Hyperadrenocorticism: Treating Dogs

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ABSTRACT: This article is a complete review of all reported therapies for hyperadrenocorticism in dogs. Both medical and surgical options for treating pituitary-dependent hyperadrenocorticism and adrenal tumor-related disease are discussed, and the efficacy, safety, and use of these treatments are compared.

Hyperadrenocorticism is one of the most commonly recognized endocrinopathies in dogs. Two forms exist. Excessive adrenocorticotropic hormone (ACTH) secretion is the result of pituitary-dependent hyperadrenocorticism (PDH) and is responsible for approximately 80% to 85% of naturally occurring cases in dogs. An autonomously functioning adrenocortical tumor (AT) is reported in the vast majority of the other naturally occurring cases. Both causes of hyperadrenocorticism result in prolonged hypercortisolemia and cause the constellation of clinical signs associated with this endocrinopathy.

Newer therapeutic options for canine hyperadrenocorticism have recently been introduced, and their use is becoming more widespread. Trilostane, a 3β-hydroxysteroid dehydrogenase inhibitor, has reportedly been effective in treating PDH. Recent interest in hypophysectomy for the treatment of clinical PDH has been piqued by reports of good clinical outcomes in 150 dogs treated in this manner over a 10-year period at Utrecht University Clinic for Companion Animals in The Netherlands. This article reviews the mechanisms of action, treatment protocols, monitoring, efficacy, adverse effects, and survival times of these more recent treatment options as well as other treatments, including mitotane, selegiline, ketoconazole, adrenalectomy (for ATs), radiation therapy, metyrapone, aminogluthethimide, cyproheptadine, bromocriptine, and RU-486.

MITOTANE
Mitotane (Lysodren [Bristol-Myers Squibb], o,p-DDD) is the most common medical therapy for hyperadrenocorticism in dogs. A potent adrenocorticolytic agent, mitotane results in progressive adrenocortical necrosis of the zona fasciculata and zona reticularis. Mitotane is activated within adrenocortical tissue to a reactive acyl chloride intermediate and subsequently is covalently bound to adrenal proteins, resulting in progressive cortical necrosis. The therapeutic goal for patients with PDH is to achieve a relatively hypoadrenal state that is sufficient for the patient’s physiologic needs but unable to respond to continued excessive ACTH stimulation from the untreated pituitary disease.

Two phases of classic mitotane administration for treatment of PDH exist:

- Induction
- Maintenance
Treatment induction begins with daily administration of 50 mg/kg of mitotane, divided and given with meals. In the vast majority of cases, induction therapy lasts 5 to 14 days. \(^6\) Completion of induction is based on ACTH stimulation test documentation of a subnormal post-stimulation serum concentration of cortisol (normal: 1 to 5 µg/dl). Pet owners must be vigilant during this treatment period and able to monitor appetite, water consumption, behavior, and episodes of vomiting or diarrhea. Daily mitotane should be discontinued when clear decreases in appetite or water consumption are noted or when listlessness, vomiting, or diarrhea is documented. An ACTH stimulation test should be conducted within 24 hours to evaluate adrenal function and determine whether induction therapy is complete. Because mitotane reliably reduces cortisol production, the dog should be examined by a veterinarian on day 8 or 9 of induction, and an ACTH stimulation test should be conducted even if no clinical signs of completion of induction are noted. Induction should be continued for an additional 3 to 7 days if post-ACTH stimulation cortisol levels remain elevated above the goal of 1 to 5 µg/dl. This process should continue until control is achieved. Because the urine cortisol:creatinine ratio is unreliable for monitoring mitotane therapy, it should not be used.\(^7,8\)

