Update on the treatment options for canine hyperadrenocorticism

Background: Canine hyperadrenocorticism (or Cushing’s syndrome) occurs due to a functional pituitary or adrenal tumour, resulting in excessive circulatory glucocorticoids, which produce the classical clinical signs in affected dogs. Although management of the disease traditionally focuses on treating these endocrine consequences, the pathology reflects an oncological disease with the possibility of progression of the underlying neoplasia. Surgical options for these tumours are now becoming increasingly available and successful.

Aim of the article: This article covers how to distinguish between pituitary and adrenal hyperadrenocorticism as well as outlining the treatment options for this important disease in dogs.

In recent study looking at hyperadrenocorticism (HAC) in dogs attending first-opinion practice, an estimated prevalence of 0.28 per cent was found, which means this disease is nearly as common as diabetes mellitus in a similar population (Mattin and others 2014, O’Neill and others 2016). The disease is generally associated with older age (with the average age of onset being nine years in a UK study [O’Neill and others 2016]) and certain breeds (such as the Yorkshire terrier and bichon frise). Cases of HAC typically show various combinations of the following signs:

- polydipsia;
- polyuria;
- polyphagia;
- muscle atrophy;
- hepatomegaly;
- lethargy; and
- dermatological changes.

The clinical presentation and diagnosis of this condition have been described in many textbooks (such as Hertridge and Ramsey 2012, Behrend 2015) and so are not reviewed here.

Pituitary- v adrenal-dependent disease

After a diagnosis of HAC is made, a discussion should be had with the owner about the options available to them and their pet. Differentiating between pituitary-dependent hyperadrenocorticism (PDH) and adrenal dependent-hyperadrenocorticism (ADH) is generally considered an important step in the diagnostic workup, due to the different treatment options available and the different prognostic outcomes (Behrend and others 2013). However, this differentiation was rarely recorded in a study of primary care practice (Schofield and others 2019).

PDH is the most common form of HAC, but ADH still accounts for about one in every five cases. The majority of PDH cases are caused by pituitary microadenomas; however, roughly 10 to 25 per cent of masses develop into macroadenomas following diagnosis (Behrend and others 2013). While there is a lack of consensus on the definition of pituitary macro versus microadenoma in dogs, for the purposes of this article, pituitary gland enlargement will be defined as a pituitary height-to-brain area ratio greater than 0.31 (Kooistra and others 1997).

Pituitary masses are usually slow growing but can eventually result in neurological signs from their space-occupying effects. Adrenal masses tend to be faster growing and produce a wider range of clinical effects – from very subtle signs to severe signs of HAC. Most masses will invade local tissues, particularly the local blood vessels, and about 50 per cent will eventually spread to other parts of the body. Therefore, adrenalectomy should be considered the first-line treatment for ADH.

Although ADH tends to occur in slightly younger dogs, there is no easy way of distinguishing one form of HAC from the other without further testing.
Differentiation between PDH and ADH can be made using biochemical tests and/or diagnostic imaging. If surgery is being considered, then diagnostic imaging is essential to assess for evidence of metastases.

**Differentiating between PDH and ADH**

Measurement of endogenous adrenocorticotropic hormone (ACTH) concentration is recognized to be the most accurate biochemical test for differentiating between the two forms of HAC (Behrend and others 2013). However, this should only be performed once a diagnosis of HAC has been made, to aid interpretation of the result. ACTH concentrations should be within the reference interval or increased in dogs with PDH, but are decreased/unmeasurable in dogs with ADH. Correct sample handling is critical. The sample must be taken into EDTA anti-coagulant, centrifuged immediately and the supernatant frozen straight away. If it is not possible to process samples immediately, they may be kept on ice for up to 15 minutes before centrifugation. Rapid degradation can occur with inadequate sample cooling.

