Canine Cushing's Syndrome: Diagnosis and Treatment

Part 1: Typical, Atypical, and Pseudo-Cushing's Disease

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Hyperadrenocorticism (HAC) or Cushing's disease is one of the most common endocrine disorders in middle-aged and older dogs. Presently, there are three clinical variants of this disorder: typical, atypical, and pseudo-Cushing's disease.

What is typical Cushing's disease?

Hyperadrenocorticism or typical Cushing's disease can be spontaneous or iatrogenic. Spontaneously occurring may be associated with inappropriate secretion of ACTH by the pituitary gland (pituitary-dependent hyperadrenocorticism or PDH) or an adrenocortical tumor (adrenal-dependent). Clinical signs include polyuria and polydipsia, polyphagia, panting, pot-bellied appearance, and bilateral alopecia. Common biochemical profile and urinalysis abnormalities include SAP and cholesterol elevations, low urine specific gravity and proteinuria (with microalbuminuria or overt proteinuria). The diagnosis is confirmed by cortisol assay analysis following an ACTH response or LDDS test.

Medical treatment of hyperadrenocorticism. No treatment (mild cases of PDH), L-deprenyl (mild cases of PDH), mitotane, trilostane.

What is atypical Cushing's disease?

Some dogs with classic signs of HAC and typical hematological and biochemical findings have a normal response to ACTH administration or LDDS testing. These cases have been termed atypical Cushing's disease. It has been suggested that cases of atypical Cushing's disease may have a derangement of the steroid production pathway and that some of the precursors of cortisol, such as 17-OH progesterone may be abnormally increased. Circulating 17-OH progesterone concentrations show an exaggerated response to ACTH administration in cases of atypical as well as typical HAC. Both pituitary-dependent and adrenal-dependent atypical HAC have been reported.

Medical treatment of atypical Cushing's disease. Dogs with this disorder may respond to mitotane or trilostane although no therapy in mild cases in an option.

What is Pseudo-Cushing's disease?

Pseudo-Cushing's disease is more commonly known as Alopecia X, and is associated with intense hyperpigmentation of alopecic areas principally recognized in young "plush-coated" breeds such as the Pomeranian, Miniature poodle, Samoyed, and Alaskan malamute. Alopecia X has been previously termed growth-hormone responsive alopecia, adrenal sex hormone imbalance, castration responsive dermatosis, and congenital adrenal hyperplasia. These names reflect the lack of clear understanding of the pathogenesis, although recent data suggest this condition is associated with abnormal steroidogenesis and thought to be a mild form of pituitary-dependent HAC. Alopecia is

often first observed between 1 and 5 years of age. Symmetrical alopecia affects the caudal thighs, the trunk, perineum or neck, and often there are changes in coat color. There are no other clinical signs and no biochemical or urinalysis changes. The measurement of 17-OH progesterone before and after administration of ACTH has been recommended in the investigation of dogs with Alopecia X as an indicator of abnormal steroidogenesis. Concentrations of 17-OH progesterone were elevated post-ACTH stimulation in all 31 affected Pomeranians in one European clinical study. While an elevation of 17-OH progesterone in part supports a diagnosis of Pseudo-Cushing's disease, following exclusion of hypothyroidism and HAC, the role of the hormone in the development of the hair loss is unclear.

Treatment of Pseudo-Cushing's disease: Dogs with this disorder may respond to castration, methyltestosterone, melatonin, growth hormone supplementation, mitotane and trilostane.

What is the best screening test to diagnose Cushing's syndrome?

Screening tests are designed to diagnose Cushing's syndrome, that is, to determine if it is present or not. Tests that fit into this category are the urine cortisol:creatinine ratio (UCCR), low-dose dexamethasone suppression test (LDDST), and the corticotropin stimulation test. There is no perfect or best screening test. The choice of screening tests is dependent on many factors, such as 1) has the animal been treated previously with corticosteroids 2) are the clinical signs of moderate severity or are there minimal or no clinical signs and only biochemical abnormalities suggestive of HAC, 3) is an adrenal tumor suspected, and 4) is there a concurrent nonadrenal disease? In addition, to add to the confusion, clinical researchers disagree on which screening tests are the most sensitive and/or specific.

