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HoW I TREAT PITUItARY DEPENDANT HYPERADRENOcORTICoSM

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Trilostane
Currently the most common method for treating pituitary-dependent hyperadrenocorticism (PDH) in Europe is oral administration of trilostane on a daily basis. Trilostane is a synthetic, orally active steroid analogue that competitively inhibits 3β hydroxysteroid dehydrogenase and hence synthesis of several steroids, including cortisol and aldosterone. This competitive inhibition is reversible and seems to be dose-related. There is also increasing evidence to suggest that trilostane may modify peripheral conversion of cortisol to cortisone and cause some degree of adrenocortical destruction in dogs with PDH.

In dogs peak trilostane concentrations are seen within 1.5 hours of dosing and decrease to baseline values in about 18 hours. Trilostane is variably absorbed after oral administration, at least partly due to its poor water solubility. Absorption may be enhanced by administering the drug with food although this phenomenon has not been investigated in dogs with hyperadrenocorticism. Trilostane's safety as well as both short and long term efficacy in controlling hyperadrenalism in dogs has been documented in a number of abstracts and four controlled studies utilising a total of 180 dogs with a follow-up period of 180 days or more.

Trilostane caused a significant reduction in both the mean basal and post-ACTH cortisol concentrations after 10 days of treatment in all four studies. In one study the post-ACTH cortisol concentration decreased to less than 250 nmol/l within one month in 81% of dogs and in another 15% at some time whilst on treatment. These improvements were maintained in the study population for the duration of the trial. In the study targeting lower post-ACTH cortisol values, all dogs were well or acceptably controlled (post ACTH cortisol ≤ 75 nmol/l and ≤ 125 nmol/l respectively) although as mentioned previously, in some dogs these goals were only obtained by marked increases in the daily dose.

Using trilostane, the time to clinical remission and long-term survival rates are similar to those of mitotane. Clinical improvement is usually seen within 2 weeks of starting trilostane and in those dogs that respond to trilostane, adequate control is invariably achieved within 30 days of starting medication. In a recent report comparing survival times for PDH dogs, median survival time for those treated with trilostane was 662 days (range 8-1,971) and for mitotane it was 708 days (range 33-1,399). It is important to remember the required dose rate is variable and patients need to be monitored regularly with an ACTH stimulation test within 4-6 hours of trilostane's administration if a consistent and satisfactory level of adrenal suppression is to be achieved.

Dose rate
The current suggested starting dose rate for dogs with PDH is 5-12 mg/kg once daily given with food. As trilostane is supplied in 30, 60 and 120 mg capsules, generally dogs weighing under 5 kg receive 30 mg per day, those between 5 and 20 kg receive 60 mg per day and dogs over 20 kg in body weight receive 120 mg per day. In some dogs twice daily dosing has been explored in an attempt to achieve adequate adrenal suppression.

Re-evaluation
Because of individual variation it is imperative that each animal is re-evaluated regularly with both a clinical examination and ACTH stimulation test and the dose adjusted based on these findings. Generally control can be reliably achieved in approximately 80% of cases if dogs are re-examined and an ACTH stimulation test performed approximately 10 to 14 days, 30 days and 90 days after starting therapy. It is important that all ACTH stimulation tests are performed 4 to 6 hours after trilostane administration and interpreted in conjunction with the clinical findings. If the post-ACTH cortisol concentration is below the sensitivity of the assay (generally 30 nmol/L) the trilostane dose may be reduced. If the post-ACTH cortisol concentration is more than 1.5 times the upper limit of the basal cortisol's normal range then the dose of trilostane is increased. If the post-ACTH cortisol concentration is between these two values and the patient appears to be clinically well controlled then the dose should remain unaltered. If the post-ACTH cortisol suggests adequate adrenocortical suppression but clinical signs are not well controlled sometimes improved control can be achieved by administering trilostane twice daily.

Estimating urinary corticoid-creatinine ratio has proved a poor method of monitoring trilostane therapy, at least partly because of increased urinary secretion of cross-reacting 17keto-steroid metabolites. In the future estimation of endogenous ACTH values may be a valuable method of individualising the trilostane dose.

Once the clinical condition of the animal and trilostane dose has been stabilized, dogs should be examined and an ACTH stimulation test performed every 3 to 6 months.
Serum biochemistry (especially electrolytes) should be performed periodically to check for hyperkalaemia.

Based on the results of these ACTH stimulation tests, regular dose adjustments can be made to achieve ongoing satisfactory adrenal suppression. In the author’s opinion, ‘satisfactory adrenal suppression’ could be defined as basal and stimulated plasma cortisol levels within the relevant laboratory’s normal range for basal plasma cortisol concentration.

**Side-effects**

In general trilostane is well tolerated. However a proportion of dogs receiving trilostane may develop mild side-effects including lethargy, depression, inappetance, vomiting and diarrhoea which are usually self-limiting or corrected by adjusting the total dose or dose frequency. Clearly one of the difficulties is that these signs are relatively vague and while they may be attributable to a direct adverse drug reaction, they could also be caused by relative hypoadrenocorticism through either a direct effect of over-dosage or possible adrenal necrosis. Given trilostane’s relatively short duration of action, hypoadrenocorticism might not be considered an expected consequence. However while it cannot be considered a common event, it is particularly important for clinicians using trilostane to be aware of the potential for an animal receiving the drug to develop fulminant hypoadrenocorticism. It is because of this potential, that patients should be monitored regularly to ensure there is adequate adrenal reserve.

