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ISSUES IN ENDOCRINOLOGY

Treatment of Pituitary-Dependent Hyperadrenocorticism

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Pituitary-dependent hyperadrenocorticism (PDH) is the most common cause of spontaneous Cushing's syndrome in dogs. It is the result of the inappropriate secretion of adrenocorticotropic hormone (ACTH) by a pituitary adenoma.

Currently, the vast majority of dogs with PDH are managed medically. This approach does not address the underlying pathology (i.e., the pituitary tumor), but it mitigates the clinical manifestations of the disease and reduces patient morbidity from complications associated with hyperadrenocorticism (HAC). Lifelong therapy is necessary to maintain wellness, and owners need to commit to regular monitoring and diligent follow-up. Although medical therapy for PDH has not been consistently shown to improve longevity, most practitioners feel that quality of life for both patient and owner is substantially improved when the disease is successfully managed.[1]

TREATMENT OPTIONS

In people, PDH is routinely cured by excision of the adenoma using a minimally invasive endoscopic approach through the nose. This methodology is not technically possible in dogs, but a small number of institutions now offer hypophysectomy using a transsphenoidal approach. Long-term outcomes are positive, with a greater than 75% survival at 2 years, although the cost of surgery is substantial and treated dogs need lifelong hormone supplementation (prednisone, thyroxine, +/– desmopressin).[2]

Radiotherapy is also an option for canine patients, but it may require multiple anesthetic events (depending on the method and protocol selected) and complete reversal of hypercortisolemia is unusual. It is hard to compare survival rates between hypophysectomy and radiation therapy, as patient selection criteria likely bias the results. In addition, outcomes with radiation appear to be influenced by the method selected. A cohort of 12 dogs with PDH receiving 10 fractions of 3.8 Gy over 4 weeks achieved a median survival

TREATING PDH
Pituitary-dependent hyperadrenocorticism (PDH), which can be challenging to manage successfully, is a common endocrinopathy in geriatric dogs.

time of 961 days (range, 28 to 1328 days)[3]; in contrast, 29 dogs receiving stereotactic radiotherapy (one 15-Gy fraction or three 8-Gy fractions) had a median survival time of just 245 days.[4]

Several medical therapies have been used in dogs with PDH, including mitotane (o,p'-DDD; Lysodren®; bms.com), L-deprenyl (selegiline; Anipryl®; zoetisus.com), ketoconazole, and trilostane (Vetoryl®; dechra-us.com). Many clinicians feel that L-deprenyl and ketoconazole have limited impact on adrenal function, and these drugs are not widely used. Mitotane is a chemotherapeutic agent and is directly toxic to adrenal tissue; the dose must therefore be carefully titrated to avoid complete adrenal necrosis. Although mitotane can provide excellent control of HAC, practitioners should familiarize themselves with published protocols or consult with an internist when using this drug. It is not licensed for use in dogs, and owners should be provided with appropriate written guidelines regarding handling and use. Trilostane was FDA approved for treatment of both pituitary- and adrenal-dependent HAC in dogs in 2008 and is now the first choice of most practitioners.

TRILOSTANE

Background

Trilostane is a synthetic steroid analogue. It is a competitive inhibitor of 3-β hydroxysteroid dehydrogenase (3-β HSD), which plays a crucial role in the production of several adrenal cortical hormones. Therapeutic concentrations of trilostane therefore limit the production of cortisol. Although the production pathway for aldosterone also depends on 3-β HSD,

