Hyperadrenocorticism (HAC) or Cushing’s disease is a common endocrine disorder of dogs. It develops as a result of chronically elevated serum cortisol concentrations. Spontaneous HAC can be caused by a functional pituitary tumor (typically a microadenoma) that secretes excessive corticotropin (ACTH) or, a functional adrenal tumor that secretes cortisol independently of the pituitary gland. Pituitary-dependent HAC (PDH) occurs in 80%-85% of dogs and, adrenal-dependent HAC (ADH) accounts for the other 15%-20% cases.

For decades, mitotane was the only essentially efficacious drug to manage canine HAC in the United States. During the past 15 years; however, trilostane has also become widely available and, most clinicians are primarily using this drug to manage canine HAC. In 2009, Vetoryl (brand name) was approved by the FDA for the treatment of PDH and ADH in dogs and, it is currently the only FDA-approved drug for the treatment of both forms of HAC.

Is trilostane better than mitotane to treat canine HAC? There is no consensus as to the answer to this question but, the following can be said: (i) both drugs have similar efficacy; (ii) trilostane could be considered safer because side effects resolve more rapidly with discontinuation of therapy (if adrenal necrosis has not occurred), (iii) the median survival time when using either drug to treat PDH was not statistically different according to one study; however, it was longer in dogs treated with trilostane (900 days; trilostane was given BID) compared to mitotane (720 days), (iv) the median survival time of dogs with ADH treated with trilostane was significantly longer (353 days) than that of the dogs treated with mitotane (102 days), and (v) it is arguably easier to manage patients with HAC with trilostane than mitotane.

Using trilostane to manage HAC
Trilostane is a competitive inhibitor of 3-beta hydroxysteroid dehydrogenase, and inhibits the synthesis of adrenocortical steroid (primarily cortisol) hormones and also aldosterone, however, to a lesser extent. In contrast to mitotane that damages the adrenal cortex, the inhibitory effect of trilostane on cortisol synthesis and secretion is reduced as the drug is metabolized (i.e. the effect is reversible).

Treatment protocol
To this date, there is no consensus regarding the ideal trilostane dose and frequency of administration. The manufacture’s recommended starting dose is 2.2 to 6.7 mg/kg once daily (SID). However, various studies have shown that doses at the low end of this range or, even lower, are efficacious and associated with lesser side effects.

Trilostane blood concentrations peak at 1.5-2.0 hours post-administration and, return to baseline values after about 10 to 18 hours. The duration of cortisol suppression is variable but, in most dogs, trilostane may lose its efficacy 8-10 hours after administration. Therefore, twice daily (BID) administration may be needed at least in some dogs.

Dose recommendation
Most clinicians currently recommend the starting dose of 1 to 2 mg/kg SID or, 1 mg/kg BID. If possible, and taking into consideration the capsule size and owner desire, I prefer to use the twice daily protocol because it will likely control the cortisol secretion better throughout the day. If the dog has concurrent diabetes mellitus, the twice daily administration is recommended to avoid significant fluctuation in cortisol concentrations during the day.

The dose will need to be adjusted according to each patient response, results of routine blood tests and, ACTH stimulation tests. In general, smaller breeds require a higher dosage than larger dogs to control the disease.

Administer trilostane with food to improve absorption. It should be avoided in dogs with primary liver disease (not dogs with steroid hepatopathy associated with HAC) and significant renal disease. It should not be used with spironolactone to prevent hyperkalemia (trilostane may inhibit aldosterone secretion).

Monitoring
The patient’s clinical response and the ACTH results will dictate if the dose should be changed at any point during therapy.

Initially, the re-evaluation visits should be scheduled in 7-10 days, 1 month, and 3 months after starting therapy. If the dog is doing well and the post-ACTH cortisol level is within an acceptable range, evaluations can be performed every 3 months. The patient should be evaluated in 7-10 days, every time a dose is changed or, immediately if not doing well.

At each visit, an ACTH stimulation test, CBC, and chemistry profile should be performed.

Interpretation of ACTH stimulation tests
The ACTH stimulation test should be performed between 2 and 6 hours post-pill (I prefer to perform the test closer to 2-3 hours), which corresponds to its peak effect. It is important to always perform the test at the same time during re-evaluations because there will be variations in the post-ACTH cortisol values (e.g. the post-ACTH cortisol value measured at 2 hours post-pill will be lower than the value measured at 4 hour post-pill).
Consider the following scenarios:

**Improvement or resolution of clinical signs**
- If the post-ACTH cortisol level is between 2mcg/dl (55 nmol/L) and 7mcg/dl (200 nmol/L) and, the patient is doing well (i.e. no signs of hypocortisolism), do not change the dose.
- If the post-ACTH cortisol level is lower than 2mcg/dl, discontinue trilostane for 5 to 7 days. Thereafter, reduce the dosage to 25% - 50% of the previous dose, and retest in 2 weeks.
- If the post-ACTH cortisol value is still less than 2mcg/dl, discontinue trilostane for 30 days and retest at this time and, every 3 months until recovery.
- If the post-ACTH cortisol level is > 7mcg/dl but, clinical signs have improved, do not change the dose and monitor the dog closely for signs of recurrence.
- If the dog shows mild hyperkalemia but, the post-ACTH cortisol level is between the desired range (i.e. 2 to 7mcg/dl) and, the dog is doing well clinically, do not change the dose.

