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Update on the Use of Trilostane

You have asked...

How is trilostane currently used to treat PDH in dogs?

Illustration by Bill Celander

The expert says...

As a synthetic steroid analog that inhibits the adrenocortical enzyme 3-beta-hydroxysteroid dehydrogenase, trilostane (Vetoryl, dechra.com) suppresses production of progesterone and its end products, including cortisol and aldosterone. Additional enzymes such as 11-beta-hydroxylase and 11-beta-hydroxysteroid dehydrogenase may also be affected.[1] Trilostane is approved by the U.S. Food and Drug Administration (FDA) for the treatment of canine hyperadrenocorticism.

Overall, trilostane is highly effective in suppressing cortisol secretion and controlling clinical signs in dogs with pituitary-dependent hyperadrenocorticism (PDH).[2-8] Clinical signs typically resolve quickly with control of cortisol concentrations, but some abnormalities, including dermatologic manifestations, can take up to 3 months, and others, such as calcinosis cutis, may never fully resolve. A small proportion of dogs with PDH are not well controlled with trilostane.[5,8,9]

The doses and warnings associated with trilostane treatment of PDH have changed over time. Some areas are still controversial.

DOSE

Originally, the recommended starting dose for trilostane in Europe was 2 to 10 mg/kg Q 24 H. However, as experience with the drug grew, it became apparent that lower doses were needed. Accordingly, the dosing recommendation on the U.S. package insert is 2.2 to 6.7 mg/kg Q 24 H.

CONTINUES

PDH = pituitary-dependent hyperadrenocorticism

UCCR & Monitoring

- An early study found that the urine cortisol:creatinine ratio (UCCR) before administering trilostane could be an indication of duration of action, but 2 later studies yielded conflicting results.[2,5,13]
- Interestingly, in one report of 6 dogs that had UCCRs within the reference range "most of the time," 3 developed hypocortisolism (Addison's disease) and hypocortisolism was suspected but not confirmed in the other 3 dogs.[13]

Further research is needed to determine whether UCCR will prove useful as a monitoring tool.

The ACTH stimulation test should be started according to the package insert, that is, 4 to 6 hours after trilostane administration.

Whether to start with once- or twice-daily administration is controversial. Although most dogs are controlled clinically with once-daily dosing (ie, clinical signs apparent to the owner resolve), trilostane may begin losing effectiveness 8 to 10 hours after administration,[2,10,11] so twice-daily dosing may be necessary.[2-4] In addition, the efficacy of once-daily dosing in controlling all complications of PDH, such as proteinuria or hypertension, is unknown.

My recommended starting dose is either 2 mg/kg Q 24 H or 1 mg/kg Q 12 H, with adjustments made as needed based on adrenocorticotropic hormone (ACTH) stimulation testing. Until it is proven which treatment approach is better, I prefer to start with a twice-daily regimen if the owner agrees because controlling cortisol concentration throughout as much of the day as possible makes sense. In diabetic patients with hyperadrenocorticism, twice-daily dosing is absolutely recommended to avoid large fluctuations in serum cortisol concentrations. In approximately 50% of dogs, dose adjustments, either up or down, are required during treatment. The authors of one study noted that in most dogs an initial sensitivity to the drug existed, followed by a need for a dose increase. After time, the dose required often reached a plateau.[5]

TIMING POSTPILL MONITORING

An ACTH stimulation test must be conducted to evaluate therapy. However, the optimal post-ACTH serum cortisol concentration and timing of sampling remain to be elucidated. Cortisol concentrations may vary with the interval between dosing and testing.[10] In accordance with the package insert, I recommend starting the ACTH stimulation test 4 to 6 hours after administration. It is helpful to time postpill ACTH testing consistently.