The urine cortisol:creatinine ratio (UCCR)

The sensitivity is relatively high, being estimated at 75% to 100%. However, the major disadvantage of the UCCR is the test's low specificity, estimated by three studies to be between 20% to 25%. Because of the low specificity, the UCCR is advocated as a good test to rule out HAC but never rule it in. Therefore, if the patient has an elevated UCCR, a diagnosis of HAC should always be confirmed with the ACTH stimulation test or LDDST.

The low-dose dexamethasone suppression test (LDDST)

The sensitivity has been estimated to be between 85% and 100% (in case reports > 20 dogs). If all reports are combined, the sensitivity is 95% (640 positive tests in 673 dogs). The specificity of this test has been estimated to be 44%, 70%, and 73%. In general the more severe the nonadrenal illness, the more likely is a false-positive test result.

The corticotropin stimulation test (ACTH stimulation or response test)

In the United States there are only two forms of corticotropin recommended, corticotropin gel (Acthar) or synthetic corticotropin (Cosyntropin). Cosyntropin can be reconstituted and stored frozen at -20C in plastic syringes for 6 months.

The sensitivity of this test has been reported to be between 73% and 95% overall if dogs with both pituitary-dependent hyperadrenocorticism (PDH) and adrenal tumors (AT) were included in the study. If these reports are combined with other reports looking at PDH or AT alone the sensitivity is 80%, (279 of 348 dogs with HAC tested positive), which is lower than that for the LDDST. For PDH alone, the sensitivity is 87%. For AT alone the sensitivity is 62%.

What about a less than normal response to ACTH in an animal being screened for HAC? This is usually due to inactive corticotropin, previous corticosteroid therapy, and a large percentage of dogs with an AT.

Final screening recommendations

What if the patient has only biochemical changes and no or mild clinical signs suggestive of Cushing's syndrome? The ACTH response test may be the preferred test. In these patients, it may be better to miss a diagnosis of HAC in early stages by using a test with lower sensitivity than falsely diagnose HAC by using a test with lower specificity.

Is nonadrenal illness present? The LDDS and ACTH response tests can give false positive results in the face of nonadrenal illness, but the LDDST is more likely to do so. Thus, the ACTH response test is recommended when nonadrenal illness is present.

What if the patient has moderate to severe clinical signs of HAC and has no known nonadrenal illness? The LDDST is preferred as the initial screening test. This test has a higher sensitivity as compared to the ACTH response test.

Is an AT is suspected? The LDDST is recommended because the sensitivity of the ACTH response test for HAC caused by an AT is only 62%.

Has the Cushing's syndrome suspect been treated with a cortisone preparation? The ACTH response test is the preferred test if an animal has a definitive or questionable history of receiving exogenous corticosteroids and has signs compatible with HAC. The response to corticotropin differentiates between spontaneous HAC (an above-normal response in association with clinical signs) and iatrogenic Cushing's syndrome (a below-normal response in association with clinical signs). The LDDST can give a false positive test result in dogs recovering from glucocorticoid therapy

Based on the lab tests, does the dog have Cushing's syndrome?

The most important criteria for making a diagnosis of Cushing's syndrome or hyperadrenocorticism (HAC) is the patient must have signs and symptoms consistent with the disorder. The importance of signalment, history, and physical examination findings cannot be overstated. The predictive value for HAC based on a positive screening test result increases in direct proportion to the number and severity of clinical signs and biochemical changes occurring in the disease. A dog with at least three of the typical signs of hyperadrenocorticism (e.g., polyuria and polydipsia, panting, and

polyphagia) and a positive LDDS or ACTH response test has Cushing's syndrome until proven otherwise. If there are no clinical signs (e.g., a clinically normal dog with an elevated ALP) the patient either does not have the disorder or may have subclinical Cushing's syndrome. In the latter case, a wait and see approach is advised whereby the patient is followed clinically and with laboratory testing over time. In the dog that has signs and symptoms of Cushing's syndrome and the screening tests are negative, consider repeating the tests in 3 to 6 months or initiating a workup for atypical Cushing's syndrome.