Dexamethasone suppression testing (high or low dose) can also be used to differentiate PDH from ADH. Dexamethasone does not suppress cortisol secretion in dogs with ADH. However, a low-dose dexamethasone suppression test (LDDST) inadequately suppresses cortisol secretion at four hours after dexamethasone administration in 40 per cent of dogs with PDH (ie, ADH and PDH cannot be distinguished), and lack of suppression from a high-dose dexamethasone test means there is a 50:50 chance the dog has PDH or ADH (Behrend and others 2013). Therefore, dexamethasone suppression testing may confirm PDH, but can never confirm ADH. We do not recommend these tests are used routinely for this purpose, but find that the LDDST can be a useful additional result when it has been used for diagnosis of HAC.

Recommended imaging methods to differentiate PDH and ADH include assessment of the adrenal glands using ultrasonography or CT. In PDH dogs, bilaterally enlarged or normal-sized adrenals can be demonstrated. Contrast-enhanced CT and/or MRI can both be used to identify a pituitary mass to support suspicion of PDH (Fig 1). ADH can be defined by some or any of the following findings: adrenal asymmetry, contralateral adrenal atrophy or loss of normal adrenal architecture. However, it is not possible to decide if the tumour is malignant with imaging alone unless there is already evidence of local infiltration and metastasis. It must also be noted that it is rare, but possible, for dogs to have both PDH and ADH.

**Medical options for hyperadrenocorticism**

**Trilostane**

Canine HAC is most commonly treated medically with trilostane (Vetoryl; Dechra). Vetoryl is the only licensed medical product for treating HAC in the UK and so should be prescribed first according to the cascade system. Trilostane is largely a safe and effective drug for managing both PDH and ADH. Side effects are generally mild and transient and include lethargy, diarrhoea and decreased appetite. A small subset of cases may develop iatrogenic hypoadrenocorticism, which can be permanent in rare cases (King and Morton 2017). The estimated cumulative incidence of iatrogenic hypoadrenocorticism is reported to be 15 per cent by two years and 26 per cent by 4.3 years (King and Morton 2017). For PDH, reported median survival times range from 569 to 930 days in trilostane-treated dogs (Table 1). With ADH, the reported median survival times in trilostane-treated dogs range from 353 to 484 days, highlighting the difference in prognosis between PDH and ADH. However, trilostane is a reasonable option in cases of ADH where surgery is not possible (Box 1).

The starting dose of trilostane is 2 mg/kg once daily, administered orally. Dose increases are commonly required to achieve clinical control. The final dose is usually in the range 3 to 8 mg/kg/day. The dose can be divided and given twice daily, but there are a few factors that need to be considered before deciding to do this. Twice-daily dosing likely achieves control more rapidly than trilostane administered once a day, and effective control of clinical signs may be better achieved in some dogs with twice-daily dosing. However, this dosing regime tends to be more expensive. Although compliance with trilostane administration has never been specifically investigated, it is known that twice-daily administration of many other medications has a lower compliance than once daily. Thus, costs and compliance need to be considered against efficacy and speed in each case before switching to twice-daily administration.

Regardless of once- or twice-daily administration, the dose is mainly adjusted on the basis of clinical signs, although endocrine monitoring is a useful adjunct and an important early warning system for overdosing. It was previously considered that an ACTH stimulation test performed two to four hours after trilostane administration was the most useful endocrine monitoring test. However, it is now thought that a cortisol measurement obtained
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at the time of the next trilostane dose (so-called ‘pretrilostane cortisol’) may be superior to an ACTH stimulation test (Macfarlane and others 2016). The test also benefits from being cheaper and quicker than the ACTH stimulation test. The pretrilostane cortisol is interpreted as shown in Fig 2. This method of monitoring provides an early warning system of potential overdoses and a guide to the magnitude of any dose increases. However, pretrilostane cortisol is not a perfect monitoring tool, and cortisol measurements should always be interpreted in the light of clinical findings. Additionally, the pretrilostane cortisol is not the test of choice for dogs showing clinical signs consistent with overdosage of trilostane, or in aggressive or stressed dogs. The ACTH stimulation test should be performed in these circumstances.