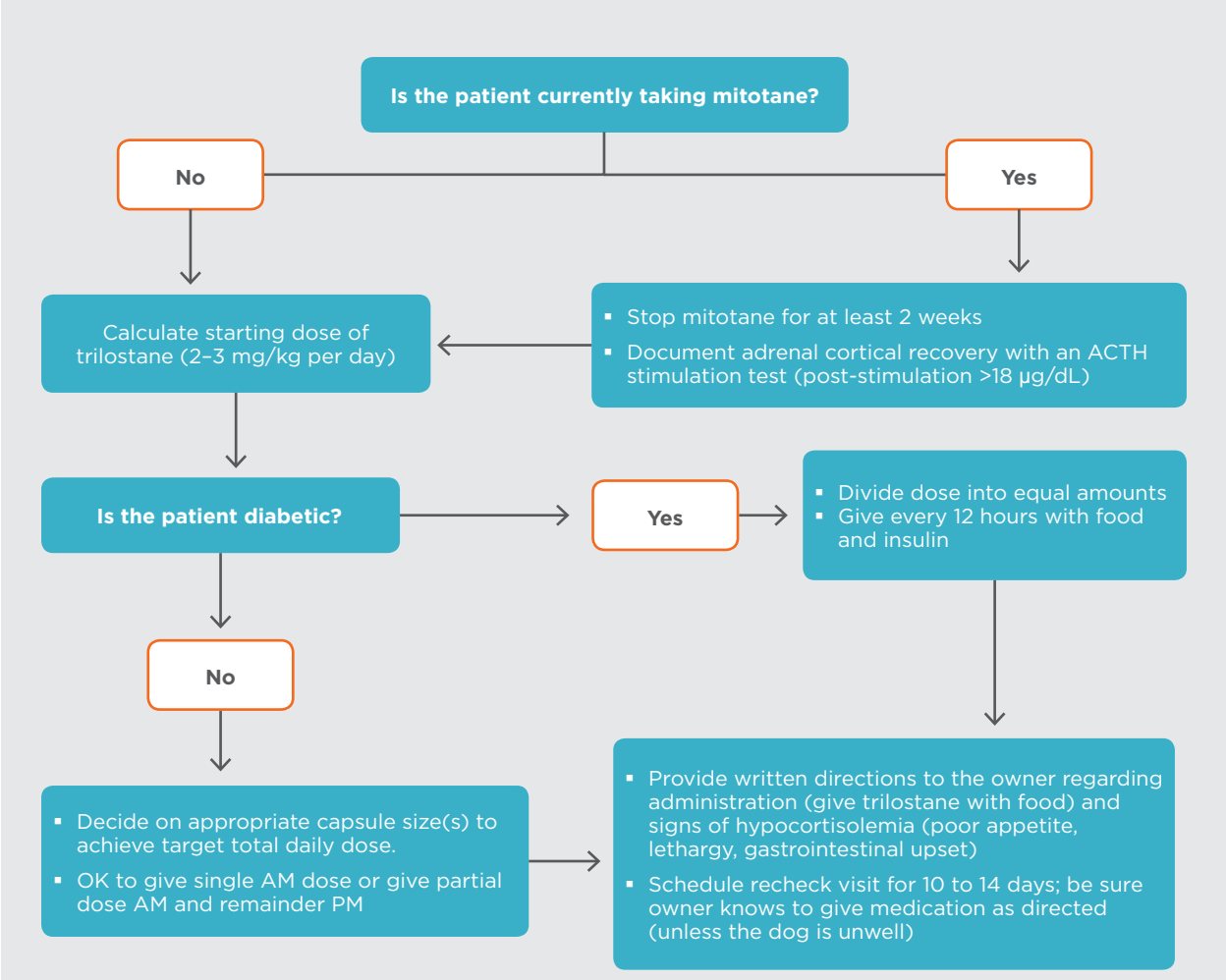

FIGURE 1. Algorithm for starting trilostane.

trilostane's effects on aldosterone are usually modest.[5] Evidence indicates that trilostane also promotes the intracellular conversion of cortisol to cortisone, which has no biologic activity.[6] This limits activation of the glucocorticoid receptor and its downstream effects. Because of trilostane's mechanism of action, its effects are reversible and dose dependent.

Trilostane is administered orally. Peak plasma levels occur about 2 hours after ingestion. Absorption appears to be somewhat erratic, and administration with food is recommended. The drug undergoes hepatic metabolism; clearance time varies, but is generally within 18 hours.[7]

The manufacturer states that trilostane should not be used in dogs with renal or hepatic compromise and should be avoided in animals intended for breeding.[8] The caveats regarding renal and hepatic disease reflect the fact that trilostane has not been specifically evaluated in these patient populations; however, the author routinely uses trilostane in dogs with stage 1 or 2 chronic kidney disease or stable hepatic disease. The drug should be used with caution in anemic patients. Dogs with a history of congestive heart failure and those on drugs such as spironolactone and angiotensin-converting enzyme inhibitors may be prone to hyperkalemia. Trilostane should therefore be used cautiously in these patients, with close monitoring of serum electrolytes.

