# Updates in Canine Hyperadrenocorticism

In Australia, canine hyperadrenocorticism resulting in hypercortisolaemia is most commonly managed with medication, with surgical options such as adrenalectomy for adrenal tumours or hypophysectomy for the pituitary form being uncommonly to rarely performed.

Vetoryl® (trilostane) is a safe and effective reversible enzyme inhibitor of cortisol production.

## TRADITIONAL MONITORING

In order to monitor treatment efficacy, ACTH stimulation tests, using synthetic ACTH in the form of Synacthen, have traditionally been used.

When performing ACTH stimulation tests at 10 days, 28 days and 3 months after starting Vetoryl® and for every dose change, then every 3 months once a stable dose has been reached, the cost to the client is significant. Additionally, Synacthen has been unavailable for purchase in Australia at times, and Synacthen Depot, a possible alternative, continues to increase in price.

## UPDATES IN MONITORING

While ACTH stimulation tests are the main test used for monitoring treatment, a lack of correlation between post-ACTH cortisol levels and clinical control (based on owner questionnaires) has been demonstrated[1].

Another recent study[2] demonstrated that while pre-trilostane cortisol, three-hour post trilostane cortisol and post-ACTH cortisol levels all correlated with clinical control, pre-trilostane and 3-hour post trilostane cortisols were better at differentiating between dogs with excellent control and those that were under-controlled.

In making that differentiation, they summarised the sensitivity and specificity of each test as follows:

| Cortisol | Cut-off | Sensitivity | Specificity |
|---|---|---|---|
| Pre-trilostane | ≤ 138nmol/L | 55.4% | 86.5% |
| 3-hour-post trilostane | ≤62nmol/L | 58.9% | 81.1.% |
| Post-ACTH | ≤130nmol/L | 41.1% | 70.3% |

Note that all dogs enrolled in the study had been treated with Vetoryl® for at least 10 days, with a median treatment duration at their current dose (median 3.47mg/kg/day) of 2 months.

This study resulted in a suggested target range for pre-trilostane cortisol of greater than 40nmol/L and less than 138nmol/L. The lower limit of 40nmol/L was chosen as levels above this usually exclude hypoadrenocorticism in trilostane-treated dogs, and a cut-off of 138nmol/L was chosen to maximise the specificity of results.

## PRE-VETORYL CORTISOL (PVC)

This study has resulted in a monitoring protocol for Vetoryl® known as Pre-Vetoryl Cortisol testing. The dog is started on 2mg/kg Vetoryl® SID, examined at day 10, and if clinically well, maintained on that dose until day 28.

At day 28, a clinical evaluation determines if the dog is still symptomatic for hypercortisolism. A PVC is performed, assessed in relation to clinical signs, and if the PVC is outside of the reference range of 40-138nmol/L, the dose is adjusted appropriately.

If the dose has been adjusted, the process then starts again with examinations at days 10 and 28, and a PVC at day 28. Once the dose is stable, a clinical examination and a PVC are performed every 3 months.

If the dog is clinically unwell at any point, a standard ACTH stimulation test is performed and dose adjustments made as necessary.

The protocol emphasises the importance of a clinical evaluation by the veterinarian, and not just a reliance on a numerical test result.

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## CONCERNS WITH PVC

While it is tempting to adopt a protocol that is significantly cheaper than the alternative and is independent of the availability of Synacthen, it warrants careful consideration and relies heavily on the veterinarian's clinical experience with treating hypercortisolaemia.

The protocol uses a basal cortisol measurement, a value which is widely regarded as variable – a study of 351 dogs with non-adrenal illness demonstrated basal cortisol levels between 5.5nmol/L and approximately 700nmol/L[3], while a study of 30 healthy young dogs preparing to undergo ovariohysterectomy had a mean basal cortisol level of 174.6nmol/L with a standard deviation of 78.5[4].

Additionally, PVC testing assesses the effectiveness of a drug, by measuring the biological parameter affected by that drug, once the drug has worn off. This is an uncommon concept, and should not be confused with testing trough serum levels of the actual drug itself, as used in say phenobarbital monitoring.

Finally, the upper limit of the reference range, and the concept itself, is based on a single paper, so it has been suggested by various laboratories and specialists here in Australia that the protocol should not be adopted until further research has been done. There is a wealth of experience in monitoring and adjusting doses using ACTH stimulation tests, and therefore this is likely to be the continued recommendation until further information is available.

## OTHER WAYS TO REDUCE COST

As expense is one of the main concerns in performing ACTH stimulation tests, we should consider ways to reduce the cost. Testing only a post-ACTH cortisol and forgoing the basal cortisol has been recommended by some specialists. It is also well accepted that lower amounts of Synacthen can be used for monitoring tests. Dermcare recommends using 1-5µg/kg Synacthen IV, which is 0.2mL Synacthen for any dog from 10-50kg. For dogs <10kg, 5µg/kg can used. A vial of Synacthen can be frozen into 0.2mL aliquots for up to 6 months[5].

For further information, please discuss your requirements for testing with your laboratory, who will be able to advise you on their recommended protocols and reference ranges. For cases where Vetoryl® is being used, Dermcare provides comprehensive technical advice.

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The most important aspect of management is a thorough assessment of the control of clinical signs. Our aim is to improve the quality of life of the patient.

[1]Boretti et al (2016) Lack of association between clinical signs and laboratory parameters in dogs with hyperadrenocorticism before and during trilostane treatment. Schweiz Arch Tierheilkd, 158:631-638.
[2]Macfarlane et al (2016) Pre-trilostane and three-hour post-trilostane cortisol to monitor trilostane therapy in dogs. Veterinary Record, 179:597-605.¬
[3]Gold et al (2016) Evaluation of basal serum or plasma cortisol concentrations for the diagnosis of hypoadrenocorticism in dogs. Journal of Veterinary Internal Medicine, 30:1798-1805.
[4]Srithunyarat et al (2016) Catestatin, vasostatin, cortisol, temperature, heart rate, respiratory rate, scores of the short form of the Glasgow composite measure pain scale and visual analog scale for stress and pain behaviour in dogs before and after ovariohysterectomy. BMC Research Notes, 9:381.
[5]Frank and Oliver (1998) Comparison of serum cortisol concentrations in clinically normal dogs after administration of freshly reconstituted versus reconstituted and stored frozen tetracosactrin. Journal of the American Veterinary Medical Association, 212:1569-1571.

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