

Canine hyperadrenocorticism – a diagnostic and therapeutic update

Author : GERARD MCLAUCHLAN

Categories : [Vets](#)

Date : July 29, 2013

GERARD MCLAUCHLAN provides an update on developments in diagnosis, medical management and surgical options for this canine endocrinopathy

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 adrenocorticotrophic hormone (ACTH) production from a pituitary tumour (pituitary-dependent hyperadrenocorticism or PDH). Pituitary tumours may arise from the pars distalis (70 per cent of PDH) and the pars intermedia (30 per cent). While most pituitary tumours are small and do not cause intracranial signs (so-called microadenomas), larger macroadenomas can result in concurrent neurological abnormalities.

The remaining 15 per cent of HAC cases are due to a functional adrenocortical adenoma or carcinoma (adrenal-dependent hyperadrenocorticism or ADH). There have been a small number of dogs reported with concurrent pituitary and adrenocortical tumours; however, this is uncommon (Melian et al, 2010).

Clinical signs

Hyperadrenocorticism is known to be particularly common in older terriers, although any breed, of any age, can be affected ([Figure 1](#)). The mean age at diagnosis is 11 years old, with more than 75 per cent of PDH cases and 90 per cent of cases of ADH being older than nine years at the time of

diagnosis. In general, it is thought PDH tends to occur in smaller dogs (75 per cent of PDH cases are reported in dogs weighing less than 20kg).

The clinical signs in dogs with HAC are mainly attributable to the chronic excessive glucocorticoid secretion, although in some cases signs can also result due to local tumour growth/ invasion or metastatic spread.

Clinical signs commonly associated with the disease include polyuria/polydipsia, polyphagia, lethargy, abdominal distension, hepatomegaly, muscle atrophy and dermatological changes (bilateral truncal alopecia, generalised coat thinning, development of a “rat” tail, calcinosis cutis, thinning of the skin and hyperpigmentation).

Other clinical signs reported less commonly include facial nerve paralysis, other peripheral neuropathies/myopathies and, in cases of macroadenomas, blindness, anorexia and mental dullness.

Diagnosis

A diagnosis of HAC can be difficult to reach and should only be sought in animals with consistent history and physical examination. In general, animals with uncomplicated HAC are clinically well; if at all possible, testing for HAC should be avoided in sick animals (for example, those with concurrent pancreatitis should have recovered from the pancreatitis prior to testing for HAC).

To help support the diagnosis all dogs should undergo clinicopathological testing, including haematology, serum biochemistry, urinalysis and specific endocrine testing. Animals diagnosed with HAC should also have abdominal ultrasonography performed alongside assessment of endogenous ACTH to help differentiate PDH from ADH.

Routine clinicopathological abnormalities may include mild erythrocytosis, a stress leucogram, increased liver enzymes (with a particular increase in alkaline phosphatase), hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia and increased bile acids.

Urinalysis commonly shows an increased urine protein:creatinine-ratio (UPCR) and a USG of less than 1.020 with occasional glucose present in those dogs with HAC. Despite dogs with HAC commonly having a mild to moderate hyperglycaemia, the urine is normally negative for glucose unless overt diabetes mellitus is also present. Dogs with HAC are also prone to urinary tract infections (thought to occur in around 25 per cent of cases), but sediment examination often shows an inactive sediment due to high endogenous circulating cortisol levels suppressing any inflammatory response.

Various adrenal function tests are recommended for the diagnosis of HAC in dogs. There is a wide variation in invasiveness, time and cost between the tests and each differs significantly with regard

to diagnostic sensitivity and specificity.

The ACTH stimulation test measures the adrenal response to maximal ACTH stimulation. A basal blood cortisol sample is obtained and then synthetic ACTH is administered either intravenously or intramuscularly before a second cortisol measurement is made 60 minutes later. It can be used to differentiate naturally occurring disease from iatrogenic HAC, but not between PDH and ADH.