As trilostane may cause hyperkalaemia, caution should be exercised when using trilostane with a potassium-sparing diuretic such as spironolactone or ACE inhibitors, although a recent study suggested plasma aldosterone was not significantly different in trilostane treated hyperadrenocorticoid dogs with hyperkalaemia, subnormal post-ACTH or normal post-ACTH cortisol values, and no correlation between potassium and aldosterone could be found. Additionally no unwanted drug interactions have been seen in dogs on trilostane receiving other medications such as various non-steroidal anti-inflammatory, antibiotics, insulin and levethroxine.

Although trilostane seems to be well tolerated by most dogs, in one study acute death was described in two dogs two and four days after starting therapy and another two developed signs and biochemical evidence of hypoadrenocorticism. One of these dogs recovered with appropriate therapy. The other died despite withdrawal of trilostane and administration of appropriate therapy. The question of how a drug with the capacity to suppress cortisol levels for no more than 20 hours could create clinically significant hypoadrenocorticism remains unanswered. Interestingly, trilostane's mechanism of action in controlling canine hyperadrenocorticism may be more complex than originally proposed. Increasing evidence suggests its effects maybe at least partly mediated through its capacity to modify other enzymes in the steroid synthetic pathway (including possible inhibition of 21-hydroxylase or 11- hydroxylase) and/or up-regulation of one of the isoforms of 11- hydroxysteroid-dehydrogenase resulting in enhanced conversion of cortisol to its inactive metabolite cortisone. Additionally, some authors have speculated that the initial increased ACTH levels likely to be seen in a PDH patient receiving trilostane (due to the reduced cortisol levels) may result in adrenocortical damage through enhanced ACTH-stimulated adrenal blood flow with consequent haemorrhage and regional necrosis.

This hypothesis is to some extent supported by the enhanced bilateral adrenomegaly and accompanying characteristic hypoechoic adrenocortical margins that consistently accompany sub-acute trilostane treatment. It is also supported by the sporadic reports of adrenal haemorrhage and necrosis seen in the small proportion of dogs with adrenal histopathology in which trilostane has created acute but long-term hypoadrenocorticism.

**Mitotane**

An alternative to trilostane remains the use of long term mitotane administration. The essence of this regime is to destroy most of the hyperplastic adrenal cortex. The remaining tissue provides normal plasma cortisol concentrations despite being subjected to almost supraphysiological levels of ACTH.

In other words the animal no longer has the capacity to raise its plasma cortisol level above 20-50 nmol/l. This magnitude of adrenal destruction is essential to achieve significant clinical improvement.

This ‘chemical adrenalectomy’ can be achieved using two different protocols, one aimed at achieving complete and permanent adrenocorticalysis and the other at reducing adrenocortical activity to normal levels through partial adrenocorticalysis. The second protocol has been generally accepted as the favoured method and involves administration of mitotane (25 mg/kg/12hr with food) for five to seven days. During this period water consumption, appetite and general demeanour are closely monitored. If any of these parameters change for more than 12 hours the mitotane therapy is stopped. Animals are evaluated with an ACTH response test 48 hours after the last dose of mitotane. Adrenal destruction is deemed satisfactory when both pre and post ACTH cortisols are similar and below the mid-range for the laboratory’s normal basal cortisol concentration. In approximately 15% of cases this may require a second or more courses of daily mitotane. Once satisfactory adrenal destruction has been achieved it can be maintained by once or twice weekly mitotane administration (25 mg/kg/12hr with food on one or two
patients can be rechecked with an ACTH response test once every 8-12 weeks to ensure adequate control is being maintained. Animals treated in this way cannot mount an appropriate stress response to trauma or illness. Consequently, from the start of mitotane therapy, prednisolone should always be available and the owners instructed to administer 1-2 mg/kg orally in an emergency while awaiting veterinary attention.

The main disadvantage of using mitotane to induce a selective degree of adrenocorticolysis is the relatively high proportion of dogs who do not respond reliably and consistently to either the induction or the remission dose. The resultant need for ongoing regular ACTH stimulation tests in the context of unreliable responses to dose adjustment with similar relapse rates makes this regime complicated, involved and often expensive.

Summary of medical options
In summary both trilostane and mitotane seem to be effective in correcting clinical signs and hormonal abnormalities associated with pituitary dependent hyperadrenocorticism in approximately 80 - 85% of cases. Unfortunately this means a substantial number of affected dogs may not respond to standard medical therapy and in these cases a practical alternative needs to be considered sooner rather than later.

Surgical alternatives to mitotane / trilostane
Investigators at the University of Utrecht have had considerable success using hypophysectomy, however, this is a specialised surgical procedure and not widely available. Additionally, despite apparently complete removal of the adenohypophysis, relapses have been common. Another therapeutic alternative is bilateral adrenalectomy.

Bilateral adrenalectomy
Although this procedure has been proposed as a possible treatment for some time, reported difficulties in the post-operative management of the adrenalectomised patient has resulted in the technique not achieving widespread acceptance as a feasible alternative to chemical adrenalectomy. However the surgery itself is relatively simple and management of the surgically-induced 'panhypoadrenocorticism' is inexpensive and uncomplicated by potential hyperadrenocorticoid relapses. In the author's opinion the reported difficulties with this procedure can be largely overcome by reducing the potential for perioperative glucocorticoid and mineralocorticoid deficiencies with a continuous hydrocortisone infusion at an initial rate of 0.5 mg/kg/hr until the animal is taking food and water orally and then changing to a combination of cortisone acetate with or without fludrocortisone for long term replacement therapy. This procedure may be a practical alternative for the treatment of PDH in the dog.