Canine hyperadrenocorticism (part II)

In her second article instalment on canine hyperadrenocorticism, Lorraine McDonnell RVN discusses the diagnosis and management of hyperadrenocorticism, including how to distinguish between pituitary and adrenal-dependent disease (in which the treatment options can vary)

ENDOCRINE TESTING

The most common tests used in the diagnosis of hyperadrenocorticism are the adrenocorticotropic hormone (ACTH) stimulation test and the low-dose dexamethasone suppression test (LDDST).

The ACTH stimulation test is commonly used in the diagnosis of hyperadrenocorticism, however, it can't distinguish between pituitary-dependent or adrenal-dependent disease. It can be used to monitor the effectiveness of therapy and is also the most reliable test for distinguishing spontaneous disease from iatrogenic hyperadrenocorticism.

A pre-ACTH baseline sample is taken to measure the resting cortisol level before administering ACTH (Synacthen 250µg/dogs over 5kg or 125ug for dogs under 5kg) either intravenously or intramuscularly. A post sample is taken one hour after administration. The one-hour period gives time for the Synacthen to stimulate the adrenal glands to produce cortisol and determine if the body's response is appropriate. In cases of hyperadrenocorticism, an excessive response to Synacthen would be expected. If there is a 'flat-line' response to Synacthen on the second blood sample, then either the dog has hypoadenocorticism (Addison's disease) or iatrogenic hyperadrenocorticism. This reduced response can also occur in dogs that are receiving mitotane or trilostane therapy for hyperadrenocorticism. Patients need to be kept calm during the test as any stress can cause an abnormal result, ie. it is important not to schedule other tests (such as abdominal ultrasound [US]/blood pressure [BP] measurement) during this time.

This test is more specific but less sensitive than the LDDST (with a sensitivity of only ~60% for adrenal-dependent disease) therefore, a negative result cannot completely exclude the possibility the dog has hyperadrenocorticism (Ettinger SJ, Feldman EC. *Veterinary Internal Medicine* 2010, 7th edition).

The LDDST, by contrast, is a more sensitive test (with a sensitivity of ~90-95% in dogs with pituitary-dependent disease and up to 100% in dogs with adrenal-dependent disease). This means a dog with a negative result is highly unlikely to have the disease. Unfortunately, the specificity of the test is poorer (ie. there are more false positives). This means a positive test result should be interpreted carefully (alongside appropriate clinical signs and typical clinical pathological changes) to ensure 'sick' dogs with non-adrenal illness are not misdiagnosed with hyperadrenocorticism.

Blood is collected for a basal cortisol level prior to an intravenous injection of dexamethasone (0.015mg/kg). A three-hour and eight-hour post sample is taken.

Dexamethasone is used because it is a potent suppressor of ACTH secretion from the pituitary gland (and corticotropin-releasing hormone [CRH] from the hypothalamus) and does not interfere with the cortisol assay. Serum or heparinised plasma may be used (laboratory dependent). For example, a dog with no clinical signs, history, or abnormalities in biochemistry and a normal LDDST, is considered negative for hyperadrenocorticism. However, a dog with clinical signs and history, and biochemistry abnormalities consistent with hyperadrenocorticism and increased cortisol levels after the eight-hour LDDST, is considered to have hyperadrenocorticism.

Another aid in the diagnosis of hyperadrenocorticism is the urinary cortisol:creatinine ratio. Ideally, samples should be collected in the morning and it is preferable that samples should be obtained at home where the dog is less likely to be stressed as this can adversely affect results.

PITUITARY VERSUS ADRENAL-DEPENDENT DISEASE

Diagnostic imaging cannot be used to definitively diagnose hyperadrenocorticism, however it can be useful in differentiating pituitary-dependent from adrenal-dependent disease. Abdominal ultrasound can be used to visualise both adrenal glands (in the hands of an experienced ultrasonographer). If both adrenal glands are enlarged then pituitary dependent disease is more likely, whereas if one adrenal gland is enlarged (or a mass is seen within it) and the other gland is small, adrenal-dependent disease is more likely.

Radiographs of abdomen and thorax may form part of the dog's diagnostic investigation in some cases (however, signs may be non-specific, eg. liver enlargement, distended bladder, etc).