Mitotane
If trilostane treatment is unsuccessful and surgical options are not appropriate for financial or clinical reasons, then mitotane therapy can be selected as a second choice. Mitotane is a cytotoxic drug that should be handled carefully. It causes selective adrenocortical necrosis. It is a very successful treatment for HAC but requires careful monitoring to avoid and detect dogs developing hypoadrenocorticism. It is administered as an induction phase followed by a maintenance phase (for further information see Herrtage and Ramsey 2012). Although the induction phase can be quite expensive for clients, the longer-term costs are broadly similar to trilostane when given at higher doses. Mitotane should be monitored with the ACTH stimulation test, as it is a test of adrenal reserve.

Other drugs
Other drugs that have been used in the management of hyperadrenocorticism include ketoconazole, seleagine and cabergoline. None offer any advantages on conventional medical therapy, but studies are ongoing into using some of them as part of combination therapies. Also, recent studies have reported novel medical treatment options that could be used for HAC in the future (De Wit and others 2018, Sanders and others 2018); however, further research into these is required.

Surgical options for pituitary-dependent hyperadrenocorticism
Transsphenoidal hypophysectomy is the surgical

Table 1: Summary of the treatment options available for hyperadrenocorticism (HAC), their associated complications and survival estimates

<table>
<thead>
<tr>
<th>Treatment options</th>
<th>An option for pituitary (PDH) or adrenal (ADH) disease?</th>
<th>Treatment procedure details and ongoing medication</th>
<th>Complications</th>
<th>Survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trilostane</td>
<td>PDH or ADH</td>
<td>Ongoing daily medication and regular monitoring of cortisol concentrations. Vetoryl (Dechra) is a licensed product.</td>
<td>Mild and transient lethargy, diarrhoea +/− reduced appetite. Continued growth of pituitary tumour. ~15% reported to develop transient signs of iatrogenic hypoadrenocorticism over two years.</td>
<td>PDH: 50% of dogs survive to 549−930 days. ADH: 50% of dogs survive to 353−484 days.</td>
</tr>
<tr>
<td>Mitotane</td>
<td>PDH or ADH</td>
<td>Non-licensed medication. Initial induction phase followed by ongoing maintenance phase.</td>
<td>Gastrointestinal signs and weakness are common (reported in up to 42% of dogs). Frequent relapse in clinical signs requiring repetition of induction phase.</td>
<td>PDH: 50% of dogs survive to 662−720 days. ADH: 50% of dogs survive to 102−469 days.</td>
</tr>
<tr>
<td>Transsphenoidal hypophysectomy</td>
<td>PDH only</td>
<td>Preoperative assessment, surgery and three- to five-day postoperative care. Ongoing supplementation with hydrocortisone acetate and thyroxine.</td>
<td>Reduced tear production (transient), central diabetes insipidus (usually transient), recurrence of pituitary growth (in about 10−20% cases). Reported perioperative mortality of ~10%.</td>
<td>PDH: 50% of dogs survive to 662−720 days. ADH: 50% of dogs survive to 102−469 days.</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>ADH only</td>
<td>Preoperative assessment, surgery and postoperative care. Glucocorticoid supplementation for approximately six weeks following surgery.</td>
<td>Reported intraoperative mortality of ~2% and postoperative mortality rate of ~13−20%. A small proportion of dogs can have recurrence of hyperadrenocorticism.</td>
<td>50% of dogs survive to 533−953 days.</td>
</tr>
<tr>
<td>Radiation therapy of pituitary</td>
<td>PDH only</td>
<td>Multiple repeated treatments over several weeks, under general anaesthetic.</td>
<td>Partial alopecia, erythema, otitis externa reported from radiation exposure. Incomplete resolution of HAC signs in 60−80% and infrequent remission of PDH.</td>
<td>Insufficient data.</td>
</tr>
</tbody>
</table>
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removal of the pituitary gland using the approach through the soft palate. This procedure is the most widely used treatment option for people with PDH in the UK and is the one that is most likely to be curative. It is increasingly being recognised in the veterinary field as an effective treatment option for dogs and cats. While hundreds of canine patients with PDH have been successfully treated in the Netherlands in recent decades (Hanson and others 2007, van Rijn and others 2016), this treatment option has only recently become available to pets with PDH in the UK, with several centres now offering it.