In dogs with naturally occurring HAC an exaggerated response to ACTH administration is accepted (post-ACTH cortisol level greater than 600 nmol/L). The sensitivity of the ACTH stimulation test for diagnosing HAC is 85 per cent and the specificity 90 per cent. Due to the simple nature of the test, the ACTH stimulation test is often the initial diagnostic test performed.

The low dose dexamethasone suppression test (LDDST) is more sensitive than the ACTH stimulation test, but less specific and is considered by many the initial screening test of choice. The sensitivity of the LDDST is thought to be almost 100 per cent in ADH and greater than 90 per cent in PDH; however, the specificity of the test is reported to be as low as 40 per cent.

The protocol involves an initial basal cortisol sample followed by an injection of dexamethasone (either IV or IM). Circulating cortisol levels are measured three hours and eight hours after dexamethasone injection. A dog with HAC will escape the normal negative feedback of the glucocorticoid and will fail to suppress adequately (less than 40 nmol/L). Although the basal and eight hour samples are most important, the sample obtained at three hours may also be helpful and can potentially help differentiate PDH from ADH (30 per cent of cases with PDH may suppress at three hours, but escape from suppression at eight hours; cases that do not suppress completely but have a three and eight hours postdexamethasone administration cortisol concentrations less than 50 per cent of basal value may have PDH). Due to the low specificity of the LDDST, it should never be used as the single diagnostic test from HAC and care should be taken in particular in dogs with nonadrenal illness.

The urine cortisol creatinine ratio (UCCR) is a reflection of adrenal glucocorticoid secretion and can be used in the investigation of hyperadrenocorticism in dogs. Morning urine should be obtained by owners at home to avoid the influence of stress due to hospitalisation. It is the most sensitive of the diagnostic tests available (approximately 98 per cent), however it lacks specificity (approximately 20 per cent) and so false-positive results are possible. In particular, stressed animals or those with significant non-adrenal illness are prone to false-positive results with the UCCR. It is most useful to rule out HAC (high negative predictive value). Due to the low sensitivity of the UCCR a positive result should rarely be used as the single diagnostic criteria of HAC. A combination of the UCCR and an oral LDDST has been reported, but is rarely performed.

In animals with "atypical" HAC, 17-OH progesterone can be measured pre and postsynthetic ACTH administration. It has been shown excessive production of this cortisol precursor (and others) can occur in dogs with HAC and with adrenal tumours in particular. Cases of "atypical"

HAC may show normal response on the ACTH stimulation test and LDDST, but have exaggerated post-ACTH 17-OH progesterone. The diagnosis of HAC based solely on the 17-OH progesterone measurement is controversial.

Management

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 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 author commonly aims 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 (see examples below).

Dose frequency

Bell et al (2006) reported 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 twicedaily dosing, some showed an improvement in both their clinical signs and post-ACTH cortisol concentrations. More recent publications have shown twice daily low-dose dosing with trilostane results in adequate clinical control and that this may be achieved more quickly than with sid dosing; however, the frequency of adverse effects may be slightly increased (Augusto et al, 2012; Vaughan et al, 2008). The total daily dose when administering bid medication is generally lower than that required with sid dosing.

Therefore, it would seem sensible to start with once-daily dosing (2mg/kg to 5mg/kg is the author's 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.

If the patient requires twicedaily trilostane then 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 HAC may be the primary problem in at least some of the cases, as HAC leads to insulin resistance (Peterson et al, 1981).

In most cases, it is unlikely 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.

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).

A publication reported on eight dogs with concurrent HAC/DM and 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 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 an HAC diagnosis may be more difficult, as chronic stress placed on an animal with poorly controlled diabetes may result in a falsepositive 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 rare. 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 belowreference 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 thyroidstimulating 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 Neiger, 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.