In a study\(^6\) of 200 dogs treated with induction doses of mitotane, 50 dogs developed adverse effects, such as gastrointestinal (GI) upset, weakness, and ataxia, during the induction phase. The dogs in this study also received physiologic daily glucocorticoids (e.g., prednisone at 0.1 mg/kg/day). In 184 of the 200 dogs, mitotane was subsequently administered after induction at maintenance doses, and 107 of these dogs had relapses during maintenance treatment. Two years following the initial induction therapy, all 184 dogs were still alive and were receiving mitotane at a dose of 26.8 to 330 mg/kg/wk. In another study\(^9\) of 60 dogs, a median survival time of 30 months was reported. The median survival time in a small number of dogs (25) with PDH treated with mitotane was 708 days (range: 33 to 1,399 days).\(^10\)

Medical adrenalectomy is an alternative mitotane protocol for the treatment of PDH. In this protocol, reported for PDH patients (mean: 101.6 mg/kg/wk). Adverse drug reactions were reported in 19 of 32 dogs.\(^12\) Adverse effects of mitotane include GI upset, idiosyncratic hepatotoxicity, central nervous system (CNS) toxicity, and development of transient or permanent hypocortisolism.\(^6\) Two dogs treated with mitotane reportedly developed bone marrow necrosis when receiving appropriate doses of the drug.\(^13\)

**TRILOSTANE**

Trilostane is a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase enzyme system and blocks the production of both aldosterone and cortisol. Trilostane competes with pregnenolone as a substrate for 3β-hydroxysteroid dehydrogenase and results in decreased production of progesterone, the progenitor of almost all steroid hormone production in not only the adrenal gland but also gonadal and placental tissue.\(^14\) Excessive ACTH production continues in cases of PDH treated with trilostane, and adrenal gland size increases during
The treatment protocol for trilostane differs from that for mitotane in that no distinct induction and maintenance periods exist for trilostane. Trilostane dosing is variable, but recommendations for initial therapy have been reported as follows:\textsuperscript{2,19}:

- Dogs weighing less than 11 lb (5 kg) should receive 30 mg PO q24h or q48h.
- Dogs weighing 11 to 44 lb (5 to 20 kg) should receive 60 mg PO q24h.
- Dogs weighing more than 44 lb (20 kg) should receive 120 mg PO q24h.

ACTH stimulation testing is the recommended monitoring method and should be conducted 10 to 14 days following initiation of therapy and again 2 weeks later, followed by repeated testing every 3 months. Current recommendations\textsuperscript{20} include stimulation testing 4 to 6 hours after trilostane administration. If poor control of hyperadrenocorticism is documented based on clinical history and ACTH stimulation test results, the dose of trilostane should be modified by either administering the drug twice daily or prescribing serial increases in once-daily administration.

Dose modifications of trilostane are limited by the medication’s formulation: 30-, 60-, or 120-mg capsules. Although the medication can be compounded by some pharmacies, availability in the United States is limited. This drug is not fully FDA approved, and special dispensation from the FDA is required to import the drug from the United Kingdom, where it is commercially available.

KETOCONAZOLE

Ketoconazole is an antifungal that inhibits ergosterol synthesis and fungal cell membrane growth.\textsuperscript{1} It also inhibits mammalian steroidogenesis by inhibiting the cytochrome P-450 enzyme system responsible for both androgen and cortisol production. Ketoconazole inhibits both the first and last steps in cortisol synthesis (11-deoxy to cortisol). Ketoconazole also inhibits ACTH secretion from pituitary corticotrophs.\textsuperscript{22} In many ways, ketoconazole is the most sensible steroidogenesis inhibitor, considering the potential effects of the drug.

Treatment involves oral administration of ketoconazole at an initial dose of 5 mg/kg q12h. This dose should be increased to 10 mg/kg PO q12h after 7 days if no adverse clinical effects are noted. Twenty-one days after initiation of treatment, an ACTH stimulation test should be conducted several hours after drug administration. The dose should be increased—based on incomplete clinical sign response and ACTH stimulation testing—in 5 mg/kg/dose increments. Most dogs require 15 mg/kg q12h.\textsuperscript{1} In a study\textsuperscript{23} of 60 dogs with hyperadrenocorticism (i.e., both PDH and AT), 75% to 80% of the dogs reportedly had a good clinical response to ketoconazole. The plasma cortisol response to ketoconazole was not significantly different in dogs with PDH versus those with AT. Twenty percent to 25% of dogs fail to respond to ketoconazole, which is likely the result of poor intestinal absorption. Rarely reported side effects include transient hypocortisolism, GI upset, and hepatotoxicity.

