Hyperadrenocorticism, Pituitary-Dependent

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Contributors:

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Synonyms:

Cushing's syndrome
Adrenal gland hyperplasia

Disease description:

Hyperadrenocorticism (HAC) occurs with chronic, excessive production or exposure to glucocorticoids. Three main types of HAC exist in dogs:[1]
1) **ACTH-dependent** forms include pituitary-dependent hyperadrenocorticism (PDH) and very rare cases of ectopic adrenocorticotropic hormone (ACTH) production.
2) **ACTH-independent** forms include functional adrenocortical adenoma or carcinoma, which are also known as *adrenal-dependent hyperadrenocorticism* (ADH) or *functional adrenal tumors* (FAT).
3) **Iatrogenic** forms involve excessive or prolonged administration of glucocorticoids that leads to adrenal atrophy and suppressed ACTH levels. Iatrogenic HAC is clinically indistinguishable from naturally occurring HAC.[1]

Etiology and Pathophysiology

Pituitary-dependent hyperadrenocorticism (PDH) is the most common form of HAC, accounting for 80-85% of cases.[2] With PDH, the pituitary gland secretes an excessive amount of ACTH, which leads to bilateral adrenal gland hyperplasia and excessive secretion of glucocorticoids.[2] More than 90% of patients with PDH have a pituitary tumor that is responsible for the excessive ACTH secretion. Of these pituitary tumors, 70% arise from the pars distalis and 30% arise from the pars intermedia.[2]

Hypothalamic disease leading to pituitary hyperplasia and excessive ACTH secretion has been documented in people but not in dogs (to date). Rarely, ectopic ACTH secretion by nonpituitary tumors occurs in dogs.[1,2]

Diagnosis

Examination, Routine Laboratory Tests, Imaging Studies

Clinical Signs and Physical Exam Findings: The most common clinical manifestations of HAC are polydipsia (PD), polyuria(PU), polyphagia, panting, abdominal distension, alopecia, muscle weakness, and weight gain.[2,3] Approximately 80-90% of patients with HAC exhibit PU/PD. Glucocorticoids decrease renal tubular resorption of water and inhibit the action of antidiuretic hormone at the tubular level.[2]

Polyphagia results directly from glucocorticoid excess. It can lead to weight gain; however, some patients with concurrent diseases (e.g. diabetes mellitus) may lose weight. Patients may have a pot-bellied appearance secondary to abdominal musculature weakness from the catabolic effects of steroids; redistribution of fat to the abdominal mesentery; and hepatomegaly.[2]

Patients with HAC can pant excessively due to decreased pulmonary compliance, weakness of the respiratory muscles, and pulmonary hypertension.[2] Pulmonary thromboembolic disease can also be a complication of HAC.[4]

Lethargy can occur from the effects of excessive cortisol on cerebral enzymes and neurotransmitter synthesis. Large pituitary tumors can cause other neurologic signs, such as behavioral changes, circling, and seizures.[2] Sudden acquired retinal degeneration (SARD) is an idiopathic retinal disorder characterized by degeneration and loss of retinal photoreceptors, resulting in acute, permanent blindness. It has been associated with HAC, although an exact cause and effect relationship has not been established.[4,5]

Dermatological abnormalities are common findings. Truncal, bilaterally symmetrical alopecia is common. Other changes may include thin skin, comedones, failure to regrow shaved hair, hyperpigmentation, and

seborrhea.[2,3] Calcinosis cutis can occur secondary to dystrophic calcium deposition in the dermis and subcutis. Calcinosis cutis lesions are typically firm, irregular plaques. Approximately 50% of HAC patients also develop skin infections.[2]

Other less common clinical signs or physical abnormalities include facial nerve paralysis, testicular atrophy, infertility, persistent anestrus, ligament rupture, and Cushing's pseudomyotonia (characterized by stiff gait and persistent muscle contractions).[2,3]

Complete Blood Count: A stress leukogram (i.e. neutrophilia without a left shift, lymphopenia, eosinopenia), mild erythrocytosis, and thrombocytosis are the most common findings but are nonspecific.[3]

Biochemistry Panel: The most common abnormality is an elevation of ALP (due to increased steroid-induced isoenzyme). Elevations of ALP are found in 85-95% of dogs with HAC. Even though elevations can be marked (>1000 IU/L), the degree of ALP elevation does not correlate with the severity of HAC.[2]

Other abnormalities can include increased ALT, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, hypophosphatemia, and decreased BUN.[2,3] Hyperglycemia may be mild but 5-10% of untreated patients have diabetes mellitus.[2]

Urinalysis: Most dogs have decreased urine specific gravity (<1.020).[3] Glucosuria is uncommon but can occur with concurrent diabetes mellitus.[2] Proteinuria secondary to protein-losing glomerulopathy is another common abnormality. Urine protein:creatinine ratio >1.0 is present in 60-80% of patients with HAC.[2] One study documented proteinuria in 12/26 dogs with untreated PDH and 5/16 dogs with poorly controlled PDH.[6]

Urinary tract infections (UTI) are present in 40-50% of HAC patients at the time of presentation; however, since excessive glucocorticoids suppress inflammation, affected dogs may not have pyuria, hematuria, stranguria, or pollakiuria.[2] Urine culture should be performed to rule out concurrent UTIs.