Where adrenal imaging is equivocal/not possible in practice, measurement of endogenous ACTH can help differentiate pituitary and adrenal forms of the disease. Careful sampling handling and strict adherence to laboratory protocols is necessary to prevent falsely low values.

TREATMENT

1. PITUITARY-DEPENDENT HYPERADRENOCORTICISM

(i) Trilostane

Trilostane (Vetoryl) acts to reversibly block the synthesis of several steroids including cortisol and aldosterone from the adrenal gland. Vetoryl capsules are available in various sizes for oral administration and dosing is based on body weight. The initial starting dose recommended is 2mg/kg/day. Trilostane undergoes hepatic metabolism, and the pharmacokinetics may be altered in patients with liver dysfunction.The manufacturers state that trilostane should not be used in patients with primary hepatic disease or

renal insufficiency. It should be used with caution in anaemic patients and avoided in pregnant or nursing bitches or any animal intended for breeding. (Vetoryl Package Insert. Shrewsbury, Shropshire: Arnolds Veterinary Products/Dechra Veterinary Products.)

Once treatment has commenced dogs will often show clinical improvement (reduced polydipsia and polyphagia) within the first week; skin and coat changes, however, may take weeks or months to resolve. Dogs needs to be re-evaluated within the first two weeks of commencing treatment. At this time, apart from clinical exam, an ACTH stimulation test must also be performed. Timing is crucial and must commence four to six hours after trilostane administration. Once the optimum dose of trilostane has been reached the dog must be retested at day 30, then day 90 and every three to six months. Patients should also be monitored for renal and hepatic dysfunction. These checks are necessary, along with a thorough history from owners, especially if any new or returning symptoms are reported. It is also essential to monitor the dog's electrolytes to ensure there is not complete suppression of adrenal hormones (ie. the development of Addison's disease) as it may indicate that the patient may proceed to develop hypoadrenocorticism (Addison's). In this instance, electrolyes may reveal hyponatraemia and/or hyperkalaemia. Should this happen, trilostane must be stopped and reintroduced at a lower dose once clinical signs of hyperadrencorticism have returned; this is why regular monitoring is crucial.

It is essential to educate owners on the importance of reporting any signs of an excessively low-cortisol level (such as anorexia, vomiting, diarrhoea or abdominal pain) to ensure prompt recognition and management.

(ii) Mitotane

Mitotane is an adrenocorticolytic drug. It selectively destroys the zona fasciculata and zona reticularis whilst tending to preserve the zona glomerulosa. Mitotane should only be used for dogs that have not responded appropriately to trilostane (Peterson M, Mooney CT. *BSAVA Manual of Canine and Feline Endocrinology* 2012, 4th edition).

For the initial treatment induction dogs are often hospitalised and a dose rate of 50mg/kg/day is given orally along with food. Mitotane must be given with food as it is a fat-soluble drug that is primarily stored in adipose tissue. Once started, patients must be monitored closely for symptoms like:

- vomiting;
- diarrhoea;
- lethargy;
- depression;
- anorexia; and
- possible neurological signs.

Water consumption needs to be monitored closely in dogs that presented with polydipsia, especially if water consumption is <60ml/kg/day in which case mitotane must be stopped immediately.

If the dog is polydispsic it should take on average seven to 10 days before water consumption reduces to 60ml/kg/day, if symptoms have not resolved then treatment must continue until cortisol level in blood concentration is within normal range.

Once induction has been achieved, patients are maintained on average at a weekly dose of 50mg/kg. Patients need to be re-evaluated between four to eight weeks after commencing maintenance dose unless clinical signs reappear. Improvement should be noticed by eight weeks, eg. a decrease in water consumption, urine output and appetite. Once on maintenance therapy, the dog should be re-evaluated every three to six months for the rest of its life, adjusting levels if required depending on ACTH stimulation test results.

ADRENAL-DEPENDENT DISEASE

Adrenalectomy is considered the gold standard treatment for the management of functional adrenal tumours and may be curative in cases of benign tumours. However, the cost and availability of this procedure may be unfeasible for some owners. In these cases, palliative management with trilostane or mitotane may be considered.

Please refer to part I for an overview of the pathophysiology, clinical signs and clinicopathological changes associated with hyperadrenocorticism