Diagnosis and Treatment of Canine Hyperadrenocorticism

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Canine hyperadrenocorticism (HAC) has been most commonly treated with the adrenolytic drug o, p'-DDD (mitotane). However, it is well recognised that mitotane has several side effects, is associated with a high frequency of relapses and is not without risk to owners. Other drugs such as ketoconazole and l-deprenyl (selegeline) have also been investigated for the treatment of HAC. Recently it has been suggested that trilostane was an effective treatment for canine hyperadrenocorticism. Several workers in the field have subsequently used trilostane in canine pituitary dependent and adrenal dependent hyperadrenocorticism, in feline hyperadrenocorticism and in equine Cushing's syndrome. Trilostane is a synthetic, orally active steroid analogue. It can act as a competitive inhibitor of the 3ß hydroxysteroid dehydrogenase enzyme system and thereby inhibit the synthesis of several steroids, including cortisol and aldosterone. This blockade is reversible and seems to be dose-related.

Pharmacology of trilostane

Few pharmacokinetic studies have been performed on trilostane. In the rat and monkey trilostane is rapidly absorbed after oral dosing with peak blood concentrations occurring between 0.5-1 hour (rat) and between 2-4 hours (monkey). In human volunteers the peak concentrations were between 2 and 4 hours 5. In dogs peak trilostane concentrations are seen within 1.5 hours and decrease to baseline values in about 18 hours (Arnolds

Veterinary Products Limited, UK, data on file). The variability exhibited in systemic levels of trilostane following oral administration is possibly due in part to suboptimal absorption owing to its low water solubility.The decline of trilostane follows a triexponential decrease with trilostane cleared from the blood after 7 hours (rat), 6-8 hours (human) and 48 hours (monkey). Following the administration of trilostane to rats, the metabolite ketotrilostane is formed within a few minutes. Ketotrilostane has about 1.7 times the activity of trilostane in steroid inhibition. Conversely, when ketotrilostane is given to rats, trilostane is rapidly formed, suggesting that these compounds exist in equilibrium in vivo. Trilostane and ketotrilostane are metabolised into any one of 4 further metabolites. Excretion in rats is mainly via faeces, whilst in monkeys urinary excretion is more important 4.

Use in humans

In humans, trilostane has been mainly used for Cushing's syndrome. However the clinical response was rather disappointing with only few patients showing clinical improvement. Decreases in cortisol levels and in blood pressure were even less common. Other conditions in humans treated with trilostane are Conn's disease (primary aldosteronism) and advanced breast cancer. In humans, trilostane is given orally at a dose of 60 mg four times daily for three days with adjustment according to the patient's response. Usually a final dose of 120-480 mg daily in divided doses is required with a maximal dose of 960 mg recommended. Uncommon dose-related side effects of trilostane in humans include flushing, nausea and vomiting, diarrhoea, rhinorhoea and palatal oedema. Acute addisonian episodes have also been reported.

Clinical studies

Canine pituitary dependent hyperadrenocorticism (PDH)

The efficacy and safety of trilostane in the treatment of canine PDH were evaluated in a multicentre study at the Royal Veterinary College in London, the Veterinary Teaching Hospital in Dublin and Small Animal Hospital in Glasgow. Seventy-eight dogs with confirmed PDH were treated with trilostane for up to 3 years. The starting dose varied from 1.8 to 20 mg/kg (mean = 5.9 mg/kg).

Trilostane appeared to be well tolerated by almost all dogs with only 2 dogs developing 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. A further two dogs died within one week of starting trilostane but in neither case could a direct link with the trilostane therapy be established. The low prevalence of side effects compared favourably to those reported with mitotane.

Trilostane was found to be nearly as effective as mitotane in resolving the signs of hyperadrenocorticsm. Polyuria, polydipsia and polyphagia had dissipated in 40 dogs within 3 weeks after starting trilostane. Within 2 months, a further 20 dogs showed decreases in their water and food consumption. These improvements were maintained as long as the dogs remained on adequate doses of trilostane. Skin changes resolved in 24 out of 39 (62%) of dogs that initially presented with dermatological signs. All of these improvements were maintained as long as the dogs remained on adequate doses of trilostane. Only 8 dogs that were treated with trilostane for more than 2 months showed poor control of clinical signs. In contrast, mitotane is effective in about 80% of cases of pituitary dependent hyperadrenocorticism (PDH).

Trilostane caused a significant ($p<0.001$) reduction in both the mean basal and post-ACTH stimulation cortisol concentrations after 10 days of treatment. The post ACTH cortisol concentration decreased to less than 250 nmol/l (9 µg/dl) in 81% of dogs within one month and in another 15% at some time whilst on treatment. These improvements were also maintained in the study population for the duration of the trial.

Thirty-five dogs had at least one dose adjustment over the treatment period. The dose was increased in 23 dogs up to four times the starting dose. In one dog the dose was increased nine fold over a period of six months. The dose was decreased in nine dogs to as low as a quarter of the starting dose.

The mean survival of all trilostane treated dogs was 661 days. Direct comparison with mitotane was difficult as 65% of the dogs were still alive at the time of censor and therefore the mean survival may still increase.By comparison, the mean survival of mitotane treated dogs has been reported to be 810 to 900 days.

