

Medical treatment of hyperadrenocorticism in the dog

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The aim of most medical treatments of hyperadrenocorticism (mitotane, ketoconazole, trilostane) is to suppress adrenal production of cortisol to a relative hypoadrenocorticoic state, leaving the animal with enough cortisol production for day-to-day existence but abolishing adrenal reserve, thus limiting adrenal responsiveness to excessive ACTH secretion or suppressing cortisol production by tumour cells.

The centrally acting medical treatments (for example selegiline, cyproheptadine and bromocriptine) are believed to influence pituitary production of ACTH, and their use (if any) is restricted to PDH.

Mitotane

Mitotane is the most commonly used treatment for PDH and it is generally accepted as the most efficacious.

Mitotane is administered orally and should be given with food to optimise absorption.¹ It is metabolised to its active metabolite in the adrenal cortex² where its main action is to bind to mitochondrial macromolecules and destroy them, leading to cell death and thus destruction of the affected tissues. The adrenal gland zonae reticularis and fasciculata are selectively affected, generally sparing the zona glomerulosa unless destruction is very extensive.³

There are two widely practised protocols utilising mitotane.⁴⁻⁷ Generally, it is either administered daily for an induction period of 5 to 14 days to induce controlled partial destruction of the adrenal cortex, followed by weekly maintenance treatment ('standard protocol'), or it is administered for a longer induction period until the adrenal cortex has been chemically ablated, and then administration ceases ('alternative protocol'). In either protocol glucocorticoid supplementation may be used in the induction period to ameliorate signs of rapidly declining cortisol concentrations, and in the latter protocol, both glucocorticoid and mineralocorticoid should be administered to prevent signs from iatrogenic hypoadrenocorticism as adrenal ablation is achieved.

Up to 25% of dogs have adverse affects during the induction period and up to 30% have adverse effects during maintenance therapy.⁴ Most of these adverse effects are attributable to absolute or relative hypoadrenocorticism. Other adverse effects are neurological signs and gastrointestinal disturbances. Relapses requiring further induction are not uncommon, and a number of animals will develop permanent iatrogenic hypoadrenocorticism.

The 'alternative' treatment protocol of chemical ablation of the adrenal cortex⁵ seems to have the advantage of fewer relapses in the first 12 months of treatment (27% compared to 58%) and lower costs because less mitotane is used, but the prevalence of side effects during induction is comparable.

The author's preference is to use the standard protocol initially, usually giving the induction dose of mitotane for 5 days, then performing an ACTH stimulation test to assess response to treatment before proceeding with further induction or maintenance dosing. ACTH response testing is performed 48 hours after the last mitotane dose is administered to assess the maximal effect of the mitotane dose on the adrenal gland as full cytotoxic effect is not attained until this time. If an animal proves very difficult to control on the standard mitotane protocol, then the 'alternative protocol' or, more often, surgical adrenalectomy is considered.

Mitotane can be used as a chemotherapeutic option for dogs with adrenal tumours. It is palliative only, and reserved for cases in which the tumour is inoperable, has metastasised, or in which surgical treatment is declined. The induction period required to suppress adrenal cortisol production satisfactorily is generally longer than that needed for PDH dogs, and the maintenance dose higher.

Ketoconazole

Ketoconazole is used much less frequently than mitotane, but is currently the main alternative medical treatment for PDH. It reduces cortisol production principally by inhibition of enzyme systems integral to mammalian steroidogenesis.^{8,9}

Ketoconazole has been shown to be effective in controlling hypercortisolaemia in dogs with PDH.¹⁰ It needs to be administered twice daily and up to 20 to 25% of dogs will not respond to ketoconazole,⁷ due to poor intestinal drug absorption or other undefined reasons. Side effects are generally caused by inadequate circulating cortisol concentrations due to overdose. Gastrointestinal signs such as anorexia and vomiting are reported, as well as altered coat colour and temporary increase of plasma enzymes of hepatic origin, though this usually reverses on withdrawal of the drug.¹¹ The most serious toxicity reported in people is idiosyncratic hepatic necrosis¹² at therapeutic drug doses.

Ketoconazole can also be used for symptomatic treatment of adrenal tumour disease when surgical treatment is not possible.

Etomidate

Etomidate, an anaesthetic agent, is another imidazole derivative and is the most powerful adrenal enzyme inhibitor known.^{13,14} While this drug has a place in human endocrine therapy for acute treatment of endocrinopathic psychoses or severe hyperadrenocorticoic complications, its brief effect and parenteral administration limit its usefulness in veterinary patients.

ACTH	Adrenocorticotrophic hormone
LDDST	Low-dose dexamethasone suppression test
PDH	Pituitary-dependent hyperadrenocorticism OR pituitary-dependent hyperadrenocorticoic
UVCS	University Veterinary Centre, Sydney



Figure 1. Dog in UVCS trilostane treatment trial before (a) and after (b) successful treatment with trilostane.