Adrenal-dependent Cushing's disease

Trilostane has been shown to be effective in dogs with ADH and results in similar survival time when compared to mitotane (Helm et al, 2011). At this time no recommendations are 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 shows animals undergoing surgery to remove an adrenal tumour have an improved survival time over those receiving medical management ([Figure 2](#)).

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 author recommends 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.

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).

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 author 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 (anti-emetics, 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 author recommends trilostane should be stopped for at least one week before starting mitotane therapy; this is not based on any published evidence, but is purely precautionary.

References

- Anderson C R, Birchard S J, Powers B E, Belandria G A, Kuntz C A and Withrow S J (2001). Surgical treatment of adrenocortical tumours: 21 cases (1990-1996), *Journal of the American Animal Hospital Association* **37**: 93-97.

- Augusto M, Burden A, Neiger R and Ramsey I (2012) A comparison of once daily and twice daily trilostane to dogs with hyperadrenocorticism, *Tierarztl Prax Ausg K Kleintiere Heimtiere* **40**: 415-424.
- Bell R, Neiger R, McGrotty Y and Ramsey I K (2006). Study of the effect of once daily doses of trilostane on cortisol concentrations and responsiveness to adrenocorticotrophic hormone in hyperadrenocorticoid dogs, *Vet Rec* **159**: 277-281.
- Helm J R, McLauchlan G, Boden L A, Frowde P E, Collings A J, Tebb A J, Elwood C M, Herrtage M E, Parkin T D and Ramsey I K (2011). A comparison of factors that influenced survival in dogs with adrenal dependent hyperadrenocorticism treated with mitotane or trilostane, *Journal of Veterinary Internal Medicine* **25**: 251-260.
- Kenefick S J and Neiger R (2008). The effect of trilostane treatment on circulating thyroid hormone concentrations in dogs with pituitarydependent hyperadrenocorticism, *Journal of Small Animal Practice* **49**: 139-143.
- Neiger R, Ramsey I, O'Connor J, Hurley K J and Mooney C T (2002). Trilostane treatment of 78 dogs with pituitary-dependent hyperadrenocorticism, *Vet Rec* **150**: 799-804.
- McLauchlan G, Knottenbelt C, Augusto M, McGrotty Y, Helm J and Ramsey I (2010). The effect of trilostane on the insulin requirements and fructosamine concentrations in diabetic dogs being treated for hyperadrenocorticism, *Journal of Small Animal Practice* **51**: 642-648.
- Melian C, Dolores Perez-Alenza M and Peterson M (2010). Hyperadrenocorticism. In Ettinger S J and Feldman E C (eds), *Textbook of Veterinary Medicine*(7th edn), W B Saunders, Philadelphia: 1,816-1,840.
- Peterson M E, Nesbitt G H and Schaer M (1981). Diagnosis and management of concurrent diabetes mellitus and hyperadrenocorticism in 30 dogs, *Journal of American Veterinary Medical Association* **1**: 66-69.
- Peterson M E, Ferguson D C, Kintzer P P and Drucker W D (1984). Effects of spontaneous hyperadrenocorticism on serum thyroid hormone concentrations in the dog, *American Journal of Veterinary Research* **45**: 2,034-2,038.
- Ramsey I K (2010). Trilostane in dogs, *Veterinary Clinics of North America* **40**: 269-283.
- Vaughan M A, Feldman E C, Hoar B R and Nelson R W (2008). Evaluation of twice daily, low-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism, *Journal of American Veterinary Medical Association* **232**: 1,321-1,328.



Figure 1. A dog showing typical dermatological/coat changes seen in HAC.

