Continue on the current dose if clinical signs are well controlled or increase the dose if clinical signs are still present.
- **Cortisol >9.1 µg/dL:** Increase initial dose.

Clinical Examples

The author uses the following guidelines in his patients.

ACTH Stimulation Testing

First Recheck After Starting Therapy

- **Cortisol <2 µg/dL:** Stop therapy. Restart at a lower dose once the adrenal axis recovers.
- **Cortisol ≥2 µg/dL and no clinical signs of hypocortisolism:** Continue on same dosage. If cortisol is closer to 2, you could also consider a dosage decrease.

Subsequent Rechecks

If the patient has been on the current trilostane dose for 4 weeks or more with no clinical signs of hypocortisolism:

- **Cortisol <1.6 µg/dL:** Choose one of the following options.
  - Stop therapy. Restart at a lower dose once the adrenal axis recovers.
  - Decrease dosage (25% to 50%) and perform ACTH stimulation test in 2 weeks.
  - Repeat the ACTH stimulation test 9 to 12 hours after administration of current trilostane dose to assess recovery of the adrenal axis later in the dosing interval (see below).
- **Cortisol ≥1.6 µg/dL:**
  - If there is resolution of clinical signs, continue on same dose.
  - If the patient has ongoing clinical signs, consider increasing the dose or frequency depending on the current cortisol value and dosage/frequency. If dosing is once daily, consider splitting the dose in half and giving as twice-daily dosing. Alternatively, the dosage could be increased if the cortisol is high enough (the author currently uses a cortisol value >4).

In general, if cortisol measured by ACTH stimulation testing is too low in a well-controlled dog (<1.6 µg/dL in a dog with resolution of clinical signs of hyperadrenocorticism), an option other than stopping or decreasing therapy is to consider performing the ACTH stimulation test 9 to 12 hours after dosing. In one study, dogs well-controlled for hyperadrenocorticism and showing no clinical signs of hypoadrenocorticism that had low post-ACTH stimulation cortisol levels showed an increase in cortisol at the later ACTH stimulation test, supporting continuation of treatment at the current dose.[11] If the ACTH stimulation test is performed 9 to 12 hours after dosing and cortisol is still too low, trilostane therapy should be stopped or decreased and cortisol testing rechecked to ensure recovery of the adrenal axis.

Pre-Pill Cortisol Testing

If the patient is clinically well (no clinical signs of hypocortisolism) with well-controlled clinical signs of hyperadrenocorticism:

- **Cortisol <2 µg/dL:** Complete an ACTH stimulation test or decrease trilostane dose.
- **Cortisol ≥2 µg/dL:** Likely safe to continue the current dose.

If the patient is clinically well (no clinical signs of hypocortisolism) with persistent clinical signs of hyperadrenocorticism:

- **Cortisol <2 µg/dL:** Perform an ACTH stimulation test.
- **Cortisol between 2 and 5 µg/dL:** Best to perform an ACTH stimulation test. If trilostane is being given once a day, consider splitting the dose and administering twice daily. The author increases the dose if cortisol is >3.
- **Cortisol >5 µg/dL:** Likely safe to increase dose or frequency.

EFFICACY

The author considers trilostane to be highly effective for successful treatment of canine PDH, and it is his treatment of choice for medical management of this condition. Trilostane can also be considered for medical management of ADH. When comparing mitotane with trilostane, there appears to be no difference in effectiveness or survival.[12,13] Both drugs have advantages and disadvantages, and the veterinarian overseeing the case ultimately must choose which drug to use based on their comfort with it and the specifics of the case.

BENEFITS, ADVERSE EFFECTS, AND CONTRAINDICATIONS

Treatment with trilostane is not curative, and adjustments in therapy may be needed over time to medically manage hyperadrenocorticism. The benefit of therapy is a resolution of clinical signs. Patients vary in how fast therapy works to resolve clinical signs. In general, with appropriate treatment and monitoring, polyuria, polydipsia, polyphagia, panting, and energy levels should improve in a period of weeks. However, improvement in the hair coat often takes months.

Adverse effects of trilostane therapy are seen in some dogs. Mild lethargy and a decreased appetite can be seen within a few days of initiating therapy.[14] Iatrogenic hypocortisolism can occur during trilostane therapy, caused by excessive enzyme inhibition or by the more serious and life-threatening complication of adrenal necrosis, which may result in an addisonian crisis.[15]

Distinguishing between excessive enzyme inhibition and adrenal necrosis can be challenging, and owners need to be advised to watch for clinical signs such as gastrointestinal upset (e.g., vomiting, diarrhea, inappetence), lethargy, collapse, or any other signs of being unwell. *If an addisonian crisis is suspected, owners are to **stop** trilostane, administer oral dexamethasone, and seek immediate veterinary care.* Cortisol testing should be with an ACTH stimulation test. The adrenal axis may or may not recover. If the axis recovers, clinical signs of hyperadrenocorticism often return and necessitate starting trilostane therapy at a lower dose. However, if the axis does not recover, ongoing treatment for hypoadrenocorticism will be needed.

Drug interactions are possible. Caution should be used with angiotensin-converting enzyme inhibitors in patients receiving trilostane, and potassium-sparing diuretics should not be used in patients on trilostane.[1] Concurrent administration of ketoconazole and trilostane should be undertaken with extreme caution or not at all, as ketoconazole can cause iatrogenic hypoadrenocorticism at typical antifungal dosages and its addition to trilostane therapy could cause hypoadrenocorticism.[16] Trilostane should not be used in dogs with primary hepatic disease or renal insufficiency and should not be used in pregnant dogs or handled by pregnant women.[1] TVP

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Disclosure

Dr. Archer has received speaking fees from Dechra Veterinary Products.