Thoracic and Abdominal Radiography: Bronchial and tracheal ring mineralization may be present. Dogs with HAC are at increased risk for pulmonary thromboembolism (PTE) due to their hypercoagulable state. Abnormalities seen with PTE include hypovascular lung fields, alveolar pulmonary infiltrates, enlargement of the main pulmonary artery segment, right-sided cardiomegaly, and pleural effusion.[2,4] See the Associate chapter on PTE.

Hepatomegaly is the most common abnormality on abdominal radiographs and is found in 80-90% of patients with HAC. Calcium-containing uroliths may be noted since affected patients may have increased urinary calcium excretion.[2]

Abdominal Ultrasonography: Abdominal ultrasonography can be very useful to diagnose HAC, as well as to help determine if a patient has PDH or FAT. Patients with PDH typically have bilaterally symmetrical adrenomegaly, with normal echogenicity of the glands.[2,7] The upper limit of normal adrenal gland width has been reported at 7.5 mm; however, some dogs may normally have smaller adrenal glands. In one report of small breed dogs, the median gland width for patients with PDH was 6.3 mm, and the sensitivity and specificity of adrenal gland measurements for detecting PDH was 75% and 94% when using a cut-off value of 6.0 mm instead of 7.5 mm.[8] A size overlap of the glands occurs between normal and affected dogs, so ultrasonography cannot be used as the sole diagnostic test for PDH.[2]

Advanced Imaging: Computed tomography (CT) or magnetic resonance imaging (MRI) can readily detect pituitary tumors >1 cm in diameter. MRI is more sensitive than CT for detection of pituitary macroadenomas.[2,17,18]

Endocrine Screening Tests

ACTH Stimulation Test: This test measures adrenal gland response to ACTH stimulation. Patients with HAC have exaggerated cortisol production in response to an ACTH injection.[1] For information on how to perform the test, see the Medical FAQ on the ACTH stimulation test.

The sensitivity of the ACTH stimulation test for PDH is approximately 80-85% and the specificity is 59-93%.[1,3,9] The ACTH stimulation test is considered the gold standard for diagnosis of iatrogenic HAC. A

suppressed response to ACTH in patients with clinical signs consistent with HAC occurs with iatrogenic HAC.[1,3]

Compared with other screening tests (e.g. low-dose dexamethasone suppression test, LDDST), the ACTH stimulation test has a low sensitivity. Many clinicians recommend the use of the LDDST for diagnosis of HAC over the ACTH stimulation test. However, the ACTH stimulation test is still used for a variety of reasons. It is less time consuming to perform LDDST (1-2 hrs vs. 8 hrs for LDDST), and it is less affected by nonadrenal illness compared to other endocrine screening tests.[2]

Low-Dose Dexamethasone Suppression Test: The 2012 ACVIM Consensus Statement considers the LDDST the screening test of choice unless iatrogenic HAC is suspected.[3] In normal dogs, low doses of dexamethasone inhibit ACTH secretion from the pituitary through a negative feedback loop, so cortisol secretion subsequently drops. The pituitary-adrenal axis in patients with HAC is abnormally resistant to steroid suppression; therefore, patients with HAC demonstrate a lack of suppression in response to dexamethasone administration.[1,2]

Serum or plasma cortisol concentrations are determined before, 4 hours after, and 8 hours after administration of dexamethasone sodium phosphate or dexamethasone in polyethylene glycol (0.01-0.015 mg/kg IV).[3] Interpretation of test results should be based on reference ranges for the particular laboratory performing the assay. Failure to show suppression (cortisol levels at 8 hr >1.4 µg/dL and >50% baseline cortisol level) is diagnostic for some form of HAC.[2]

The LDDST has a sensitivity of 90-95% in patients with PDH.[1-3] However, specificity is lower specificity (40-50%). Results can be affected by concurrent nonadrenal illness. When a concurrent illness is present, the LDDST can be delayed or ACTH stimulation testing may be done.[2] See the Medical FAQ on Diagnosing HAC.

