Canine hyperadrenocorticism – management

Dr Christine Griebsch DipECVIM-CA, University Veterinary Teaching Hospital Sydney, Australia, discusses management of canine hyperadrenocorticism in the second instalment of this two-part series

Treatment recommendations for dogs with hyperadrenocorticism (HAC) include medical management (trilostane, mitotane), surgical management (adrenalectomy, hypophysectomy) and radiation therapy in dogs with pituitary dependent hyperadrenocorticism (PDH). The adrenocorticotrophic hormone (ACTH) stimulation test (ACTH-ST) has long been considered the gold standard to monitor medical management. Recent studies have investigated the use of lower doses of trilostane and twice or even three times daily administration. The optimal timing of when to perform an ACTH-ST after trilostane administration has been questioned. Lack of availability of synthetic ACTH and costs associated with performing an ACTH-ST have led to investigation of different monitoring tools. Radiation therapy and hypophysectomy are becoming increasingly available. This article will review recent changes in treatment recommendations and management of HAC in dogs.

INDICATIONS FOR TREATMENT

Treatment is indicated in the presence of typical clinical signs or complications of HAC such as hypertension, thromboembolic disease, diabetes mellitus, recurrent urinary tract infection (UTI), proteinuria, calcinosis cutis or severe muscle weakness. A dog with no, or only mild, clinical signs of HAC but with clinicopathologic and endocrine test results supportive of the diagnosis should not be treated. In older dogs with multiple other concurrent disorders (eg. osteoarthritis), treatment should be carefully considered. Often, the increased cortisol concentration is the only thing that ‘keeps the animal going’. In some cases, sub-optimal control of HAC might be a good compromise.

PITUITARY DEPENDENT HYPERADRENOCORTICISM

Options for treatment of PDH include medical management with trilostane or mitotane, surgical treatment with hypophysectomy or radiation therapy.

MEDICAL TREATMENT

TRILOSTANE

Trilostane is a synthetic steroid analogue which results in reversible and dose dependent inhibition of the enzyme 3beta-hydroxysteroid dehydrogenase (3beta-HSD), therefore suppressing the production of all steroid hormones. Trilostane also seems to alter other enzyme activities, has effects on intracellular cortisol metabolism and potentially modulates glucocorticoid receptor function which might explain the discordance between clinical signs and results of ACTH-ST when used to monitor response to trilostane treatment in some dogs.

STARTING DOSE AND FREQUENCY OF ADMINISTRATION

There is no consensus on the recommended starting dose and frequency of administration. The dose required to control clinical signs is variable. Small dogs seem to need a relatively larger dose to control clinical signs compared to large breed dogs.1 Vetoryl® is the Food and Drug Administration (FDA)-approved product manufactured by Dechra. There were limited capsule sizes available when the product was first released. The recommended starting dose according to the package insert is 2.2-6.7mg/kg PO once daily and this dose seemed to be well tolerated by most dogs in earlier studies.2 Newer studies then suggested twice daily dosing3 and lower starting doses.4 In a study from 2011, the initial starting dose was 0.2-1.1mg/kg BID. After one year, the mean trilostane dose was 1.7mg/kg BID in dogs with PDH.4 Control of HAC was achieved more quickly, effectively and successfully with the twice daily administration despite using a lower total daily dose but differences were only minor in another study looking at 56 dogs with PDH treated with trilostane.5 Chow et al (2013) compared a high dose (30mg/dog) once daily with a low dose (0.78±0.26mg) BID in dogs <5kg. They found that twice daily administration of low-dose trilostane was effective and had fewer potential adverse effects.5 Three times daily dosing has been suggested by Vaughan et al in dogs that were clinically not well controlled on twice daily dosing. In these dogs with poor clinical control, an ACTH-ST was performed eight to nine hours post dosing; however, there was no cut-off value provided in this study that prompted the authors to increase the frequency to three times daily administration. The mean dose of trilostane was 1.3mg/kg TID.7

RECOMMENDATION

Based on the information available, the author’s preferred starting dose is 1mg/kg twice daily or 2mg/kg once daily depending on the owner’s convenience.