Aminoglutethimide

Aminoglutethimide is a non-selective blocker of adrenal steroid synthesis affecting cortisol, aldosterone and adrenal androgen production. This drug causes only partial blockade, and excessive secretion of ACTH eventually over-rides the blockade and causes return of cortisol concentrations to pre-treatment values within days.¹⁵ For this reason, when used for pituitary dependent disease in people, it is combined with other treatments such as metyrapone (which exerts a synergistic effect) or pituitary irradiation. Side-effects in people are frequent and include anorexia, nausea, vomiting, lethargy, sedation, blurred vision, headache and myalgia. A transient skin rash is common and hypothyroidism is thought to occur in 5% of patients.¹⁶

Little is known about aminoglutethimide use for treatment of hyperadrenocorticism in dogs. It has been shown to reduce circulating cortisol concentrations in normal dogs without adverse side-effects.¹⁷ The drug has been used in 12 dogs with PDH and was reported to have induced clinical remission and 'tendency toward normalisation' of a number of laboratory variables including blood cortisol concentrations.¹⁸

Metyrapone

Like aminoglutethimide, metyrapone is an enzyme blocker that works at the level of the adrenal gland. It has a more selective effect, acting to block transformation of 11-deoxycortisol to cortisol.¹⁹ As a result of this, large amounts of precursor steroids with mineralocorticoid effect accumulate, and hypertension and hypokalaemia can result. Nausea, vomiting and dizziness are common side effects in people and, because of this and the cost of the drug, it has been relegated largely to combination therapy (often with aminoglutethimide).²⁰ As with aminoglutethimide, ACTH secretion in PDH can eventually overcome the incomplete enzyme blockade but metyrapone can be very useful to control hypercortisolaemia in the short-term.²¹ To the author's knowledge, there are no reports of use of metyrapone for treatment of canine PDH, but it has been used successfully in two affected cats for stabilisation and alleviation of signs prior to bilateral adrenalectomy.^{22,23}

Trilostane

Trilostane (WIN 24,450) is a synthetic, hormonally inactive steroid that competes with pregnenolone as a substrate for 3- β -hydroxysteroid dehydrogenase and thus inhibits pregnenolone conversion to progesterone.²⁴ It is therefore a non-selective

inhibitor of almost all steroid hormone production including adrenal, gonadal and placental sources. Inhibition of adrenal steroidogenesis has been shown to occur at lower doses than that inhibiting steroidogenesis in other organs.^{24,25}

There are three published abstracts reporting trilostane use in the dog²⁶⁻²⁸ with variable results. A recent 2-year clinical trial conducted by the author at UVCS,²⁹ found this drug to be a very successful treatment for medical management of PDH in 30 dogs, although dose rates and frequency varied considerably between dogs. No adverse side effects were observed. Figures 1a and 1b show one of the dogs in the UVCS trial before, and after treatment with trilostane.

The author's experience in treating a single dog with adrenal tumour has been similarly successful.

Trilostane is not currently available in Australia, and if it does become available, cost will be a major impediment to its routine use for treating hyperadrenocorticism in dogs. The cost of medical treatment with trilostane is likely to be triple that of maintaining a dog on mitotane treatment.

Selegiline

Selegiline (L-deprenyl) is a monoamine oxidase B inhibitor that acts centrally as a dopamine agonist. In dogs it has been reported as useful for geriatric canine cognitive disorder³⁰ but recent interest has largely been focussed on its role in treating excessive ACTH secretion in PDH dogs. The rationale for such use is based on the belief that dopamine secretion from higher centres regulates ACTH secretion from the pituitary, however experimental data is conflicting regarding both the influence of dopamine on ACTH secretion, and the effect of selegiline on dopamine concentrations in the central nervous system and pituitary.

There have been two published clinical studies examining the effects of selegiline in PDH patients, with conflicting results. The first^{31,32} was the basis for national registration of this drug in Canada for treatment of PDH in dogs. Response to treatment was judged primarily on subjective assessment by the owner and physical examination by a veterinarian. LDDSTs, haematological examinations and biochemical tests were performed monthly to assess endocrine changes. Fifteen percent of patients achieved 'normalisation' of their LDDST, and mean plasma cortisol measurements decreased sufficiently to be statistically significant. The drug was assessed to be an effective treatment in some dogs with PDH.

The second selegiline study³³ concluded that selegiline could not be recommended for treatment of PDH in dogs due to lack of consistent improvement in clinical signs and endocrine abnormalities.

In a clinical trial with 11 dogs, this author found the drug to have no appreciable effect on clinical signs or endocrine testing in PDH patients during 3 months treatment,³⁴ and the conclusion was that this drug could not be recommended for treatment of canine PDH.

Bromocriptine and cyproheptadine

Bromocriptine and cyproheptadine are two other centrally acting drugs proposed to act by suppression of ACTH production by the pituitary. Both have been shown to be ineffective in the treatment of PDH in dogs^{35,36} and bromocriptine was found to have unacceptable side-effects.³⁶

Conclusion

From the above discussion it can be seen that there are a number of medical therapies and protocols for the treatment of hyperadrenocorticism in the dog, and in combination with surgical options, these provide some scope to individualise treatment and select that which best suits the needs of a particular patient.

In discussion of treatment options with owners, it is important to make them aware of possible deleterious effects as well as benefits to the various treatment options. One aspect of long-term treatment that is often neglected in discussions is cost. Maintenance treatment for a 20 kg dog treated with mitotane will cost approximately \$2000 per annum, including drug costs and 3-monthly consultation and ACTH stimulation testing. This is often not appreciated by owners until long after the decision has been made to treat their dog.

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