HYPOPHYSECTOMY

PDH is the result of excess ACTH secretion from adenomatous pituitary corticotrophs that vary in size from microscopic to space-occupying, large pituitary masses. Most of the other available therapies target the adrenal gland and not the true cause of the disease. This results in effective, if only symptomatic, treatment in
most cases; however, in approximately 10% of patients with PDH, signs of a space-occupying intracranial mass develop because of macroadenomas. Therapy with both trilostane and mitotane, as already described, actually results in increased ACTH secretion partly due to the removal of negative feedback mechanisms still in effect. This may at least be theorized to promote pituitary tumor growth.

Hypophysectomy methods have been described in dogs. Dynamic computed tomography or magnetic resonance imaging (MRI) is necessary to accurately localize the pituitary lesion and surgical landmarks. The pituitary is located within the bony sella turcica and varies in position among dogs. With the use of advanced imaging, the sphenoid bone can be removed ventral to the location of the pituitary via a transoral or ventral cervical approach. Complete hypophysectomy can be attempted manually or by using an ultrasonic aspirator. Ideally, the adenoma would be removed while leaving the remaining normal pituitary tissue intact, but the limited field of view and relatively small size of macroadenomas make this impossible. Therefore, following hypophysectomy, secondary hypothyroidism and hypoadrenocorticism are anticipated; thyroid and glucocorticoid hormone supplementation must be continued lifelong. Desmopressin (synthetic antidiuretic hormone) is routinely administered for 2 weeks following surgery and then continued if signs of polyuria persist, indicating persistent central diabetes insipidus. Schirmer’s tear test values should be monitored and ocular lubrication instituted if the values decrease.

In the most comprehensive review of hypophysectomy in the treatment of canine hyperadrenocorticism, 150 dogs were evaluated in a prospective study. Twelve of these dogs died within 4 weeks after surgery: Two died during surgery because of cerebral arterial hemorrhage, and the remainder died from a variety of complications, including thromboembolism, hypernatremia, diabetic ketoacidosis, and pneumonia. Of the remaining 138 dogs, 127 had remission of PDH. Nine dogs had residual disease based on persistently elevated urine cortisol:creatinine ratios and/or residual pituitary tissue found on follow-up imaging. Within 5 months of hypophysectomy, five of nine dogs died or were euthanized for reasons related to hyperadrenocorticism, three were treated with mitotane, and one subsequently underwent bilateral adrenalectomy. Hyperadrenocorticism did not recur in 95 (75%) of 127 dogs that were hypophysectomized. The median survival time after surgery for these dogs was 28 months. Hyperadrenocorticism recurred in 32 (25%) of 127 dogs a median of 18.3 months after surgery. Fourteen dogs were euthanized because of complications of hyperadrenocorticism, 14 died or were euthanized because of unrelated causes, and four were still alive at the time of publication. Another study reported an 82% 2-year survival for dogs undergoing hypophysectomy.

Complications of hypophysectomy include the anticipated secondary hypothyroidism and hypocortisolism and central diabetes insipidus resulting from complete removal of the pituitary. Central diabetes insipidus is often transient because hypothalamic production of arginine vasopressin can result in antidiuresis. Keratoconjunctivitis sicca developed in 47 of 150 dogs after surgery and is theorized to be the result of traumatic or ischemic injury to the innervation of the lacrimal glands.