Other timing strategies have been reported but are not currently recommended. Baseline cortisol concentration has been evaluated as a monitoring tool[12]; however, because the clinical status of the study dogs was not reported, the results are difficult to interpret. In addition, baseline cortisol concentration was deemed adequate only for dogs doing well clinically and whose basal concentration fell within a narrow range. For twice-daily therapy, although one study suggested starting the test 8 to 12 hours after dosing,[4] such timing has not been critically evaluated.

TIMING DOSE ADJUSTMENTS

Once trilostane therapy has been initiated, a recheck should be performed at 10 to 14 days or sooner if needed. Recommendations for when to alter dose have become less stringent. The dose should be raised at the first recheck only if the owner reports no improvement, clinical signs are still striking, and the post-ACTH cortisol concentration is markedly above ideal. If any improvement is noted, the dose should remain the same as long as cortisol concentrations are within the ideal range or higher. Current impression is that basal and ACTH-stimulated cortisol concentrations continue to decrease until the 4-week recheck even if the same trilostane dose is administered. If the basal or ACTH-stimulated cortisol concentrations are below ideal at any time, trilostane administration should be discontinued temporarily and the dose decreased when resumed. If no adjustment was made at the first recheck, a second recheck should be done at about day 30 after initiating trilostane administration. Future rechecks are based on the dog's

Check It Out!

See page 32 for a handy algorithm on trilostane treatment for PDH and page 35 for a capsule on atypical Cushing's.

ACTH = adrenocorticotropic hormone, PDH = pituitary-dependent hyperadrenocorticism, UCCR = urine cortisol:creatinine ratio

clinical progress, previous ACTH stimulation test results, and whether dose adjustment was needed.

SAFETY

A majority of reported adverse effects, including lethargy and vomiting, are relatively mild, but fatalities have occurred.[5,8,9] Although some studies reported a relatively low incidence of side effects, one non–peer-reviewed report states mild, self-limiting side effects such as diarrhea, vomiting, and lethargy occur in 63% of treated dogs.[14] Since the clinical signs of drug toxicity and hypocortisolemia are the same, an ACTH stimulation test is usually required to differentiate them.

As with mitotane therapy, excess adrenal gland suppression can occur and warrants discontinuing trilostane administration temporarily. Although in theory the effects of trilostane as an enzyme inhibitor should be rapidly reversible (ie, within a couple days), suppression can last weeks to years.[4,5,15,16] With oversuppression, recommendations from many sources are to simply discontinue the medication for a few days and then begin again at a reduced dose. I prefer to perform an ACTH stimulation test to document return of function first. One dog developed hypocortisolism after only 3 doses of trilostane and it lasted at least 1 year.[15]

Adrenal necrosis can occur secondary to trilostane administration.[17] The hypoadrenocorticism reported after complete adrenocortical necrosis in one dog lasted at least 3 months but likely would be permanent. How often acute iatrogenic hypoadrenocorticism will occur with trilostane is unknown but is likely more common than originally believed. In one study, 4 of 6 dogs with PDH and 1 dog with adrenal tumor treated with trilostane had some degree of adrenal necrosis at necropsy.

FIND MORE

For additional information about canine PDH, see **Do These Dogs Have Cushing's Disease?** (February 2009) & **Low-Dose Dexamethasone Suppression Testing for Hyperadrenocorticism** (October 2010) at **cliniciansbrief.com**

TX AT A GLANCE

Starting dose of trilostane for PDH treatment:

- 2 mg/kg Q 24 H ***or***
- 1 mg/kg Q 12 H
- Q 12 H administration is preferred if the owner will comply but is absolutely recommended for diabetic dogs to stabilize serum cortisol concentration.

- Recheck at 10 to 14 days or sooner if adverse events are noted; if any improvement occurs, the dose should not be changed if the cortisol concentrations are ideal or above.
- If no adjustment is made at the first recheck, recheck at about day 30 after initiating trilostane administration, as dose adjustments are generally needed.
- The need for future rechecks is based on clinical progress, previous test results, and whether a dose adjustment was needed.