COMPLICATED CUSHING’S CASES AND CONCURRENT CONDITIONS

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Gerard Mclauchlan and Ian Ramsey discuss diagnosis and management, with a particular focus on parallel problems such as diabetes mellitus and hypothyroidism.

NATURALLY occurring canine hyperadrenocorticism (HAC), or Cushing’s disease, is a commonly seen endocrinopathy in small animal medicine.

Eighty-five per cent of cases are attributed to excessive adrenocorticotropic hormone (ACTH) production from a pituitary tumour (pituitary-dependent hyperadrenocorticism or PDH), and 15 per cent are due to a functional adrenocortical adenoma or carcinoma (adrenaldependent hyperadrenocorticism or ADH; Reusch, 2005).

It is known to be particularly common in older terriers, although any breed, of any age, can be affected (Figure 1).

PDH is normally managed successfully with trilostane, a 17-beta-hydroxysteroid inhibitor that is the licensed treatment for hyperadrenocorticism in the UK (Neiger et al, 2002). Monitoring is carried out based on the patient’s clinical response and by performing an ACTH stimulation test two to four hours after trilostane administration, although the optimal method for assessing control of the disease is still under investigation.

Some literature has suggested a post-ACTH cortisol concentration ranging from 70nmol/L to 250nmol/L equates with good control of the disease (Neiger et al, 2002; Ruckstuhl et al, 2002;
Vaughan et al, 2008). The authors commonly aim for a post-ACTH cortisol concentration between 40nmol/L and 140nmol/L. However, if the animal has a post-ACTH cortisol level between 140nmol/L and 200nmol/L and is clinically well, regular monitoring rather than a dose increase is also acceptable.

While most animals with HAC will respond favourably to trilostane therapy, some may prove more complicated to the clinician. In this article, the authors discuss their approach to such cases.

**Unresponsive cases**

No clinical studies have directly compared different frequencies of trilostane administration, but it has been demonstrated that in most cases, the effects of trilostane last less than 24 hours.

Bell et al (2006) report six dogs receiving once-daily trilostane with ongoing clinical signs of HAC, whose post-ACTH concentrations at four and 24 hours after trilostane administration were higher than in four dogs whose clinical signs were well controlled. When these poorly controlled animals were switched to twice-daily dosing, some showed an improvement in both their clinical signs and post-ACTH cortisol concentrations. Subsequently, other publications have described the administration of twice-daily trilostane, but their overall results were similar to previous reports on once-daily dosing (Vaughan et al, 2008). It was also noted that animals on twice-daily trilostane appeared more likely to suffer adverse effects from the medication. Therefore, it can be concluded that some animals may require twice-daily doses of trilostane, but it is probably not necessary to divide the starting dose for all dogs.

It may be sensible to start with once-daily dosing (2mg/kg to 5mg/kg is the authors’ recommended dose regimen) and monitor animals via an ACTH stimulation test at 10 days, four weeks, 12 weeks and then every three months thereafter.

In animals showing good control, based on a two to four-hour post-trilostane ACTH stimulation test, but with ongoing clinical signs, the need for twice-daily trilostane should be investigated via a 23-hour post-trilostane ACTH stimulation test.

It would seem sensible that if the patient requires twice-daily trilostane, perhaps the dose should be reduced (such as from a 30mg tablet once daily, to a 10mg tablet twice daily) to avoid a potential overdose. However, the patient may eventually require the initial dose twice daily.

**Concurrent diabetes mellitus**

Concurrent HAC and diabetes mellitus (DM) has been documented in the veterinary literature, and these cases represent a considerable diagnostic and therapeutic challenge.

It may be sensible to contact or refer these animals to a specialist centre for stabilisation advice.
Although most published reports of these concurrent diseases document that diabetes is the first condition diagnosed, it seems logical that HAC may be the primary problem in at least some of the cases, as HAC leads to insulin resistance (Peterson et al, 1981). In many cases, it is unlikely that controlling HAC will result in complete resolution of the diabetes and, as such, insulin therapy will be required. However, it also seems logical that reducing cortisol levels will increase responsiveness to insulin, and thus reduce the chance of a diabetic animal becoming ketoacidotic.

The absence of large-scale, published studies on dogs with these concurrent endocrinopathies receiving trilostane means recommendations are vague. Previous reports found mitotane was associated with a rapid reduction in insulin requirement within three weeks and, therefore, many papers recommend prospective reductions in insulin therapy when starting treatment for HAC (Peterson et al, 1981).

An abstract reporting eight dogs with concurrent HAC/DM showed that instigating trilostane therapy was not consistently associated with a reduction in insulin requirements (McLauchlan et al, 2010). While the number in this series was small, and the management of the cases varied (in relation to frequency of insulin/trilostane administration), it is possible that reductions in insulin at the start of trilostane may not be required in all cases. Therefore, prospective trials are required before further recommendations can be provided regarding use of trilostane in diabetics.

Confirming a HAC diagnosis may be more difficult, as chronic stress placed on an animal with poorly controlled diabetes may result in a false-positive on any of the tests that assess the adrenal axis. It is important, therefore, to attempt stabilisation of diabetes prior to attempting to confirm concurrent HAC.

