



# TRILOSTANE FOR THE TREATMENT OF CANINE CUSHING'S DISEASE

Dr. Katrina Smith, Internal Medicine

24 Hour Emergency & Referral Hospital

Hyperadrenocorticism, or Cushing's disease, is one of the most common endocrinopathies in dogs. Spontaneous Cushing's disease results from a chronic excess production of glucocorticoids by the adrenal glands. In most cases, this occurs because of over-production of adrenocorticotropic hormone (ACTH) by a benign pituitary microadenoma (pituitary-dependent disease). However, approximately 15% of cases are the result of a functional (cortisol secreting) adrenal gland tumour.

Treatment of Cushing's disease can be both medical and surgical, although the latter is most often offered in the presence of an adrenal gland tumour. Mitotane has long been the standard medical therapy for pituitary-dependent hyperadrenocorticism (PDH); this cytotoxic agent causes necrosis of the zona fasciculata and zona reticularis of the adrenal glands. Side effects, particularly gastrointestinal, are quite common, and some dogs will develop signs of acute life-threatening hypoadrenocorticism. More recently, the use of trilostane has provided an excellent alternative medical therapy for PDH that is potentially safer for our patients.

Trilostane is a synthetic steroid that competitively inhibits steroid synthesis by blocking the 3 $\beta$ -hydroxysteroid dehydrogenase enzyme. Trilostane is safer to handle than mitotane, and very well tolerated by most dogs. Signs of hypoadrenocorticism are uncommon, and generally respond quickly to appropriate therapy. However, some dogs have developed surprisingly prolonged adrenal suppression secondary to adrenocortical necrosis with trilostane, and careful monitoring is therefore required.

Trilostane (Vetoryl) is available as 30-, 60-, and 120-mg capsules, or can be formulated in other dosage strengths. The recommended starting dose ranges from 3-6 mg/kg given once daily, although some authors recommend a lower starting dose of 1-2.5 mg/kg, particularly in small dogs. It is common for dose adjustments to be required, and some dogs will take much higher doses (40-50 mg/kg/day) without apparent side effects. Trilostane is absorbed better if given with food. Mild lethargy, decreased appetite, and slight electrolyte abnormalities can be seen at the initiation of therapy; with more serious lethargy, anorexia, vomiting, or diarrhea, trilostane should be stopped and prednisolone given for 1-2 days.

Dose adjustments are best determined by clinical response and results of an ACTH stimulation test. This should be done at 7-14 days, 30 days, and 90 days after first starting therapy, or after a change in dose. ACTH stimulation tests should be started at 4 hours after dosing for the best results. Post-ACTH cortisol concentrations should be between 40 and 150 nmol/L. If the value is lower than 40 nmol/L, trilostane is stopped for 5-7 days and then reinstated at a lower dose. If the value is higher than 150 nmol/L, the dose may need to be increased, particularly if there is no improvement in clinical signs after 30 days. In dogs that are showing a clinical response, but the post-ACTH cortisol level remains higher than 150 nmol/L, twice daily administration is likely required. PU/PD and polyphagia will typically resolve within four weeks; skin changes should resolve within four months. Once the clinical condition and the dose have been stabilized, an ACTH stimulation test should be done every three months. Relapses can occur with treatment of Cushing's disease, and further dose adjustments may need to be made. Long-term adverse effects of trilostane have not yet been documented, but increased adrenal gland size may occur. Median survival time for dogs with PDH treated with trilostane has been reported as 662 days (range 8-1971 days), similar to that reported for dogs treated with mitotane.

There are isolated case reports documenting the use of trilostane with adrenocortical neoplasia, in which improved clinical signs, lower post-ACTH cortisol concentrations, and extended survival times have been reported, suggesting that trilostane may be an effective palliative treatment for this disease as well.