**PITUITARY RADIATION**

Pituitary radiation should be considered in dogs with PDH and a macroadenoma resulting in CNS signs. In a study of 24 dogs with PDH and associated CNS signs and 19 dogs with ACTH–secreting pituitary tumors and no clinical signs of intracranial disease, radiation therapy reduced clinical signs of intracranial disease, but not of hyperadrenocorticism. Radiation therapy was reportedly more effective when the pituitary tumor size was small. Radiation therapy has also been evaluated in treating PDH when no signs of CNS disease are present. Six dogs with PDH and pituitary tumors that were detected using MRI but without clinical signs of intracranial disease were treated with cobalt 60 irradiation for 3 1/2 weeks. Clinical signs of hyperadrenocorticism resolved in three dogs but recurred in two of them. Overall, five of six dogs did not respond clinically to radiation for the treatment of PDH; when MRI was repeated 1 year
later, however, the pituitary masses had completely resolved in four of six dogs, and the size of the masses had decreased in the other two dogs.

**ADRENALECTOMY**

Adrenalectomy is the preferred treatment of AT because it offers the opportunity for a cure. Mitotane therapy, as already discussed, has been used in nonsurgical cases of AT, but higher doses and the risk for metastatic disease with malignant tumors make it a less-than-ideal choice. Although bilateral adrenalectomy has been performed in dogs with PDH that cannot tolerate medications or in which hypophysectomy is not pursued, it is used mainly in treating AT.

Before surgery, medical management may be indicated to control clinical signs of hyperadrenocorticism, improve healing, and reduce thromboembolic complications. Steroidogenesis inhibitors such as ketoconazole or trilostane can provide these benefits without changing the preoperative adenoma size, except in cases in which trilostane might cause adrenal necrosis. Conversely, mitotane—if effective—can reduce the size of an adenoma or carcinoma. Immediately before and after surgery, glucocorticoids and mineralocorticoids should be administered because removal of autonomously functional ATs results in transient hypoadrenocorticism until the atrophied contralateral adrenal gland regains the ability to respond appropriately to ACTH. The optimal dose of steroid therapy after adrenalectomy has not been determined for dogs, but based on recommendations in people, supraphysiologic doses may be required to avoid the effects of acute steroid withdrawal. Steroid supplementation should gradually be tapered over 2 to 3 weeks following surgery.

The surgical approach to AT can be ventral midline or pericostal. The latter has the advantage of minimal dissection and trauma to other abdominal organs. The ventral midline approach enables more complete abdominal evaluation for occult or known metastatic disease. In a study of 21 dogs that underwent surgical adrenalectomy, 15 of 17 dogs that survived the perioperative period had long-term remission of their clinical signs. The median survival time of dogs with carcinomas was 778 days, and the median survival time of dogs with adenomas was not obtained because none of these dogs died from adrenal disease or related complications. Two of 21 dogs with residual disease were treated postoperatively with mitotane to control clinical signs. The four dogs that failed to survive in the postoperative period (defined as within 2 weeks after surgery) died or were euthanized as a result of ischemic jejunal necrosis, addisonian crisis and dilated cardiomyopathy, thromboembolic disease, and one unknown cause of acute abdominal pain and azotemia.

**OTHER STEROIDOGENESIS INHIBITORS**

Metyrapone is an 11β-hydroxylase inhibitor that inhibits the final step in adrenal steroidogenesis. In people, metyrapone administration has been shown to result in reduced cortisol levels. At high doses, it also seems to reduce ACTH secretion by an unknown mechanism. However, this suppressive effect on ACTH secretion is overcome by reduction in cortisol-mediated negative feedback to the pituitary. Most reported side effects in people involve GI upset. There are no reports in the veterinary literature of metyrapone administration in dogs. The drug is expensive, its availability is limited, and its use is not recommended.

Aminoglutethimide, a cytochrome P-450 enzyme inhibitor that blocks the conversion of cholesterol to pregnenolone, has been demonstrated to reduce cortisol secretion in normal dogs. In a study of 10 dogs with PDH, aminoglutethimide was administered at a dose of 15 mg/kg/day. Reductions in serum cortisol levels were documented, but complete response was achieved in only one dog and a partial response in four. Side effects included hepatotoxicity, GI upset, and weakness. Given the poor response rate to the drug compared with the response rates to mitotane, trilostane, ketoconazole, and hypophysectomy, the use of aminoglutethimide alone should be questioned.

