

TREATMENT OF CANINE HYPERADRENOCORTICISM: MITOTANE OR TRILOSTANE?

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In the United States, most dogs with canine pituitary dependant hyperadrenocorticism (PDH) are treated medically with either opDDD (mitotane) or trilostane. Hypophysectomy, the treatment of choice for PDH in people is not commonly performed in dogs in the US, although it is more commonly performed in Europe. Although surgery is often considered the treatment of choice for adrenal tumors, medical therapy with mitotane and trilostane can also be effective. It is ideal to identify which form of hyperadrenocorticism is present when formulating an approach to treatment. Tests that may be used to differentiate PDH from AT include the low and/or high dose dexamethasone suppression tests, measurement of endogenous ACTH concentration, and imaging studies such as ultrasound and computed tomography. If identification of the cause of hyperadrenocorticism is not possible, mitotane is a good choice for treatment when the underlying cause of the problem is unknown.

Both mitotane and trilostane may be effective in management of both pituitary dependent and adrenal dependent forms of hyperadrenocorticism, and both drugs have advantages and disadvantages. In some cases it may be necessary to transition a patient from trilostane to mitotane or vice versa. Reasons for changing from one drug to the other include adverse drug effects, disease relapse, owner's preference or ability to monitor the patient, and medication costs. When planning the drug transition it is important to understand the different mechanisms by which these drugs control the clinical signs of hyperadrenocorticism and the different protocols for administration of the drugs.

MITOTANE

Mitotane is derived from the insecticide DDT and is a potent adrenocorticolytic agent. The drug causes progressive necrosis of the zona fasciculata and zona reticularis of the adrenal gland and at higher doses may also cause necrosis of the zona glomerulosa. Other effects of mitotane include fatty degeneration, centrilobular atrophy and congestion of the liver. Normal dogs are clinically quite resistant to the effects of the drug. Mitotane should never be administered in animals that are not eating well. Therapy with mitotane is begun at a dose of 50 mg/kg divided q 12 hours. Glucocorticoids are not usually administered concurrently, but a small supply of prednisone should be made available to the owner for emergencies. Mitotane at induction doses is typically administered for 5-10 days, until water consumption decreases to < 100 ml/kg/day. It should be discontinued immediately if a decreased appetite, depression, diarrhea, or vomiting are observed. At this point the dog should be reevaluated and an ACTH stimulation test performed. Prednisone treatment (0.1 to 0.2 mg/kg) should be initiated in patients that are showing clinical signs of hypocortisolemia, until the results of the ACTH stimulation test are known. In patients which are not polydipsic, patients in which water consumption cannot be monitored, and patients in which polydipsia is due to another underlying disease (e.g. diabetes mellitus), mitotane should be administered for a maximum of 5-7 days prior to ACTH stimulation testing. The goal of treatment is to have both the pre- and post-cortisol measurement in the normal resting range (2-6 microg/dl). Maintenance therapy

(50 mg/kg q 7-10 days) is started once the ACTH stimulation test shows adequate suppression and prednisone therapy (if necessary) has been discontinued. Failure to use maintenance therapy will result in re-growth of the adrenal cortex and recurrence of clinical signs. Efficacy of maintenance therapy is monitored by an ACTH stimulation test in 1 month and thereafter every 3 - 4 months. The dose of mitotane required for long term maintenance is very variable (26-330 mg/kg/week). Reasons for treatment failure include incorrect diagnosis, the presence of an adrenal tumor (although some adrenal tumors will respond well), loss of drug potency due to poor storage or compounding of mitotane, or a need for a higher dose or duration of treatment in some dogs. Side effects of mitotane include gastric irritation, hypoadrenocorticism, and very occasionally neurologic signs. Mean survival time of 200 dogs treated with mitotane was 2.2 years (range 10 days to 8.2 years).

TRILOSTANE

Trilostane is a synthetic hormonally inactive steroid analogue which is a competitive inhibitor of the 3 β -hydroxysteroid dehydrogenase system. The drug blocks synthesis of adrenal steroids including cortisol and aldosterone. Trilostane is rapidly absorbed orally (peak concentrations within 1.5 hours) although suppression of plasma cortisol concentrations is short lived (< 20 hours). Current recommendations for use of trilostane are to start at a dose of 1-6 mg/kg q 12 - 24 hrs and then increase or decrease the dose based on evaluation of ACTH stimulation tests performed 4-6 hours after drug administration. Twice a day therapy at a starting dose of 1-3 mg/kg may result in good control of clinical signs at a lower total daily dose with less risk of adverse effects than higher doses q 24 hours. ACTH stimulation testing should be performed 10, 30 and 90 days after start of treatment and 30 days after each dose adjustment. Trilostane is well tolerated in most dogs. Adverse effects that are usually mild and self limiting include diarrhea, vomiting, and lethargy in up to 63% of treated dogs. Occasional dogs have developed hypoadrenocorticism which is generally glucocorticoid deficient only, although dogs with evidence of mineralocorticoid deficiency have been reported. Hypoadrenocorticism induced by trilostane is generally reversible, although in rare cases this may take several months likely because of adrenocortical necrosis. There have been anecdotal reports of acute death shortly after starting trilostane treatment. In a recent retrospective study of dogs treated with either mitotane (n= 25) or trilostane (n=123), long term survival was not statistically different between the groups. Median survival in the mitotane group was 708 days (range 33-1399), and in the trilostane group was 662 days (range 8-1971). Of the dogs that died in this study, 11% died due to causes that were attributed to the underlying PDH, and a further 17% died of causes that could have been related to their underlying PDH. In 38% of cases the cause of death could not be directly attributed to PDH, and in 34% the cause of death was unknown.