Part 2: Medical Treatment of Cushing's Disease

There are several options for the treatment of Cushing's disease in dogs and cats. No treatment, medical treatment with L-deprenyl, ketoconazole, trilostane, and mitotane, radiation therapy, and surgery (hypophysectomy and adrenalectomy). In general, the various treatment options are dependent on the severity of the Cushing's disease, the type of Cushing's (pituitary dependent versus adrenal tumor), and cost factors.

L-deprenyl

L-deprenyl (selegiline HCL) is a selective and irreversible inhibitor of monoamine oxidase Type B, which helps restore the central dopamine concentration and facilitates dopaminergic transmission by several mechanisms. L-deprenyl is postulated to increase dopamine levels in the brain, thereby reducing ACTH secretion and reverse adrenal hyperplasia and the resultant clinical signs associated with hyperadrenocorticism. In studies sponsored by Deprenyl Animal Health, investigators treated 90 dogs with Cushing's disease for up to 6 months and concluded that 83% of the dogs had partial or complete clinical improvement with negligible side effects. This drug is now licensed under the brand name Anipryl® (Pfizer Animal Health) for veterinary use.

Treatment Recommendations

L-deprenyl can be considered for the treatment of pituitary-dependent Cushing's disease (PDH), especially in cases that are mild in severity and the owners are unwilling to risk the adverse effects associated with mitotane or trilostane. Also, L-deprenyl can be quite useful as adjunctive therapy with mitotane or trilostane if signs of cognitive dysfunction are present in addition to the common metabolic signs of Cushing's disease such as pu/pd and polyphagia. The advantage of L-deprenyl is that there are no serious adverse effects with this treatment. Unlike trilostane or mitotane, monitoring therapy is not based on endocrine testing but rather on following clinical signs. The initial recommended dose is 1 mg/kg given daily in the morning for 30 to 60 days. If there is no clinical improvement, the dose should be increased to 2 mg/kg for another 30 days. If there is still no clinical improvement after 60 to 90 days of therapy, the drug should be discontinued and the patient should be treated with mitotane or trilostane. L-deprenyl is not recommended for treatment of PDH in dogs with concurrent diabetes mellitus, pancreatitis, heart failure, renal disease, or other serious illnesses.

Should L-deprenyl be used as a treatment for Cushing's disease in the dog?

Despite the high degree of efficacy of L-deprenyl in the treatment of Cushing's disease in the original clinical study, the experience of most veterinarians who have used the drug for the treatment of this condition has been poor. A recent study examined the effects of L-deprenyl in 10 dogs with PDH over a 6 month period. In this study, the dogs were assessed by owner observed signs and objective veterinarian data such as measured water consumption, CT scans of the pituitary gland, abdominal radiography, adrenal ultrasonography, and adrenal and pituitary function testing. The author's final assessment was "treatment with L-deprenyl resulted in improvement, deterioration, and stagnation of clinical signs in 2, 4, and 4 dogs respectively. The results of this study indicate that L-Deprenyl cannot be recommended as the sole treatment for canine PDH." Reusch C, Steffen T, and Hoerauf A: The Efficacy of L-deprenyl in Dogs with PDH. J Vet Intern Med 1999; 13:291-301.

Canine PDH has a complex etiology. Unlike man, where Cushing's disease is usually caused by a microadenoma in the anterior lobe of the pituitary gland or pars distalis, Cushing's disease in the dog may be caused by adenoma or hyperplasia of cells in either the pars intermedia or pars distalis. Approximately 70% of the dogs with pituitary-dependent Cushing's disease have a pituitary adenoma that arises from the pars distalis, whereas 30% have a tumor that arises from the pars intermedia. In addition, in dogs with tumors of the pars intermedia, adenomatous changes may arise from two types of pars intermedia cells (Type A and Type B). In dogs (and horses) with Type A pars intermedia tumors, dopamine primarily inhibits ACTH secretion and the secretion of other peptides that are precursors of ACTH in the pars intermedia. Interestingly bromocriptine, a dopamine agonist is effective is treating some cases of Cushing's disease in the dog, and pergolide, a dopamine receptor agonist, is a fairly successful treatment for Cushing's disease in the horse. Inasmuch as pars intermedia tumors account for approximately 30% of pituitary tumors in dogs with Cushing's disease, it is tempting to speculate that dogs who respond to L-deprenyl treatment may have a subset of disease associated with a pars intermedia tumor.