**MIFEPRISTONE (RU-486)**

Mifepristone is a steroid analogue that is a competitive inhibitor of progesterone and glucocorticoids at receptor sites. Administration of the drug results in increases in measured serum levels of both cortisol and ACTH but reduces cellular effects of cortisol and thus the clinical signs of hyperadrenocorticism. Side effects reported in people are generally attributable to hypocortisolism and resolve when the drug is removed. The drug has been shown to be effective in treating people with AT and syndromes of ectopic ACTH secretion, but not in cases of PDH because increased ACTH secretion and subsequent hypercortisolemia overwhelm the drug’s competitive receptor blockade. The pharmacokinetics of mifepristone have been studied in dogs, and significant interindividual variation in the metabol-
lism of the drug has been shown.\textsuperscript{40} Although this drug is unlikely to have a role in treating PDH, it may have a role in treating non- or presurgical cases of ATs in dogs; however, information is currently lacking.

**SELEGILINE**

Selegiline (i.e., L-deprenyl) is a monoamine oxidase inhibitor that enhances CNS dopamine concentrations. Dopamine inhibits pituitary pars intermedia ACTH secretion and thus has been proposed as a centrally acting therapy for PDH.\textsuperscript{41} However, approximately 70\% of canine PDH cases are caused by adenomatous changes of a pituitary pars distalis cell type that secretes ACTH independent of dopaminergic control. In the other 30\% of cases, immunocytochemical analysis has shown that adenomatous changes can involve multiple cell types within the pituitary pars distalis, but only one of these types is susceptible to dopaminergic inhibition.\textsuperscript{42} There is no indication for the use of L-deprenyl in treating AT.

Administration of 2 mg/kg PO q24h has reportedly had very few side effects, and no specific monitoring has been recommended.\textsuperscript{43} However, the efficacy of selegiline must be questioned. In one early study\textsuperscript{41} of the drug’s use in patients with PDH, 83\% of dogs improved within 2 months of L-deprenyl administration. However, this study was based mainly on owner observations and did not stringently evaluate objective criteria. In a more stringent evaluation of 10 dogs,\textsuperscript{44} L-deprenyl was administered as already described, and monthly evaluations included owner observations as well as results of a complete blood count, serum chemistry profile, urine cortisol:creatinine ratio, low-dose dexamethasone suppression test, and corticotropic-releasing hormone stimulation test. At the end of the 6-month study, all dogs also underwent repeat ACTH stimulation tests and adrenal ultrasonography. Improvement was noted in only two dogs, and deterioration or no change was noted in the other eight dogs. These results strongly suggest that L-deprenyl should not be used as the sole therapy for PDH.

**OTHER CENTRALLY ACTING THERAPIES FOR PDH**

Bromocriptine, a dopamine agonist, has been evaluated in treating canine PDH.\textsuperscript{45} The proposed mechanism of action of the drug (i.e., increasing CNS dopamine concentrations and inhibiting ACTH secretion) is ultimately similar to that of selegiline. Just like selegiline, bromocriptine has not been shown to be effective in cases of PDH in dogs and is not recommended.

The use of cyproheptadine in treating canine Cushing’s disease is similarly ill suited. In theory, serotonin may support excess ACTH secretion,\textsuperscript{1} and the use of cyproheptadine as antiserotonergic therapy for PDH has been evaluated. Results of a study\textsuperscript{46} of nine dogs receiving either 0.3 or 1 mg/kg/day of cyproheptadine for 2 months were disappointing. Cyproheptadine is not recommended for the treatment of hyperadrenocorticism in dogs.