Assessing surgical candidates

Assessment of a dog with PDH as a candidate for hypophysectomy should be on a case by case basis. Studies have suggested those with larger masses (particularly >10 mm diameter) may have a poorer prognosis (Hanson and others 2007). As a result, advanced imaging (CT or MRI) is required in all cases to evaluate the size and nature of the pituitary gland, as well as for surgical planning. Although some dogs are referred for surgical management of PDH due to becoming refractory to medical management with trilostane, it is important to be aware that continued pituitary adenoma growth will occur during this period of medical management. As a result, it is recommended that owners are offered the option of surgical management at the time of diagnosis, as surgical success rates are likely to be highest earlier in the disease process, with a smaller mass.

What does the procedure involve?

Surgery is performed by positioning patients in a neurosurgical head frame and operating through their soft palate, then using a high-speed surgical drill to access the pituitary fossa and remove the pituitary gland (Fig 3). When the pituitary gland is exposed, the dura mater is incised, the pituitary gland is removed using fine surgical tools and the skull defect is closed.

Follow-up management

Recovery is typically rapid following uncomplicated surgery, with most dogs being well enough to go home three to five days later. Long-term hormone supplementation with low-dose glucocorticoids and thyroxine is required after hypophysectomy, to replace the hormones lost by removal of the entire pituitary gland. Desmopressin (synthetic

BOX 1: ADRENAL DEPENDENT-HYPERADRENOCORTICISM CASE EXAMPLE

Cara, a seven-year-and-seven-month-old, female neutered, Hungarian vizsla was presented with alopecia, spontaneous bruising and polydipsia. The low-dose dexamethasone suppression test results were consistent with hyperadrenocorticism, and she had an undetectable endogenous adrenocorticotropic hormone level. The adrenal glands were asymmetric, but the larger, right adrenal was only 1 cm (Fig a). After three months of being given trilostane, she was reported to be doing very well. The skin bruising was no longer present, and her coat was returning to normal. She was much livelier at home, and her thirst decreased considerably. After six months, Cara’s coat had returned to normal, and her right adrenal measured 1.8 cm. Cara lived another two years on trilostane (Fig b).

Fig a: Ultrasonography of an enlarged right adrenal gland measuring 1 cm in a Hungarian vizsla with adrenal-dependent hyperadrenocorticism

Fig b: Hyperadrenocorticism in a Hungarian vizsla. (i) Pictured before commencing trilostane and presenting with alopecia, spontaneous bruising and polydipsia. (ii) Pictured after six months on trilostane
antidiuretic hormone) is administered initially, but, in 90 per cent of cases, this can be tapered off over a few weeks. Postoperative endogenous ACTH concentrations give an indication of the success of the procedure in resolving HAC. Patients are also monitored to check for complete resolution of the clinical signs of HAC and, longer-term, for recurrence of the condition.

**Outcome**

Research in the Netherlands has demonstrated a high success rate for transsphenoidal hypophysectomy as a treatment for dogs with PDH, with a perioperative mortality of around 10 per cent (Hanson and others 2007, van Rijn and others 2016) – we have obtained similar figures at our clinics. Furthermore, procedure-related mortalities have been found to be lower with smaller pituitary masses (<10 mm diameter) and so, again, it is important to offer this treatment option early on. Reported postoperative complications have included reduced tear production and central diabetes insipidus, although these are transient in the majority of dogs (Hanson and others 2007). Overall, the success rate of the surgery in treating PDH is high, with remission achieved in about 85 to 92 per cent of cases and recurrence after remission in about 10 to 23 per cent after a median of 16 months (Hanson and others 2007, van Rijn and others 2016). It is thought that the recurrence is due to regrowth of adenoma cells left in situ, hence a higher rate of recurrence seen in dogs with larger pituitary masses (>10 mm). In dogs having undergone hypophysectomy, 72 per cent survival has been reported after four years in the largest reported case series of 300 dogs, which included deaths in the perioperative period (van Rijn and others 2016); this indicates a better success rate compared with medical treatment options (Box 2).