Starting Therapy

The package insert for the FDA-approved product Vetoryl® recommends a starting dose of 2.2 to 6.7 mg/kg, given once daily. However, most practitioners start with a lower dose and many routinely recommend twice-daily therapy. Giving trilostane every 12 hours may hasten the achievement of target post-ACTH stimulation results (2 weeks versus 12 weeks) but has not been shown to improve clinical responses.[9] In the author's practice, most patients are started on a total daily dose of 2 to 3 mg/kg, given with food in the morning (**FIGURE 1**). In dogs with diabetes mellitus, the dose is divided evenly for twice-daily administration so that day- and nighttime cortisol levels and insulin responsiveness are well balanced. It is acceptable to round down to the nearest appropriate capsule size. There is no urgency to reverse HAC, and a cautious approach is usually appropriate.

Although mitotane can provide excellent control of HAC, practitioners should familiarize themselves with published protocols or consult with an internist when using this drug.

Owners need to understand the signs of hypocortisolemia, namely hyporexia, weakness, lethargy, vomiting, and diarrhea. If any of these are noted, they should withhold trilostane and seek veterinary advice. Particularly anxious owners can be dispensed a small supply of prednisone (0.5 mg/kg); this will reverse signs related to low cortisol within an hour. If signs of hypocortisolism do not improve rapidly following prednisone administration, the dog should be promptly evaluated by a veterinarian.

Conditions related to HAC such as clinically significant hypertension, infection, and substantial proteinuria should be addressed concurrently; it is not appropriate to simply wait and see what effect trilostane may have on these comorbidities. If a dog with evidence of HAC is found to be diabetic, insulin therapy should be initiated immediately to prevent diabetic ketoacidosis. Managing dogs with concurrent diabetes mellitus and HAC can be challenging, and consultation with a specialist may be helpful.

Monitoring Therapy

As the response to trilostane is variable, the dose needs to be adjusted on a case-by-case basis. The patient needs just enough cortisol to maintain wellbeing, but enough adrenal suppression to minimize clinical signs (e.g., thirst, urination, hunger) and complications (infection, thromboembolism, proteinuria) associated with uncontrolled HAC.

Frequency and Parameters

Dogs should be evaluated 10 to 14 days after starting trilostane, 1 month later, and then every 4 to 6 months. In addition, an evaluation is indicated any time the dog is not feeling well or if the owner notices signs of HAC.

BOX 1 Questionnaire: Owner Perception of the Effectiveness of Trilostane Therapy[a,b]

Please rate your dog's behavior/appearance for the past 4 weeks in the following categories.

QUESTION	SCORE
1. Drinking. Do you think your dog has drunk:	
Less than normal	PI
Normal	1
More than is normal (e.g., 1 or 2 times normal)	3
Very much more than is normal	4
2. Urinating. Do you think that the volume or frequency of urination is:	
Less than normal	PI
Normal	1
More than is normal (e.g., 1 or 2 times normal)	3
Very much more than is normal	4
3. Appetite. Would you describe your dog's appetite as:	
Very poor (not eating at all or hardly eating)	PI
Poor (does eat some food but requires encouragement)	PI
Normal	1
Increased (eats all food quickly and will look for more)	3
Greatly increased (seems ravenously hungry all the time)	4
4. Vomiting and diarrhea. How often has your dog had sickness and diarrhea?	
Never had sickness or diarrhea	0
Has had sickness or diarrhea once	0
Has had sickness or diarrhea more than once but not every day	PI
Has had sickness or diarrhea every day	PI
5. Exercise. How active is your dog?	
Lies in one place nearly all of the time	4/PI
Goes for walks and will also play on occasions	3
Very active, happy to run off-leash but does get tired	2
I cannot tire my dog out!	1
6. Skin and coat. How would you describe your dog's coat and skin condition?	
Very poor (e.g., thin coat, bald patches, very dull)	4
Poor (e.g., slightly thin coat, hairs dull)	3
Reasonable (e.g., no bald patches, slightly dull)	2
Very good (e.g., thick coat, shiny, no dandruff)	1
7. Other problems. Does your dog have any of the following?	
Trembling/shaking/muscle twitches more than once a week	PI
Persistent panting even at rest	3
Pain (anywhere)	PI
Difficulty moving	PI
Mental depression	PI
8. General. How do you feel your pet enjoys life?	
Miserable most of the time	PI
Has more bad days than good days	0
Happy most of the time; occasional bad days	0
Happy all of the time	0
9. Overall. How good do you feel your dog's current treatment for Cushing's is?	
My dog has more clinical signs than before treatment	5/PI
There is no difference now than before treatment	4
There is some improvement since starting treatment	3
My dog is nearly back to his/her normal self	2
If I did not know, I would think there was nothing wrong with my dog now	1

PI=possible illness.
[a] *Dog is classified as unwell and is NOT scored if PI is selected 3 or more times.*
[b] *Adapted from: Macfarlane L, Parkin T, Ramsey I. Pre-trilostane and 3-hour post-trilostane cortisol to monitor trilostane therapy in dogs.* Vet Rec *2016;179(23):597.*

Unless the dog is feeling unwell, trilostane should be given the morning of the appointment, which should be timed so that an ACTH stimulation test (if indicated) can be started 4 hours after dosing. Some sources suggest starting the stimulation test 3 hours post dose; the package insert recommends 4 to 6 hours. The objective is to assess adrenal functional capacity at the time the trilostane is likely to be maximally effective.