Other drugs that have been reported to be useful for treatment of dogs with PDH include ketoconazole, cabergoline, retinoic acid and l-deprenyl. Radiation therapy improves outcome in dogs with PDH that have associated neurological signs due to a pituitary tumor, and in dogs with pituitary tumors greater than 0.8 to 1.0 cm diameter.

TREATMENT OF ADRENOCORTICAL TUMORS

Treatment of adrenal neoplasia involves either surgical resection of the tumor or medical therapy with mitotane, trilostane or ketoconazole. Adrenalectomy should be reserved for patients that do not have evidence of extensive tumor invasion or metastasis. Abdominal ultrasound and computed tomography can assist in planning the surgical approach. The surgical approach may be made via a midline or a paracostal approach. A midline

approach allows visualization of both adrenals and other abdominal organs, however the paracostal approach allows better exposure of the affected adrenal gland. After unilateral adrenalectomy, normal adrenal gland tissue will be atrophic and glucocorticoid and sometimes mineralocorticoid supplementation are necessary in the perioperative and postoperative period. Dexamethasone provides primarily glucocorticoid replacement. This should be administered in IV fluids over 6 hours as soon as the tumor is identified. Alternatively hydrocortisone can be used as a continuous infusion to provide both glucocorticoid and mineralocorticoid supplementation. Other options for mineralocorticoid support include fludrocortisone or desoxycorticosterone pivalate administered 12-24 hours before surgery. Blood pressure, central venous pressure, electrolytes and blood glucose should be carefully monitored before, during and after surgery. The merits of pre-operative anticoagulant administration to prevent thromboembolic complications have yet to be proven. After surgery, parenteral glucocorticoids should be continued for 48 - 72 hours until the patient is bright, alert and eating. Oral supplementation with prednisone can then replace parenteral therapy. Supplementation with mineralocorticoids if utilized should be discontinued after 2 doses and the patient monitored for the development of hyperkalemia or hyponatremia. The prognosis for those adrenocortical tumors without metastatic disease that survive the initial perioperative period is good. In one study 80% of dogs survived the perioperative period.

Some dogs with inoperable tumors or metastatic disease may respond to medical treatment with high doses of op-DDD (mitotane). Mitotane is often successful in controlling clinical signs and in some cases may also result in tumor shrinkage. In one study the mean dose of mitotane required to control clinical signs in dogs with adrenal tumors ranged from 35 to 1275 mg/kg/week. Ketoconazole and/or trilostane may also be used for palliation of clinical signs or to improve clinical signs prior to adrenalectomy. In one study there was no difference in survival times for dogs with adrenal tumors treated with either mitotane or trilostane.

TRANSITIONING FROM MITOTANE TO TRILOSTANE

The most common reasons to transition from mitotane to trilostane include adverse effects of mitotane and frequent relapse of clinical signs while on mitotane treatment. Important data to obtain prior to the transition include a complete history and physical examination, review of endocrine testing, and diagnosis of cause of hyperadrenocorticism (pituitary dependent versus functional adrenal tumor). Mitotane should be discontinued prior to starting trilostane therapy. It is recommended to wait at least one month after discontinuation of mitotane before starting trilostane. Trilostane should not be initiated until there is recurrence of clinical signs of hyperadrenocorticism, and until the post-ACTH cortisol concentration is within the upper reference range or greater than the upper limit of the reference range. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane seem to be more responsive to the effects of trilostane. Trilostane treatment should be initiated at the lower end of the dose and ACTH stimulation testing performed as recommended above.

TRANSITIONING FROM MITOTANE TO TRILOSTANE

The most common reasons to transition from trilostane to mitotane include adverse effects of trilostane (e.g. hyperkalemia) and treatment of dogs with adrenal tumors. The adrenal glands become enlarged in dogs treated with trilostane and trilostane has no inherent cytotoxicity for adrenal tumors. Mitotane on the other hand can result in shrinkage of adrenal tumors. Although this would suggest that mitotane is the preferable drug to use in

dogs with functional adrenal tumors, survival studies of dogs with adrenal tumors have shown similar survival with both drugs. Important data to obtain prior to the transition include a complete history and physical examination, review of endocrine testing, and diagnosis of cause of hyperadrenocorticism (pituitary dependent versus functional adrenal tumor). Trilostane should be discontinued prior to starting mitotane therapy. Mitotane should not be initiated until there is recurrence of clinical signs of hyperadrenocorticism, and until the post-ACTH cortisol concentration is within the upper reference range or greater than the upper limit of the reference range. Because of the short half-life of trilostane, a long wash out period between the two drugs is usually not necessary, however close monitoring of adrenal function is advised, as dogs previously treated with trilostane may be more sensitive to the effects of mitotane because of the adrenal hyperplasia induced by trilostane. Mitotane should be initiated at the standard induction dose and the dog monitored carefully for signs of hypoadrenocorticism as described above. An ACTH stimulation test should be performed after induction and the after the first 30 days of maintenance therapy.

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