**Persistence of clinical signs of hyperadrenocorticism**
- If the post-ACTH cortisol level is > 7mcg/dl increase the trilostane dose by 25% - 50% and, retest in 2 to 4 weeks
- If the post-ACTH cortisol level is between 2 and 7mcg/dl consider a short effect of trilostane and divide the daily dose to twice a day administration.

**Patient is sick (i.e. decreased appetite, vomiting, trembling, dehydration, weakness)**
- If the post-ACTH cortisol level is less than 2mcg/dl, discontinue trilostane for 30 days, administer glucocorticoid as needed and retest in 30 days. If the low cortisol levels persist, adrenal necrosis is likely. If the post-ACTH cortisol levels increase to more than 7mcg/dl and the dog has signs of HAC, re-start trilostane with a 25-50% reduced dose.
- If the post-ACTH cortisol level is less than 2mcg/dl and the dog has hyperkalemia and hyponatremia, discontinue trilostane for 30 days, administer glucocorticoid and/or mineralocorticoid as needed and retest in 30 days. If the low cortisol level persists, adrenal necrosis is likely. If the post-ACTH cortisol levels increase to more than 7mcg/dl and the dog has signs of HAC, re-start trilostane with a 25-50% reduced dose.

**Using mitotane to manage HAC**
Mitotane (.p’-DDD or Lysodren) destroys primarily the zone fasciculata and reticularis of the adrenal cortex. It can rarely also destroy the zone glomerulosa which secretes aldosterone. It should be given with a fatty meal to increase absorption. Use mitotane with caution if the dog has renal insufficiency or liver disease.

**Induction phase for PDH**
Allow the animal to eat and/or drink before administering the drug. If decreased appetite or complete anorexia is noted in a dog that was previously polyuric and polydipsic, discontinue the medication and call the veterinarian immediately. Administer mitotane with food (ideally fatty food) to improve absorption.
- Start the dose at 40 – 50 mg/kg/day divided BID (the author prefers to start at the hind end of the range) and, administer it for 8 days or until clinical signs of hypocortisolism develop (i.e. lethargy, vomiting, diarrhea, decreased appetite, and decreased water consumption [i.e. < 60 ml/kg/day]), whichever occurs first. At this point, perform an ACTH stimulation test. The post-ACTH cortisol levels should be between 2mcg/dl (54 nmol/L) and 4mcg/dl (110 nmol/L).
- If the post-ACTH cortisol level is within this range, the animal is doing well, and clinical signs have improved, start maintenance therapy.
- If the post-ACTH cortisol level is below this range, or the animal is showing signs of hypocortisolism, discontinue mitotane (give glucocorticoid if signs of hypocortisolism) and retest in 30 days. If the post-ACTH cortisol level is within the desired range, start maintenance therapy. If the post-ACTH cortisol level is still below the ideal range, do not start maintenance therapy and continue retesting every 15 to 30 days.
- If the post-ACTH cortisol level is above the desired range, continue induction for an additional 5 to 7 days or until signs of hypocortisolism develop, whichever comes first. At this point, retest and start maintenance if post-ACTH cortisol levels are within the desired range (i.e. between 2mcg/dl and 4mcg/dl).

**Maintenance phase for PDH**
- The maintenance dose is 50 mg/kg/week divided into two or three doses over the course of the week. Perform an ACTH stimulation test in 30 days, then every 3 to 6 months if the disease is controlled.
- If the post-ACTH cortisol level is below 2mcg/dl, discontinue mitotane (administer glucocorticoid if signs of hypocortisolism) and, re-test in 15-30 days. If post-ACTH cortisol levels return to the ideal range, restart mitotane at a 25% lower dose. If post-ACTH cortisol levels continue below the range, retest every 15-30 days until levels achieve the desired value and do not restart mitotane.
• If post-ACTH cortisol levels are mildly elevated (i.e. 5mcg/dL [150nmol/L] – 10mcg/dl [300nmol/dl]) increase the maintenance mitotane dose by 25%-50%.

• If post-ACTH cortisol levels are moderately to severely elevated (i.e. >10mcg/dl), restart induction for 5 to 7 days or until signs of hypocortisolism develop, whichever comes first. If post-ACTH cortisol values return to the ideal range, increase the maintenance mitotane dose by 50%.

Mitotane can be used for dogs with ADH when surgery cannot be performed for any reason. In these cases, the induction dose is typically higher (i.e. 50-75 mg/kg/day) and, typically longer (10 to 14 days). The maintenance dose is also higher (i.e. 75-100 mg/kg/week). Response to therapy should be based on improvement of clinical signs and, ACTH test results, as for dogs with PDH.

**Client education**

When treating a patient with HAC with either trilostane or mitotane, the following client education should be provided:

• HAC is a non-curable disease and life-long therapy is required in most cases.

• Treating HAC requires various visits and tests, until the ideal maintenance treatment protocol is achieved, which may take weeks to months.

• Take the necessary time to explain verbally and, in writing, the potential side effects associated with either medication.

• Advice owners to discontinue the medication and contact you immediately if the dog develops any side effects.

• Advice owners to give the drug with food to increase absorption.

• Counsel owners to provide the animal with food and water before administering the medication. If the animal refuses to eat or drink (a patient with HAC is typically polyuric and polydipsic), do not administer the medication and call the veterinarian.