Urine Cortisol:Creatinine Ratio (UCCR): Measurement of urinary cortisol secretion reflects cortisol secretion over several hours. It adjusts for daily fluctuations in plasma cortisol levels. Urine samples are collected at home in the morning. Some clinicians recommend collection over several mornings. Urine should not be collected until at least 2 days after a visit to a veterinary clinic or other stressful event since stress can lead to increases in the UCCR.[2,3]

UCCR has a sensitivity of close to 100% but specificity is low. If one urine sample is collected, the specificity is 20-25%.[3] Specificity increases if two basal UCCRs are performed.[3] UCCR is also affected by nonadrenal illness, so a positive UCCR test should be followed with another screening test (e.g. LDDST) at a later time.[1]

Endocrine Differentiation Tests

LDDST: The LDDST has the ability to both diagnose HAC and to differentiate between PDH and FAT. A diagnosis of PDH is achieved if cortisol level is high at time 0 and at another time, and if suppression is demonstrated at one of the following times:

1) 4-hr cortisol concentration <1.0 µg/dL
2) 4-hr cortisol <50% of baseline cortisol levels
3) 8-hr cortisol concentration <50% baseline but >1.4 µg/dL[9]

Sixty-five percent of dogs with naturally occurring HAC can be differentiated by the LDDST. Patients who fail to meet any of the three suppression criteria (i.e. cortisol is high at all 3 times) could either have PDH or FAT.[2,9]

High-Dose Dexamethasone Suppression Test (HDDST): HDDST can be used to differentiate between FAT and PDH. Though dogs with PDH are resistant to suppression of cortisol secretion following dexamethasone, higher doses of dexamethasone can overcome this resistance. After a higher dose, secretion of ACTH decreases and cortisol levels fall in dogs with PDH.[1,2] The HDDST is performed in the same fashion as the LDDST except dexamethasone is administered at 0.1 mg/kg IV.[9]

If cortisol suppression occurs at 4 or 8 hrs (i.e. <50% basal concentrations or cortisol concentrations below the laboratory cut-off value), then PDH is present.[3] If cortisol suppression does not occur, the chances of PDH versus FAT is 50:50. Therefore, a lack of suppression is considered inconclusive.[2,9] Since the LDDST can identify approximately 65% of patients with PDH, the HDDST only identifies an additional 10% of affected dogs.[9]

Endogenous ACTH: Measurement of endogenous ACTH levels in plasma can be very useful in differentiating patients with PDH from FAT. Endogenous ACTH testing cannot be used to diagnose HAC since some affected dogs have normal levels.[2] Patients with PDH have normal to elevated ACTH levels, while patients with FAT have low to undetectable ACTH levels.[1]

Endogenous ACTH testing in private practice is limited by its expense and problems with sample handling. Samples must be collected in heparin or EDTA silicon-coated glass or plastic tubes, and centrifuged immediately. Plasma must then be put in plastic or polypropylene tubes since ACTH adheres to glass, and samples must be frozen for shipment.[2]

Diagnostic Imaging: Routine adrenal gland ultrasonography, CT or MRI can be used to differentiate PDH from FAT.[2] Contrast-enhanced ultrasonography of the adrenal glands may improve the recognition of PDH.[20,21] Using MRI, pituitary tumors in dogs with PDH were found to be intrasellar (30.8%), extrasellar (62.6%) or involve the pars intermedia (6.5%).[18] Extrasellar tumors were more common in female dogs, while intrasellar tumors were more common in males.[18]

Disease description in this species:

Hyperadrenocorticism is characterized by chronic, excessive serum glucocorticoid concentration. PDH is most commonly diagnosed in older dogs, with a mean age of 11 years.[2,18] Most (75%) dogs with PDH are >9 years of age.[2] PDH is rare in dogs <6 years old.[2] No sex predisposition has been documented. Over-represented breeds include the poodle, dachshund, miniature schnauzer, terrier breeds, and boxer. About 75% of dogs with PDH weigh <20 kg.[2]

Clinical Signs

Clinical signs are usually attributed to chronic glucocorticoid excess but occasionally signs related to enlargement of a pituitary tumor occur. The most common clinical abnormalities include PU, PD, polyphagia, abdominal distension, alopecia, muscle weakness, hepatomegaly, and signs related to systemic hypertension.[3] Other abnormalities may include comedones, thin skin, poor hair regrowth, lethargy, panting, urinary incontinence, facial nerve paralysis, sudden blindness, persistent anestrus, testicular atrophy, calcinosis cutis, recurrent skin infections, circling, seizures, mentation changes, recurrent urinary tract infections, urinary calculi, hematuria, pollakiuria, dysuria, skin hyperpigmentation, seborrhea, and respiratory distress due to pulmonary thromboembolic disease.[2,3]