**DISCUSSION**

Many factors, including cost, convenience, and owner preference, influence the decision of which treatment(s) is most suited to each patient with hyperadrenocorticism. In the long term, mitotane may be one of the most convenient treatments because maintenance therapy involves administration two or three times per week. Dogs that have undergone adrenalectomy or hypophysectomy or are receiving ketoconazole or trilostane require daily or twice-daily drug administration.

Safety of the above therapies should also influence decision making. Sudden deaths with trilostane administration have been reported in the literature.\textsuperscript{2,21} Sudden death has not been reported in the literature regarding mitotane or ketoconazole. Although immediate postoperative mortality associated with both hypophysectomy and adrenalectomy has already been discussed, acute death has not been reported subsequently in affected patients.

Steroidogenesis inhibitors are infrequently used in treating Cushing’s disease in people.\textsuperscript{47} Their use is limited to patients in whom surgery or mitotane therapy has failed or is impossible or in whom only temporary control of hypercortisolemia is desired.\textsuperscript{35} The long-term effectiveness of steroidogenesis inhibition in human Cushing’s disease has been disappointing.\textsuperscript{47,48} In addition to the many side effects of steroidogenesis inhibitors, these drugs may lose their effectiveness as increasing circulating ACTH eventually overrides incomplete enzyme...
inhibition. Although this may be an argument against the use of drugs such as trilostane for the long-term management of canine PDH, it should be remembered that surgical approaches to pituitary disease are less common in dogs, necessitating long-term drug therapy. In many dogs, mitotane therapy also becomes less effective over time, and relapses are common. However, reinduction with mitotane is usually successful in regaining remission of clinical disease. It is interesting that the most common use of mitotane in human hyperadrenocorticism, unlike in the canine disease, is for complete medical adrenalectomy. As for steroidogenesis inhibitors, ketoconazole could arguably be considered the best choice for the treatment of hyperadrenocorticism. Ketoconazole is the most effective of these drugs in people, probably owing to its inhibition of multiple enzymes and its ability to suppress ACTH production. Unfortunately, ketoconazole has not been studied extensively in dogs, so firm recommendations cannot be made.

The tools available to monitor long-term use of steroidogenesis inhibitors are noteworthy. Although the ACTH stimulation test has been extensively evaluated in monitoring mitotane therapy, the use of this test in patients receiving ketoconazole or trilostane is empiric and has not been critically evaluated. As already discussed, the efficacy of steroidogenesis inhibitors is limited by the fact that progressive increases in ACTH secretion can eventually overwhelm the ability of the drugs to inhibit adrenal cortisol production. Serial ACTH stimulation testing conducted with the same dose of ACTH may not be the most dependable means to monitor the efficacy of these medications. As with many other endocrinopathies, clinical signs and patient condition may be much more reliable than any given hormone assay.

REFERENCES


5. **L-Deprenyl** is effective in  
   a. most dogs with PDH.  
   b. dogs with adrenal tumors.  
   c. a small subset of dogs with PDH.  
   d. all dogs with hyperadrenocorticism.

6. The lowest reported recurrence rates of hyperadrenocorticism have been in dogs treated with  
   a. mitotane.  
   b. trilostane.  
   c. hypophysectomy.  
   d. ketoconazole.

7. Other than transient hypocortisolism, another reported side effect of trilostane is  
   a. hepatic necrosis.  
   b. hypoglycemia.  
   c. acute death.  
   d. GI signs.

8. The induction phase of mitotane therapy is complete when  
   a. ACTH stimulation test results are normal.  
   b. low-dose dexamethasone suppression testing is normal.  
   c. polyuria and polydipsia resolve.  
   d. the post-ACTH serum cortisol concentration is in the normal resting range.

9. The preferred therapy for an adrenal tumor is administration of  
   a. mitotane.  
   b. adrenalectomy.  
   c. trilostane.  
   d. radiation therapy.

10. After hypophysectomy, hormone replacement therapy with administration of _______ must be lifelong.  
    a. glucocorticoids  
    b. thyroid hormone  
    c. antidiuretic hormone  
    d. a and b