Each recheck visit should include a detailed history, as this information is key to making appropriate dose adjustments. A team from the United Kingdom recently created a "score sheet" for dogs on trilostane (**BOX 1**); this sheet is routinely used in the author's practice.[10] A thorough physical examination, paying close attention to the haircoat, condition of the skin, and liver size, is also important. It may take up to 6 months to see a resolution of the changes associated with HAC, but some improvement should be noted within 6 to 8 weeks. Persistent physical examination findings suggesting continued hypercortisolemia support a dose increase.

Ideally, every recheck visit would include a blood chemistry panel with electrolytes. This can be omitted if the dose of trilostane has not changed and the dog is doing well clinically. However, a blood chemistry and serum electrolyte concentration analysis is essential after a dose increase and any time the dog is ill, to identify evidence of hypoaldosteronism (hyperkalemia, hyponatremia, azotemia).

Assessing Response to Therapy

Consensus about how best to assess the effect of the current dose of trilostane is limited. The manufacturer recommends that dose adjustments be made on the basis of post-ACTH stimulation cortisol concentrations, measured 4 to 6 hours after trilostane administration, with a target range of 1.45 to 5.4 µg/dL (40 to 150 nmol/L). A post-ACTH cortisol concentration between 5.4 and 9.1 µg/dL (150 to 250 nmol/L) is acceptable if the clinical signs are controlled, but otherwise merits a dose increase.

It is clear that a markedly blunted response to exogenous ACTH indicates profound suppression of cortisol production, and ACTH stimulation is the diagnostic test of choice if clinical signs of hypoadrenocorticism are noted. What is less clear is how well post-ACTH cortisol values reflect control of HAC in dogs without signs of hypocortisolemia and what the ideal post-ACTH cortisol concentration should be. A 2015 report described 13 dogs with PDH on twice-daily trilostane; all were clinically normal despite post-ACTH cortisol concentrations <2 µg/dL (55 nmol/L) obtained 4 hours after trilostane administration. These dogs had substantially higher cortisol concentrations when retested 9 to 12 hours after trilostane administration (mean, 5.3 µg/dL [146 nmol/L]) and were successfully maintained on the same dose for extended periods.[11]

Other reports have evaluated a single baseline cortisol measurement, collected at a fixed time after trilostane administration or immediately before a dose. Monitoring methods that do not rely on an ACTH stimulation test would be advantageous, given issues with the cost and availability of synthetic ACTH.

In a report published in 2010, the author looked at repeated ACTH stimulation tests in 103 dogs on once-daily trilostane; these findings suggested that measuring baseline cortisol concentration in a sample collected 4 to 6 hours post dose could be used to monitor response to therapy.[12] It is important to note that "response to therapy" was determined by post-ACTH cortisol concentrations; clinical signs were not evaluated in this study. A resting cortisol value ≥1.3 µg/dL (35 nmol/L) was used to reliably exclude excessive suppression (defined by a post-ACTH cortisol concentration of <1.5 µg/dL [40 nmol/L]), and a value ≤2.9 µg/dL (80 nmol/L) excluded grossly inadequate control (defined by post-ACTH cortisol concentration >9.1 µg/dL [250 nmol/L]). However, a 2013 study of 40 dogs on once-daily trilostane therapy found substantial overlap between baseline cortisol concentrations in dogs with excessive, adequate, and inadequate (defined by post-ACTH stimulation of >5.4 µg/dL [150 nmol/L]) control of HAC and concluded that the baseline value had limited clinical use.[13]

In a 2016 study, owner perceptions of control (determined using the score sheet in **BOX 1**) were correlated with various objective measurements of adrenal function. Interestingly, 3-hour post-trilostane cortisol concentrations were better correlated to owner scores than ACTH stimulation results.[10] Most of the 67 dogs in this study were on once-daily therapy, and a 3-hour post-trilostane cortisol concentration <2.3 µg/dL (62 nmol/L) was predictive of excellent control. This study also looked at pre-trilostane cortisol concentrations and found that a value of 1.5 to 5 µg/dL (40 to 140 nmol/L) correlated well with owner perceptions of effective control.[10] This novel

monitoring tool may prove to be very useful moving forward, although further studies looking at larger cohorts of dogs on both once-daily and twice-daily therapy are needed. A monitoring approach based on a single cortisol measurement (either before or 4 hours after trilostane administration) is outlined in **FIGURE 2**.