MONITORING OF TREATMENT

The most important monitoring tool of treatment response is resolution of clinical signs and owner perception. Special emphasis is on resolution of polyuria (PU)/polydipsia (PD), polyphagia, panting, exercise tolerance, coat quality and demeanour. A recheck should be scheduled 10-14 days after start of treatment (and 14 days after every dose adjustment), one month later and every three to six months once good control has been achieved. Every recheck should include a thorough history with emphasis on improvement of clinical signs,
physical examination (including blood pressure measurement if possible), biochemistry with electrolytes if indicated and results of ACTH-ST (see discussion below). Monitoring of the USG can be helpful to confirm that PU/PD has resolved. Improvement of PU/PD can be seen as early as seven to 10 days after starting treatment, whereas other signs like dermatologic changes might take months to resolve. The trilostane dose should not be increased after the first visit even if clinical signs and results of ACTH-ST show poor control. Performing an ACTH-ST four to six hours post pill has long been recommended as the gold standard for monitoring response to trilostane treatment. Recommendations have, however, been extrapolated from monitoring response to mitotane treatment and have not been validated in dogs treated with trilostane. After trilostane administration the cortisol concentration decreases significantly after two to four hours. Therefore, the optimal point to perform an ACTH-ST to monitor response to treatment with trilostane may more appropriately be two to four hours post pill especially if the goal is to avoid episodes of hypocortisolism. This finding is supported by a study showing that post-ACTH-ST cortisol concentrations were lower at two hours compared to four hours post trilostane. The conclusion of the authors was that all subsequent ACTH-ST should be performed at the same time after trilostane administration. The questions remain if reference ranges for a two- to four-hour post pill ACTH-ST should be lower than the currently proposed reference ranges. Results of ACTH-ST often do not correlate well with the clinical response with some dogs doing clinically well while the ACTH-ST indicates poor control and others having poor control of clinical signs despite apparently good control of HAC based on results of the ACTH-ST. Similarly, clinically normal and well-regulated dogs on twice daily trilostane treatment showed 4h post-pill ACTH cortisol concentrations indicating over control of HAC (cortisol <2ug/dl). When tested nine to 12 hours post-trilostane the mean cortisol concentration was 5.3ug/dl and these dogs were kept on the same trilostane dose for an extended period of time without any complications. In dogs with clinical and clinicopathological findings consistent with hypocortisolism and/or hypoadrenosteronism an ACTH-ST result indicating iatrogenic hypoadrenocorticism should prompt the clinician to stop trilostane treatment immediately.

OTHER MONITORING TOOLS
Following a shortage of synthetic short-acting ACTH in Europe, studies have evaluated other possible monitoring tools. Some studies have looked at the use of cortisol concentration to monitor response to treatment. One study found that a baseline cortisol concentration could be used to monitor response to treatment. A resting cortisol >1.3ug/dl could exclude excessive suppression and a concentration <2.9ug/dl excluded inadequate control. This finding was, however, not supported by results of a study which found substantial overlap between baseline cortisol concentrations in dogs with excessive, adequate and inadequate control of HAC. Another study found that a baseline cortisol concentration >3.2ug/dl predicted that the post ACTH cortisol concentration would be >2ug/dl with 100% certainty but concluded overall that the baseline cortisol concentration should not be used as the sole monitoring tool for management of dogs with PDH treated with trilostane twice daily. ‘Control’ was, however, defined as ACTH-ST in the desired range not ‘clinical control’ in all studies. A recent study has evaluated the use of pre-trilostane, three hour post trilostane and one hour post ACTH stimulation test cortisol and found that pre-trilostane (target 1.45-5.0 ug/dl) and three hour post trilostane cortisol (target <2.3 ug/dl) were better correlated to ‘clinical control’ than the post-ACTH-cortisol. Measurement of endogenous ACTH or cortisol/ACTH ratio is not useful to monitor treatment. Measurement of UCC cannot be used as an alternative to the ACTH ST to determine the optimal dose of trilostane, but might be helpful in detecting dogs at risk for developing hypocortisolism during treatment if the UCC is in the normal range.