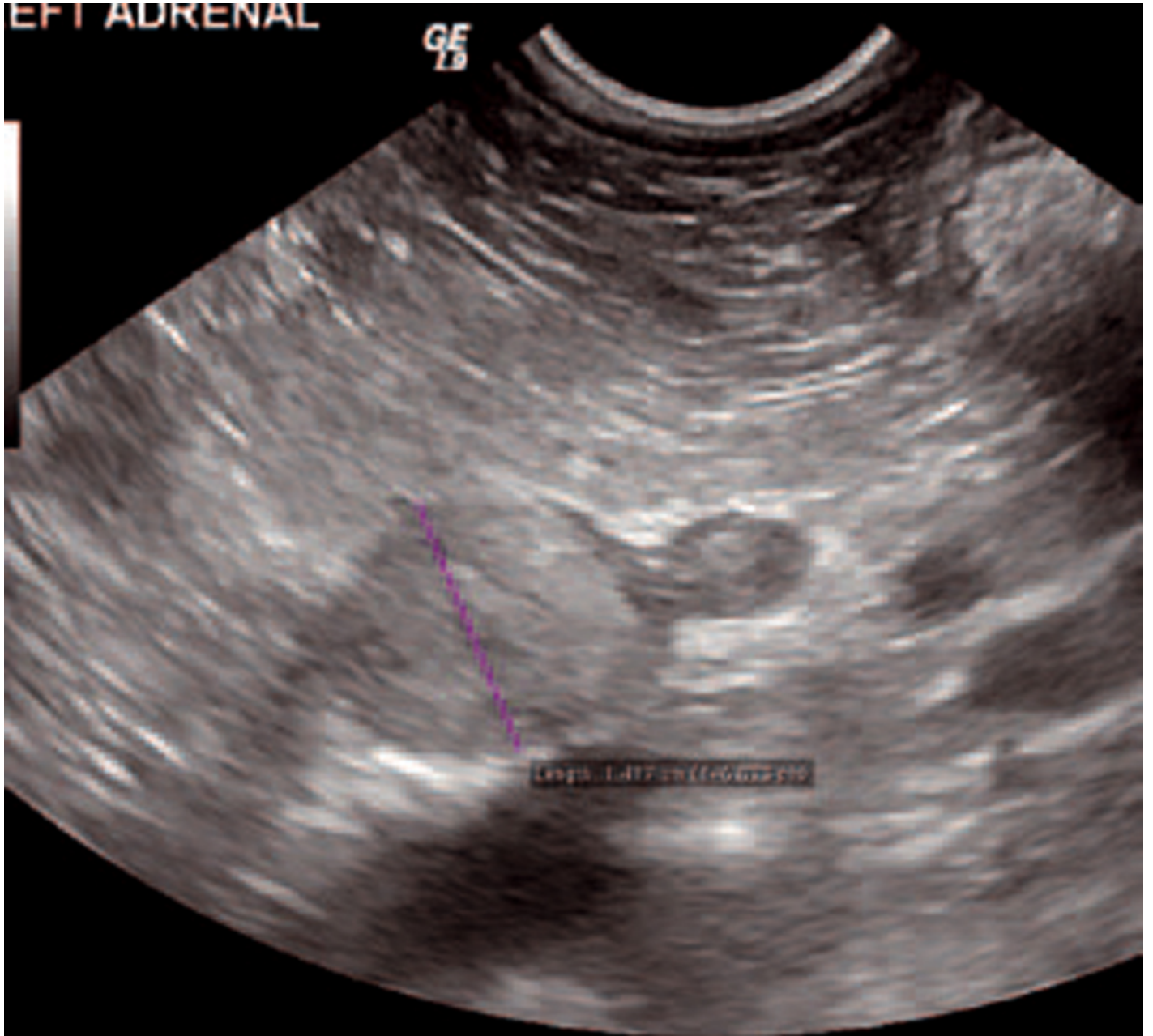


Figure 2. Ultrasound image of an enlarged adrenal gland. A hyperechoic nodule of around 14mm diameter is in the cranial pole, with the remainder of the adrenal gland appearing hypoechoic.



Figure 3. A case demonstrating loss of corneal sensation after trilostane treatment. A swab is seen touching the surface of the cornea.