Owner Observations

It is interesting to note the disconnect between owners' reports on the efficacy of trilostane and patients' ACTH stimulation test results described in various studies.[10,13] Trilostane has complex effects on the intracellular handling of cortisol, so circulating levels

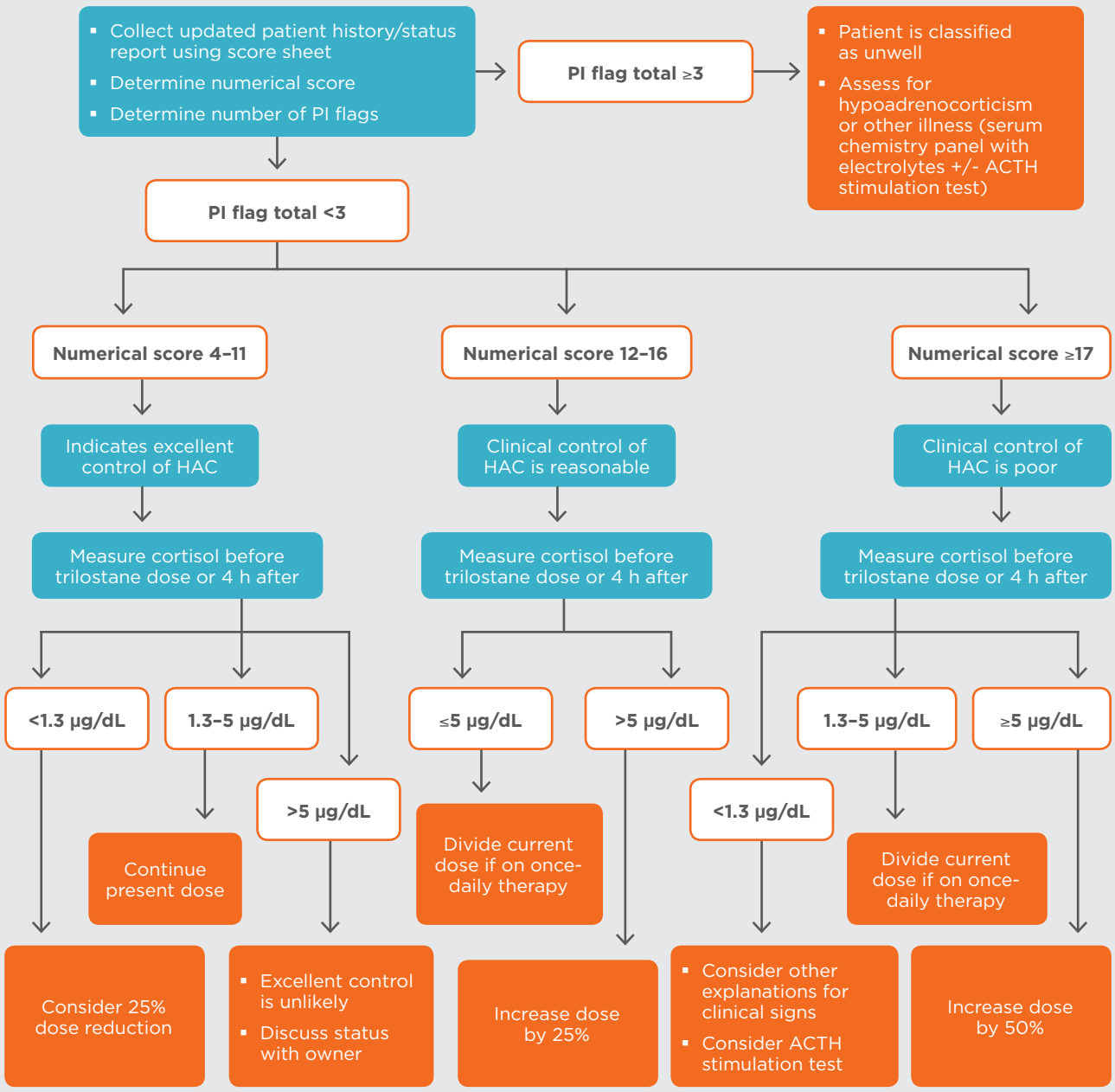

FIGURE 2. Algorithm for monitoring patients on trilostane. Numerical scores are calculated using the owner questionnaire in **BOX 1**. Note that cutoff values for cortisol are based on measurements made before or 4 hours after trilostane administration, not after ACTH stimulation.
PI=possible illness.