RECOMMENDATION
Despite often poor correlation between ACTH-ST results and clinical control, the ACTH-ST seems to be the most reliable monitoring tool in conjunction with clinical signs. Based on the information available, the author recommends performing an ACTH-ST two to three hours post trilostane 10-14 days after start of treatment with trilostane and every 14 days after making a dose adjustment. Another recheck should then be scheduled one month later. In dogs that have been newly diagnosed with HAC, it can sometimes be difficult to make decisions...
about dose adjustments based on owner observation alone. The owner might observe improvement in clinical signs and might overall be satisfied but it is often difficult for owners to decide whether clinical signs have completely resolved. Therefore, if results of the ACTH-ST are above the target range the trilostane dose is increased by 25%. In a dog that seems to be clinically well controlled with an ACTH-ST result which shows over control of HAC, no dose changes are made but the owner is warned to closely observe the dog for any clinical signs of hypoadrenocorticism (lethargy, inappetence, vomiting, diarrhea). To further assess the risk to develop clinical hypoadrenocorticism in these patients an ACTH-ST could be performed nine to 12 hours post trilostane administration. If this is also consistent with over control, the dose of trilostane should be decreased. Once good clinical control has been achieved, rechecks should be scheduled every three to six months. In dogs that have been on the same trilostane dose for a long time and clinical signs are well controlled, monitoring is based on clinical signs. In these cases, repeating an ACTH-ST might not be warranted unless progression of clinical signs of HAC or clinical signs of hypoadrenocorticism develop.

### COMPLICATIONS OF TREATMENT

Reversible iatrogenic hypoadrenocorticism can occur secondary to trilostane treatment and is diagnosed when a dog shows clinical signs of possible hypoadrenocorticism (vomiting, diarrhoea, inappetence, lethargy, weight loss, shaking, hypotension) in conjunction with an ACTH-ST consistent with HAC. Clinicopathologic changes may also be seen on bloodwork consistent with typical (aldosterone and cortisol deficient) or atypical (cortisol deficient) HAC (hyperkalaemia, hyponatraemia, azotaemia, hypoglycaemia, lack of stress leukogram). Treatment should immediately be stopped for five to seven days after which the ACTH-ST should be repeated. Treatment can be reinstituted at an at least 25% decreased dose once the post ACTH cortisol concentration is in the ideal range or above.

Adrenal necrosis with irreversible HAC was first described in 200416 and additional cases have been described in the years following this report.17 The proportions of dogs that developed hypoadrenocorticism in previous studies were 8% (5/63 with two dogs developing permanent hypocortisolism)17, 9% (2/22, transient)7, 11% (5/47, transient)17, A 13% (2/16, transient)6 and 25% (11/44, 5 of these permanent)3. A more recent paper found a 15% incidence of hypoadrenocorticism in dogs treated with trilostane for two years and around 25% when treated for four years. Hypoadrenocorticism was transient in 74% of dogs (14/19) and was permanent in five dogs. The trilostane dose or frequency of administration were not associated with the risk to develop adrenal necrosis but pituitary dependent rather than adrenal dependent HAC may increase the likelihood of hypoadrenocorticism.18 One proposed pathomechanism of adrenal necrosis is an excess of endogenous ACTH due to the lack of negative feedback mechanism of cortisol on the pituitary gland.

### MITOTANE

Mitotane is an adrenocorticolytic drug causing necrosis or atrophy of the adrenal cortex with the zona reticularis being more sensitive than the zona glomerulosa. Two different protocols have been described. If partial adrenocorticotilysis is attempted a high dose of mitotane is given daily during the loading phase followed by giving the same dose divided throughout the week. Very frequent rechecks and ACTH-ST are necessary throughout the loading phase to determine the right time to switch to maintenance therapy. Relapse of HAC is common, which requires another loading phase. Similarly, side effects are common and include gastrointestinal side effects and clinical signs due to hypoadrenocorticism. If nonselective adrenocorticolysis is attempted a higher dose of mitotane is administered. Dogs undergoing this protocol successfully will develop persistent hypoadrenocorticism and will require lifelong glucocorticoid and mineralocorticoid supplementation. The reader is referred to textbooks for a thorough description of treatment protocols. Multiple studies have compared treatment of dogs with PDH with trilostane and mitotane. In one study there was no significant difference in median survival times between dogs treated with mitotane (708 days) and trilostane (662 days).21 In a later study the median survival time of dogs treated with trilostane twice a day (900 days) was significantly longer than that of dogs treated with mitotane (720 days).21 As trilostane has milder and less frequent side effects compared to mitotane, trilostane is now considered the medical treatment of choice in dogs with HAC.