Subsequently it has been demonstrated that the effects of trilostane on basal cortisol concentrations are short lived (less than 20 hours) in most dogs with hyperadrenocorticism. Furthermore there are significant differences between the cortisol responses in ACTH stimulation tests performed at 4 and 24 hours post dosing 12. It has also been suggested that adrenal glands increase in size in response to therapy. This may be as a result of an increase in endogenous ACTH during therapy.

Canine adrenal dependent hyperadrenocorticism

Only a few cases of adrenal dependent hyperadrenocorticism (ADH) have been treated with trilostane. A reduction in post-ACTH cortisol concentrations has been demonstrated and extended survival times (more than 2 years) have been achieved in some cases. Insufficient cases have been collected to compare the long-term efficacy of trilostane with that of mitotane. Trilostane is not cytotoxic and it is likely to be inferior to mitotane for the prevention and control of metastatic disease. The value of trilostane for pre-operative therapy before adrenalectomy has not been examined in a systematic fashion. However, given the data presented above, it would suggest that trilostane might be an effective and safer alternative to ketoconazole in this respect.

Clinical studies in other species

Trilostane has been used in 20 cases of equine HAC at a dose of 120-240 mg once daily 14. The drug was effective as assessed by reduction in lethargy, laminitis and polyuria/polydipsia and a corresponding decrease in cortisol response to TRH administration. Some of these horses have been treated for up to one year so far with no side effects noticed. The use of trilostane in feline HAC has not been reported.

Current recommendations for the use of trilostane in dogs

Many aspects of trilostane use in canine HAC are still under investigation and the following recommendations are therefore likely to change.

Preparations, storage and handling

Trilostane has been available in 60 mg capsules in the UK since late 2001 under a temporary veterinary product licence as Vetoryl® (Arnolds Pharmaceuticals, Crawley, Surrey, UK). It is also available in 60 mg capsules approved for human use as Modrenal® (Wanskerne Ltd, Billingshurst, West Sussex, UK). With very small dogs, capsules might need to be split into smaller gelatin capsules. A licensed pharmacist should do this. Trilostane capsules should be stored at room temperature in airtight, light-resistant containers. Pregnant women should wear gloves when handling the drug and all users should wash their hands after handling the capsules.

Dosage and administration

As pharmacokinetic data for trilostane are not yet available, the optimal dose rate and frequency interval for the treatment of canine HAC are not yet known. The current suggested starting dose rate for dogs with PDH is 5-10 mg/kg once daily. This needs to be adjusted according to clinical signs and serum cortisol values (see below). Doses up to 40-50 mg/kg (divided twice daily) have been given with no unwanted side effects. In some dogs twice daily dosing may be necessary. The drug is given with food.

Cautions and drug interactions

In dogs only minor side effects are commonly seen such as mild lethargy and decreased appetite 2-4 days from start of therapy (potentially due to steroid withdrawal syndrome) and mild electrolyte abnormalities. Overt hypoadrenocorticism seems to be a rare event despite the marked decrease in serum cortisol values found shortly after trilostane dosing. It has been shown that trilostane terminates pregnancy in rhesus monkeys at a dose of 50mg/monkey at various time points through pregnancy. The drug should therefore not be used in pregnant animals.

As trilostane can cause hyperkalemia through its aldosterone inhibiting effect it is advised to use caution if given together with a potassium-sparing diuretic. No unwanted drug interactions have been seen in dogs on trilostane together with several non-steroidal anti-inflammatory drugs, various antibiotics, insulin and levothyroxine. The effect of angiotensin converting enzyme inhibitors might be potentiated (again due to it's aldosterone inhibiting effect) but no studies have looked into this.

Monitoring

It is important to monitor the clinical and biochemical effects of therapy and to adjust the trilostane dose to achieve optimal control. Dogs are re-examined and an ACTH stimulation test is performed at 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 the light of the history and the findings of a thorough physical examination. If the post ACTH cortisol concentration is less than 20 nmol/l (0.7 µg/dl) the trilostane is stopped for 48 hours and then re-introduced at a lower dose. If the post ACTH cortisol concentration is more than 120 nmol/l (4.3 µg/dl) 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 is unaltered. If however the post ACTH cortisol concentration is between these two values and the patient appears not to be clinically well controlled then the trilostane may need to be given twice daily. If an ACTH stimulation test is performed at times other than 4 to 6 hours after trilostane then the post ACTH cortisol concentration should be more than 20 nmol/l (0.7 µg/dl) and less than 250 nmol/l (9 µg/dl).

Once the clinical condition of the animal and the dose rate has been stabilized then dogs should be examined and an ACTH stimulation test performed every 3 to 4 months. Serum biochemistry (especially electrolytes) should be performed periodically to check for hyperkalemia.

Conclusions

It is concluded that trilostane is an acceptable alternative to mitotane for the treatment of canine PDH. However, the optimal dose rate and frequency of administration need to be determined from pharmacokinetic studies. Trilostane may also be useful in canine ADH and equine Cushing's disease but more studies are needed. Its use in any of these diseases does not remove the need for regular veterinary monitoring. As the post-ACTH cortisol concentration is variable depending on the time at which the test is performed it may not be the optimal test for assessing the efficacy of trilostane therapy. However no comparison has yet been made with other tests of adrenal gland function.