do not always reflect the clinical status of the patient. Dogs with either cortisol excess or cortisol deficiency are easily identified based on appetite, thirst, energy levels, and physical appearance; therefore, one of the most useful aspects of a recheck visit for a dog on trilostane is the conversation with the owner. How is the dog doing at home? Does it seem well? Is the owner satisfied with the dog's quality of life? Treatment decisions should be primarily based on this information, with cortisol concentrations (with or without results of ACTH stimulation tests) used to guide dose adjustments as necessary.

In the author's practice, the standard is to simply measure a baseline cortisol concentration (collected 4 hours post dose) in dogs that are clinically well, to be sure that adrenal function is not excessively suppressed. If the baseline is ≥1.3 µg/dL (35 nmol/L), the dog can be left on the same dose. If there are any concerns about the patient, an ACTH stimulation test is performed and the results used to adjust the treatment plan.

Dose Adjustments

The most reliable indicator of efficacy is the patient's behavior at home and the clinical examination. Information obtained from the owner regarding the dog's thirst, urination, appetite, energy levels, and overall status is key when making decisions about dose adjustment. It may take several months for the physical changes associated with HAC to reverse, but consistent improvement in haircoat, skin, musculature, and hepatomegaly should be noted.

In the author's practice, because trilostane simply reverses the clinical manifestations of HAC, if the dog looks good and the owner is satisfied, the dose is usually not increased based solely on test results. If the dog is showing clinical signs of HAC and the post-ACTH cortisol concentration is >7 µg/dL (190 nmol/L), the trilostane dose is increased by 25% to 50%. If the post-ACTH stimulation cortisol concentration is <7 µg/dL but the dog is clinically cushingoid, the current dose is divided into two and given every 12 hours, under the assumption that the duration of effect is too short. If no acceptable response is seen, the dose is slowly increased.

Complications

Transient oversuppression of adrenal cortical function and subsequent hypocortisolemia is the most common complication seen in dogs on trilostane. Owners may report that the dog is lethargic or dull; appetite may be decreased. Affected dogs improve within 2 hours of administration of a single dose of prednisone (0.5 mg/kg PO). Trilostane should be briefly withheld and then restarted at 50% to 75% of the previous dose when signs of HAC recur (usually 1 or 2 days).

A recent report described hypoadrenocorticism in 15% of 156 dogs treated with trilostane for up to 24 months.[14] This was generally transient (75% of instances), but irreversible adrenal necrosis has been reported in dogs after various periods of trilostane therapy. Affected dogs are systemically ill with hyperkalemia and hyponatremia. Owners should be informed of this (rare) complication but be reassured that it is easily recognized (baseline and post-ACTH stimulation cortisol concentration <1 µg/dL [28 nmol/L]) and effectively treated with short-term supportive care and long-term prednisone and desoxycorticosterone pivalate. It seems likely (based on rodent studies) that adrenal necrosis is the result of markedly elevated endogenous ACTH concentrations in dogs with tightly controlled HAC.[15]

KEY POINTS

- Trilostane is widely regarded as the treatment of choice for dogs with PDH and is the only product approved by the FDA for use in dogs with both forms of spontaneous HAC. L-deprenyl is approved for use in dogs with PDH only; ketoconazole and mitotane are not approved for the treatment of dogs with HAC.
- Most clinicians use a starting trilostane dose of 2 to 3 mg/kg daily (may be divided q12h), but dose adjustments are often necessary and clients must be prepared to return for routine reassessments.
- Patient status with respect to signs of hypo- or hypercortisolemia plays a key role in making appropriate dose adjustments. Various assessments of adrenal cortical function (including pre-trilostane, 3 to 4 hours post trilostane, or post-ACTH stimulation cortisol concentrations) may be used to guide dose adjustments.
- Adrenal necrosis is an uncommon consequence of trilostane administration but is readily identified by hyponatremia and hyperkalemia and confirmed on an ACTH stimulation test. Affected dogs need cortisol and aldosterone replacement therapy. TVP

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