With regard to the recent independent study, while L-deprenyl was not effective in controlling the clinical signs of Cushing's disease in all dogs, two dogs had a good response and other dogs showed improvement in some signs. In dogs with milder disease that is progressing very slowly, drug safety may justify its use when compared to the use of mitotane. Also L-deprenyl is beneficial in increasing the dog's level of activity and quality of life as observed by owners (probably due to the high circulating amphetamine concentrations resulting from the metabolism of L-deprenyl). Once one accepts the drug will be useful in a percentage of dogs (20% in the recent study), and one should wait only 2 or 3 months before switching to another treatment modality such as mitotane if the response to L-deprenyl is poor, the lower response rate may not really be so bad

Mitotane

During its evaluation as an insecticide, mitotane was discovered to have adrenocorticolytic effects. It selectively destroys the inner two layers of the adrenal

cortex that produce cortisol and other steroid hormones while tending to preserve the outer layer which produces aldosterone.

Initial treatment (the loading phase)

Mitotane is given orally at a dose of 50 mg/kg/day for 7 to 10 days. Since it is fat soluble, it should be given with food. Daily mitotane should be continued until any of the following changes are noted

-reduction in polydipsia (water intake < 60 ml/kg/day)
-the time to consume a meal decreases or complete anorexia occurs
-vomiting or diarrhea
-depression or listlessness

If any of the above changes occur during the initial loading phase, the mitotane is stopped and an ACTH response test should be performed to assess the "thickness" of the adrenal cortex. If none of the above changes are noted then an ACTH response test is performed at day 10 of therapy. Based on the results of the test, mitotane is either continued on a daily basis, stopped completely, or given weekly (maintenance therapy). In general, if the post-ACTH cortisol is < 1mcg/dl, mitotane is stopped, the dog is given 0.2 mg/kg/day of prednisone, and the ACTH response test is repeated in 2 to 4 weeks. If the post-ACTH cortisol is > 5 mcg/dl and the dog is still clinical for Cushing's disease, the mitotane is continued for another 3-5 days and another ACTH test is performed. If the post-ACTH cortisols are between 1 and 5 mcg/dl and the dog feels well, then the maintenance phase of therapy with mitotane is started.

Adverse effects: The adverse effects that occur most commonly are anorexia, vomiting, diarrhea. In general, these adverse effects are rarely serious provided they are noticed early so that mitotane therapy can be withheld. Owners are advised to give prednisone (0.2 mg/kg/day) if any of these adverse effects occur.

Maintenance therapy

Once the cortisol levels are in the ideal range (see above) following the loading phase of therapy, mitotane is continued at a lower dosage to inhibit further growth of the adrenal cortex. Mitotane is given at a dose of 50 mg/kg/week. Usually the total dose is divided and given every three days

Monitoring therapy and survival data

Treated dogs should be re-evaluated 6-8 weeks after the initiation of the maintenance dose. Marked improvement should be noted at this time. The most obvious and rapid response is a reduction in water intake, urine output, and appetite, which usually occur at the end of the initial course of therapy. Muscle strength and exercise tolerance improve over the first 3-4 weeks. Skin and hair coat changes take longer and the progress is variable. After the first re-evaluation, rechecks should be scheduled every 3-6 months for the rest of the pet's life to determine whether the dose of mitotane needs to be adjusted depending on the results of ACTH response testing. Overall, based on the

results of three survival studies, the mean survival time of treated dogs with pituitary-dependent Cushing's disease is 24 to 30 months with a range of 1 day to 13 years.