### SURGICAL TREATMENT

#### HYPOPHYSECTOMY

Successful hypophysectomy has been performed in dogs at the University of Utrecht. Published cases from this group undergoing hypophysectomy include 306 dogs with PDH.22 The median survival time described for these dogs was 781 days, the median disease free interval 951 days. Twenty seven per cent (27%) of dogs had recurrence of HAC 555 days after hypophysectomy. Predictors of relapse were larger pituitary masses and higher pre-operative UCCR compared to dogs with no relapse.23 An increased risk of death was seen with old age, large pituitary size and a high preoperative eACTH concentration.23 In 150 dogs described by the same group, the one-year survival rate was 84%, the two-year survival rate was 76%, the three-year survival rate was 72% and the four-year survival rate 68%. The relapse-free fraction was 88% after one year, 75% after two years, 66% after three years and 58% after four years. Complications included death in 12 dogs (8%) and incomplete removal of the tumour in nine dogs. Reduced tear production was observed in 47/150 dogs (31%) and was permanent in 10 dogs (7%). Central diabetes insipidus was transient in 78% and persistent in 22%.24 Other reported complications include mild transient hypernatraemia and secondary hypothryoidism. Medical management of dogs after hypophysectomy includes administration of synthetic vasopressin, glucocorticoids and levthyroxine. Recently successful hypophysectomy using a video telescope has been described. This group reported a 19% postoperative mortality rate in 26 dogs with PDH. The majority of dogs (95%) (20/21) were in clinical remission one year after the procedure.25 Hypophysectomy is a good treatment option for dogs with
PDH however requires an experienced surgeon.

**RADIATION THERAPY (RT)**

Radiation therapy is becoming increasingly available in veterinary medicine and has been shown to improve outcome in dogs with pituitary masses. A study comparing dogs with pituitary masses treated with RT (19, 14 with PDH) and not receiving RT (27, 17 with PDH) found a mean survival time of 1405 days in the irradiated and 359 in the non-irradiated group. Five of 14 dogs with PDH receiving RT had resolution of clinical signs of HAC. Irradiated dogs with smaller tumours lived longer than dogs with larger tumours.26

A recent study evaluated RT in nine dogs with PDH, with eight of them exhibiting neurological signs. The dogs received RT for four weeks (total of 48 Gy in 4-Gy fractions). An MRI, assessment of neurological signs, possible adverse effects of RT and hormone testing (eACTH, ACTH-ST) were performed before and 1-3, 5-7 and 7-14 months after RT. Half of the dogs with neurological signs had complete resolution and half had transient resolution of neurological signs. Adverse effects of RT included moderate to severe pituitary hemorrhage and bilateral otitis media (3/9). RT did not induce any significant changes in the dogs’ basal plasma ACTH concentration and pre- and post-ACTH serum cortisol concentrations. All dogs except one dog were still alive seven to 14 months after RT. The authors concluded that RT is effective to reduce pituitary size and improve neurological signs but does not appear to affect blood hormone concentrations, necessitating additional medical treatment against hypercortisolism.27

In conclusion radiation therapy should be considered in tumors >7mm in size. It can resolve or improve neurological signs. The prognosis is better in dogs with smaller tumours hence early RT therapy improves outcome. The goal of RT is to shrink the tumour not to cure HAC. Most dogs with PDH will require ongoing medical management of HAC.

**HAC DUE TO FUNCTIONAL ADRENAL TUMOUR (FAT)**

Adrenalectomy is the treatment of choice for FAT as this can be curative. Median survival times of two to four years have been described. Medical treatment is chosen if the dog is a poor surgical candidate due to comorbid conditions, a non-resectable tumour, metastasis are present or the owner does not want to pursue surgery.