![Fig 2: Interpretation of pretrilostane cortisol. Dose increases in trilostane referred to in the figure should be made in line with available capsule sizes. As a guide, we increase the dose by 50 per cent to 100 per cent when needed and suggest a switch to twice-daily administration if clinical signs (particularly polyuria and polydipsia) are still present after one month. However, it is accepted that some clinical signs (eg, alopecia) may take three months to resolve even when the correct dose of trilostane has been established. ACTH Adrenocorticotropic hormone](http://inpractice.bmj.com/)

![Fig 3: (a) Surgeon performing a transsphenoidal hypophysectomy with the dog placed in sternal recumbency and positioned in a neurosurgical head frame. (b) Intraoperative photograph of the surgical site during transsphenoidal hypophysectomy in a dog with pituitary-dependent hyperadrenocorticism. The soft palate has been incised and retracted with stay sutures, while the pituitary mass is extracted from the pituitary fossa through a burr hole in the sphenoid bone. Head-mounted camera, x 3 magnification](http://inpractice.bmj.com/)
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Other options for pituitary-dependent hyperadrenocorticism

Radiation therapy
In the UK, there are a small number of specialist facilities offering radiation therapy (RT) to dogs with PDH. It is mainly indicated for those patients showing neurological signs secondary to a pituitary macroadenoma. Although RT has been shown to be effective at reducing mass size in dogs with pituitary tumours and associated neurological abnormalities, it has been less successful in terms of achieving remission from the associated endocrine changes. Multiple RT treatments, and therefore general anaesthetics, are typically required over several weeks, so costs are considerable. The most common adverse effects for RT include partial alopecia, erythema, mild otitis externa and ocular changes from the exposure to radiation.

Surgical options for adrenal dependent hyperadrenocorticism

Unilateral adrenalectomy
Assessing surgical candidates
The only curative treatment option for ADH is the removal of the primary adrenal mass. It is also often a viable economic option compared with long-term medical management. In studies of adrenalectomies in referral settings, around 15 to 25 per cent of adrenal masses had signs of caval thrombi, and between 22 and 63 per cent showed signs of malignancy, including pulmonary metastasis, thrombus formation and local tissue invasion (van Sluijs and others 1995, Massari and others 2011, Arenas and others 2014). As a result, assessment for invasion of the vena cava, using ultrasonography or, more typically, contrast-enhanced CT, is mandatory before surgery. In addition, thoracic imaging (radiography or CT) to document an absence of pulmonary metastases is required.

Follow-up management
During surgery, intravenous glucocorticoid supplementation is started. Immediately following surgery, close monitoring and rapid treatment of electrolyte and blood pressure abnormalities is required. Patients require glucocorticoid supplementation for approximately six weeks following surgery due to contralateral adrenal atrophy, but this is gradually tapered off.
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Outcome
The median survival of cases undergoing adrenalectomy range from 533 to 953 days (van Sluijs and others 1995, Massari and others 2011). Studies have shown intraoperative mortality is low (around 2 per cent), but postoperative mortality is around 13 to 20 per cent (van Sluijs and others 1995, Massari and others 2011). However, with improvements in postoperative management, these rates are decreasing and reported survival times in dogs undergoing adrenalectomy are now favourable compared with medical treatment (van Sluijs and others 1995, Massari and others 2011). A small proportion of dogs can have recurrence of HAC, due to development of PDH, ADH in the remaining adrenal gland or undetected metastases present before surgery.

Summary
Once a dog has been diagnosed with HAC, the importance of distinguishing between PDH and ADH should be discussed with the owner. As part of this discussion, the different options for managing HAC should be provided. Although medical management will still be used in most cases of canine HAC, the increasing availability and reported success rates of transsphenoidal hypophysectomy and adrenalectomy means that many patients with this disease may be able to benefit from surgical management.

References