Common Problems Associated with Mitotane Therapy in Dogs with Confirmed Pituitary-Dependent Cushing's Disease

I started a dog on 50 mg/kg of mitotane divided BID for 10 days and the stimulated cortisol results are greater than 10 mcg/dl. What do I do now?

Continue the mitotane for 3-5 days intervals at the same dosage and repeat the ACTH stimulation test. The goal of therapy is a post-ACTH cortisol level between 1 and 5 mcg/dl, although some dogs appear to be clinically normal with cortisols ranging between 5 and 10 mcg/dl. The loading period can be quite variable but is usually 7 to 14 days with an average of 10 days. Some dogs, however, are appropriately loaded in 2-3 days while others can take as long as 6 weeks. If there is no response to mitotane then consider raising the dose to 75 mg/kg or having the mitotane reformulated in an oil base to increase intestinal absorption or discontinuing mitotane and starting trilostane.

I just repeated the ACTH response test after a 7 day loading period. The dog seems fine but the pre- and post-ACTH cortisols were both < 0.2 mcg/dl. What now?

Stop the mitotane immediately and start prednisone at 0.2 mg/kg/day and consider repeating the ACTH response test in 2-4 weeks. Instruct the owners to withhold the prednisone the day of the ACTH response test. If the post-ACTH cortisol is greater than 2 mcg/dl and less than 10 mcg/dl and the clinical signs associated with Cushing's disease have resolved, consider starting the maintenance dosage of mitotane (50 mg/kg per week).

I have a dog that has been well maintained on mitotane therapy for over a year and now the owners are complaining about excessive drinking and appetite again. The post-ACTH cortisol is 15 mcg/dl. Reload or increase the maintenance dose?

In general, successful remission is best achieved by reloading the dog for a short period of time (3-5 days or longer depending on the magnitude of the post-ACTH cortisol). The goal of therapy is a post-ACTH cortisol below 5 mcg/dl. Once this is achieved increase the maintenance dose by 25-50%.

I successfully loaded a dog with mitotane based on the results of an ACTH response test yet the polyuria and polydipsia has not improved. Now what?

This is a very common scenario. The best thing to do is waiting! Often these dogs have severe medullary washout and the remission of the pu/pd lags the reduction in cortisol levels. Other rule outs include UTI and diabetes insipidis.

Trilostane: A New Drug for the Treatment of Hyperadrenocorticism

Trilostane has been shown to be an effective treatment for canine and feline Cushing's syndrome. It is not approved in the US at this time; however, many veterinarians have the owner order the drug from the website mastersmarketing.com. Trilostane is a synthetic, orally active steroid analogue. It acts as a competitive inhibitor of the 3β-hydroxysteroid dehydrogenate enzyme system and thereby inhibits the synthesis of cortisol and aldosterone as well as other steroids. The blockade is reversible and appears to be dose related.

The efficacy and safety of trilostane was evaluated in a multicenter study at three veterinary schools in Europe (Neiger R et al. Vet Rec 2003). If the post-ACTH cortisol is not optimal (between 1 and 5 mcg/dl) and the dog appears to be not clinically well controlled then the dose of trilostane is increased. Seventy-eight dogs with confirmed pituitary-dependent Cushing's disease were treated with trilostane for up to 3 years. The starting dose varied from 1.8 to 20 mg/kg (mean - 5.9 mg/kg).

Trilostane was well tolerated by almost all dogs, however 2 dogs developed clinical signs and biochemical evidence of hypoadrenocorticism and two dogs died suddenly within a week after starting trilostane for no apparent reason. In addition, more recent studies have documented two cases of bilateral adrenal necrosis.