**MEDICAL TREATMENT**

It has long been postulated that mitotane is the preferred medical treatment option in dogs with FAT due to its corticolytic properties. Multiple studies showed however that survival times are not significantly different in dogs with FAT treated with trilostane versus mitotane. One study found a median survival time of 102 days for dogs treated with mitotane and 353 days for dogs treated with trilostane. A more recent study found a median survival time of 14 months in dogs treated with trilostane and 15.6 months in dogs treated with mitotane. Therefore trilostane is the medical treatment of choice in dogs with FAT.

**SURGICAL TREATMENT**

**ADRENALECTOMY**

Adrenalectomy can be performed via laparotomy or laparoscopy.28 Dogs with HAC are generally poor surgical candidates as they have fragile skin, delayed wound healing and are at increased risk of thromboembolism. Therefore pre-treatment with trilostane (one to two months prior to surgery) is recommended to stabilize the patient before surgery. Postoperative complications include pancreatitis, pulmonary thromboembolism, acute kidney injury, pneumonia, disseminated intravascular coagulation (DIC) and hypoadrenocorticism. Perioperative mortality is between 13.5-30% and decreases with experience of the surgeon. Negative prognostic factors include a tumour size >5cm, distant metastases and vein thrombosis.30 Invasion of the caudal vena cava is associated with a higher surgical mortality rate but is not a contraindication for surgery and does not affect long term prognosis.31

Patients undergoing adrenalectomy should undergo surgery and be managed at referral specialist centres hence intra- and postoperative management is not discussed in detail in this article.

**REFERENCE LIST**


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### READER QUESTIONS AND ANSWERS

1. **WHICH OF THE FOLLOWING IS NOT AN INDICATION FOR TREATMENT OF HAC?**
   - A. Calcinosis cutis
   - B. Hypertension
   - C. Diabetes mellitus
   - D. Positive LDDST with no clinical signs of HAC
   - E. Recurrent urinary tract infection.

2. **THE MOST IMPORTANT MONITORING TOOL TO MONITOR RESPONSE TO TRILOSTANE TREATMENT IS:**
   - A. ACTH-ST
   - B. UCCR
   - C. Clinical signs
   - D. Baseline cortisol concentration
   - E. eACTH

3. **WHICH ONE OF THE FOLLOWING STATEMENTS REGARDING TREATMENT OF PDH WITH TRILOSTANE IS FALSE?**
   - A. Triostane is the medical treatment of choice for dogs with PDH.
   - B. Transient hypoadrenocorticism and persistent hypoadrenocorticism due to adrenal necrosis have been described.
   - C. To monitor treatment an ACTH-ST should be performed 2-4 hours after triostane administration.
   - D. Decisions to increase or decrease the dose of triostane are always based on results of an ACTH-ST alone.
   - E. Triostane is typically given once or twice daily.

4. **WHICH ONE OF THE FOLLOWING STATEMENTS REGARDING TREATMENT OF PDH IS CORRECT?**
   - A. Successful hypophysectomy always is curative for HAC.
   - B. Radiation therapy to treat a pituitary tumour results in resolution of HAC.
   - C. After hypophysectomy lifelong administration of synthetic vasopressin is necessary.
   - D. A common complication of hypophysectomy is otitis media.
   - E. Most dogs undergoing radiation therapy will have resolution of improvement of neurological signs.

5. **WHICH ON OF THE FOLLOWING STATEMENTS REGARDING TREATMENT OF ADRENAL DEPENDENT HAC IS FALSE?**
   - A. Mitotane is the medical treatment of choice for dogs with a functional adrenal tumour.
   - B. Invasion of the caudal vena cava is not a contraindication for surgery.
   - C. There is no significant difference in survival times between dogs treated with trilostane or mitotane.
   - D. Dogs undergoing adrenalectomy should be treated with trilostane prior to surgery.
   - E. Postoperative complications in dogs undergoing adrenalectomy include pancreatitis, pulmonary thromboembolism and acute kidney injury.

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ANSWERS: D, C, D, E, A