**Concurrent hypothyroidism**

Concurrent HAC and hypothyroidism in dogs is a rare occurrence. The clinical signs of HAC and hypothyroidism may be similar (although hypothyroidism is not usually associated with polyuria and polydipsia), and it is thought that up to 50 per cent of dogs with HAC may have a below-reference range total T4.

Dogs with concurrent HAC and hypothyroidism, therefore, represent a considerable diagnostic challenge, as the hypothyroidism has to be differentiated from sick euthyroid disease. The authors would recommend assessing levels of total T4, free T4 and thyroid-stimulating hormone (TSH) in an attempt to do this. One study showed that treating HAC with trilostane resulted in a significant elevation in TSH concentration; however, there was no significant change in the total T4 level (Kenefick and Nieger, 2008).

The same report showed a significant reduction in free T4 after trilostane medication, which is in contrast to another previous publication (Peterson et al, 1984). The animals in these studies did not have hypothyroidism, and so the results cannot necessarily be applied to animals with the
concurrent endocrinopathies.

Animals with concurrent HAC and hypothyroidism should have alterations in thyroid hormone levels (increased TSH is usually seen) after stabilisation of the HAC, whereas animals that only have Cushing’s usually have normal thyroid hormone concentrations after control of HAC. Hypothyroidism treatment will not affect the HAC or vice versa, and no medication dose reductions are recommended when treating the diseases.

**Concurrent pancreatitis**

Animals suffering from HAC have been considered to have an increased risk of developing pancreatitis due to high circulating endogenous steroid concentrations that may alter lipid metabolism (Reusch, 2005). As with any other concurrent disease, an attempt to control the pancreatitis should be made prior to performing endocrine testing, as the risk of false-positives will be increased in sick patients.

Animals with concurrent disease should not be started on trilostane until clinical signs of pancreatitis have resolved. Instead, they should be managed appropriately via diet, fluids, analgesia and, in certain cases, plasma transfusions.

The authors would recommend starting these cases on medication for HAC after their discharge from practice, when their appetite has returned.

**Adrenal-dependent Cushing’s disease**

No large-scale studies have documented the use of trilostane in animals with adrenal tumours (Figure 2). Trilostane, however, does seem effective, based on the small number of publications available (Eastwood et al, 2003). No recommendations are currently available regarding dose, frequency of administration or monitoring in these cases, and, as such, caution is advisable. Some institutions may recommend surgical treatment of these cases, but this is not without risk and requires advanced staging to assess vascular involvement.

No published data currently shows that animals undergoing surgery to remove an adrenal tumour have an improved survival time over those receiving medical management.

**Cushingoid dogs requiring surgery**

Performing elective surgery on dogs with HAC is not recommended until they have been clinically stabilised. If anaesthesia and surgery are necessary then, providing attention is paid to haemostasis and infection control, most procedures would only carry a marginally increased risk.
The authors recommend that trilostane therapy is discontinued the day prior to anaesthesia, although no data has been published to support this guideline. The stress placed on a patient, even by a relatively short anaesthetic, may require the animal to mount an appropriate steroid response, which may be inhibited by trilostane administration.

Trilostane should be restarted when the animal is well enough to leave hospital, and it seems sensible to administer postoperative prednisolone therapy (0.3mg/kg to 0.5mg/kg SID) for a few days to these animals, particularly if their most recent post-ACTH cortisol concentration is less than 140nmol/L.

**Adverse reactions**

The prevalence of adverse effects to trilostane is low, but the most serious complication reported is sudden death (Neiger et al, 2002). Trilostane has also been associated with the development of hypoadrenocorticism – in most cases, it is reversible once medication has been stopped. However, reports have documented adrenal necrosis. Animals exhibit clinical signs and electrolyte abnormalities associated with hypoadrenocorticism, although there has been a report of an animal showing isolated hypocortisolism.

In animals showing adverse effects to medication, the authors would recommend stopping the trilostane, performing an ACTH stimulation test and monitoring haematology, biochemistry and serum electrolytes. Severely affected animals may require fluid therapy and steroid replacement (glucocorticoids and sometimes mineralocorticoids), as well as symptomatic treatment (antiemetics, gut protectants and, occasionally, blood transfusions).

Most cases will make a rapid recovery, and therapy with trilostane can be started at a lower dose once recovery of the adrenal axis has been documented. In cases where animals have undergone adrenal necrosis, they may require steroid supplementation for life.

Some animals with steroidresponsive disease, such as arthritis or atopy, may develop clinical signs of this following treatment with trilostane. NSAIDs have been used commonly with both trilostane and mitotane – without significant side effects – in older dogs with HAC and osteoarthritis.

Animals receiving trilostane occasionally develop neuropathy, affecting cranial nerve V, which is characterised by facial paralysis and loss of corneal sensation (unilateral or bilateral). This has been reported with both trilostane and mitotane (Figure 3). When trilostane is not tolerated, then mitotane should be considered as a treatment option. The authors recommend that trilostane should be stopped for at least one week before starting mitotane therapy; this is not based on any published evidence, but purely precautionary.

**Pituitary macroadenomas**
If the HAC is due to a pituitary macroadenoma, then the patient may show neurological signs associated with the spaceoccupying lesion.

Signs commonly seen include loss of appetite, central blindness and alterations in mental alertness. The diagnosis requires advanced imaging modalities (CT scan or MRI), and treatment options include steroid or radiation therapy (which has shown promising results).

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**References**