Trilostane was found to be nearly as effective as mitotane in resolving the signs of Cushing's syndrome. Polyuria, polydipsia, and polyphagia had resolved in 40 dogs within 3 weeks after starting the drug, while an additional 20 dogs showed reduction in water intake and food consumption within 2 months. Skin changes resolved in 24 of 39 dogs (62%) that initially presented with dermatologic signs. Only 8 dogs that were treated for more than 2 months showed poor control of clinical signs

About half the dogs needed a dosage adjustment over the treatment period. The dose was increased in 23 dogs up to four times the starting dosage, while the dose was decreased in 9 dogs to as low as a quarter of the starting dose. The mean survival time of the trilostane treated dogs was 661 days, although 65% of the dogs were still alive at the time the study was completed, and therefore, mean survival time may be longer.

Preparations, storage, and handling

Trilostane is available in 60 and 120 mg capsules under a temporary veterinary product license as Vetoryl® (Arnolds Pharmaceuticals, Crawley, Surrey, UK). It is also available in 60 mg capsules for human use as Modrenal® (Wanskerne Ltd, Billingshurst, West Sussex, UK). More recently, trilostane has become available in the United States from Wedgewood pharmacy. The cost for 100 60 mg capsules varies from $115 (UK) to $200 (US). With very small dogs the capsules should be split into smaller gelatin capsules or reformulated by a compounding pharmacy. Trilostane capsules should be stored at room temperature in airtight light-resistant containers. Pregnant women should wear gloves when handling the drug and all users should wash their hands after handling the drug

Dosage and administration

The current suggested starting dose is 2-10 mg/kg given with food once daily. The dosage may need to be adjusted according to clinical signs and cortisol determinations. In some dogs twice daily administration is necessary.

In dogs only minor side effects are commonly seen such as mild lethargy and decreased appetite 2-4 days after the start of therapy. Mild electrolyte abnormalities may also be seen, although overt hypoadrenocorticism seems to be a rare event. Because trilostane can cause hyperkalemia through its aldosterone inhibiting effect potassium sparing diuretics and ACE inhibitors should be used with caution.

Monitoring

It is important to monitor clinical signs, and biochemical parameters such as BUN, creatinine, and sodium and potassium levels. The following are monitoring guidelines:

-Perform initial recheck ACTH test at 10 to 14 days, then at 30 and 90 days.
-The timing of the ACTH stimulation test is important. All tests should be performed 4-6 hours after the morning administration of trilostane.
-If the post-ACTH cortisol is < 1 mcg/dl, the trilostane is stopped for 48 hours, then re-introduced at a lower dosage
-If the post-ACTH cortisol is > 5 mcg/dl, then the dose of trilostane is increased.
-If the post-ACTH cortisol is optimal (between 1 and 5 mcg/dl) and the dog appears to be clinically well controlled then the dose of trilostane is not altered.
-If the post-ACTH cortisol is optimal (between 1 and 5 mcg/dl) and the dog is not clinically well controlled, then the dose of trilostane may need to be given twice daily.
-Once the clinical signs of Cushing's disease are in remission an ACTH response test and serum biochemical profile should be rechecked every 3-4 months.

The use of trilostane in cats with Cushing's syndrome

Recently trilostane was shown to be effective in cats for the treatment hyperadrenocorticism (Neiger et al. J Vet Intern Med 2004, 18(2); 160-164). The same dosing and monitoring guidelines as established for the dog are recommended.

Summary

Overall, trilostane appears to be an effective alternative to the treatment of hyperadrenocorticism in dogs and cats.

How to obtain trilostane in the US

Trilostane is available in 60 and 120 mg capsules in the UK with a veterinary product license as Vetoryl (Arnolds Veterinary Products, Cartmel Drive, Harlescott, Shrewbury, Shropshire SY1 3TB, UK)

Complete a 13 part letter addressed to Tom Wooten, Division of Compliance HFA-230, Center of Veterinary FDA, Metro Park North, 7500 Standish Place, Rockville, MD 20855. Fax: 301-827-1498. Tom Wooten phone: 240-276-9220. email: twooten@cvm.fda.gov

Arnolds Veterinary Products needs a faxed copy of the FDA approval letter (takes about 2 weeks for approval) and a prescription. Only a 90 day supply will be shipped at a time. Current cost: $130 for 100 60 mg capsules, $202 for 100 of 120 mg capsules. Courier cost will be about $40.