Atypical Hyperadrenocorticism

Dogs with atypical HAC can have historical and examination findings, and CBC, biochemistry panel, urinalysis and adrenal imaging results consistent with HAC. However, these patients have normal LDDST and ACTH stimulation test results. With atypical HAC, one or more sex hormones are elevated following ACTH administration (e.g. androstenedione, progesterone, 17-hydroxyprogesterone).[15] In one study of 5 dogs with HAC and normal post-ACTH cortisol levels, 5 had elevated progesterone and 4 had elevated 17 hydroxyprogesterone levels.[16] In another study of 16 dogs with PDH, 3 were classified as atypical. These patients all responded to standard therapy with either trilostane or mitotane.[15]

It has been theorized atypical HAC may be a derangement of the steroid synthesis pathway that leads to elevated precursor levels but levels of the end product, cortisol, remain normal.[2] It has also been proposed that the cut-off values for endocrine screening tests are too high; therefore, some patients with HAC are missed.[3,15] The specificity of sex hormone panels is low, and patients with nonadrenal neoplasia may have elevations of these hormones as well.[2,3]

Laboratory Profile:

Sodikoff's Laboratory Profiles of Small Animal Diseases: Hyperadrenocorticism, Iatrogenic
Sodikoff's Laboratory Profiles of Small Animal Diseases: Hyperadrenocorticism, Pituitary-Dependent

Etiology:

Pituitary adenoma
Pituitary neoplasia

Breed predilection:

Beagle
Boston terrier

Boxer
Dachshund
Miniature schnauzer
Poodle
Small breeds
Terriers

Sex predilection:
None

Age predilection:
Mature, middle-aged
Old

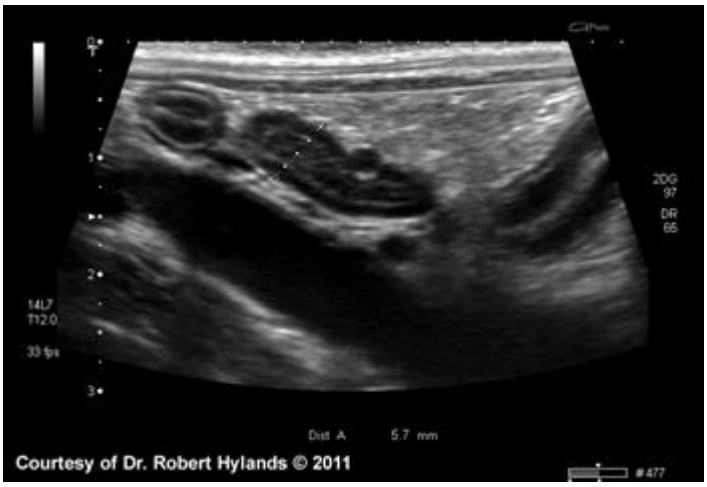
Diagnostic procedures:	Diagnostic results:
Hemogram (complete blood count)	Eosinopenia, eosinophils decreased Hemoconcentration or polycythemia Leukocytosis Lymphocytosis, lymphocytes increased Lymphopenia, blood lymphocytes decreased Neutrophilia Thrombocytosis
Serum chemistry	Alanine aminotransferase (ALT) increased Alkaline phosphatase (ALP) increased Aspartate aminotransferase (AST) increased Blood urea nitrogen (BUN) decreased Hypercholesterolemia Hyperglycemia Hypophosphatemia Lipidemia, lipids increased
Urinalysis	Bacteriuria, urine bacteria increased Glucosuria, glycosuria Proteinuria, albuminuria Pyuria, increased white blood cells Urine specific gravity decreased
Radiography of abdomen	Renal or bladder lithiasis
ACTH levels in frozen plasma	Endogenous ACTH increased
Adrenocorticotropic hormone stimulation test (ACTH)	Cortisol levels increased
Blood pressure measurement	Hypertension (>160/100 mmHg)
Cortisol levels in serum, ACTH stimulation test	Cortisol levels increased
High dose dexamethasone test	Cortisol increased initially, suppressed at 8 hours Cortisol increased initially, suppresses to <50% around 4 hrs with pituitary dependent hyperadrenocorticism
Ocular examination	Hyphema, blood anterior chamber eye
Ultrasonography of abdomen	Abdominal mass internal Symmetrical enlargement adrenal glands
Biopsy and histopathology of liver/gall bladder	Glucocorticoid hepatopathy

Low dose dexamethasone test	Cortisol increased initially, suppresses to <50% around 4 hrs with pituitary dependent hyperadrenocorticism Cortisol not decreased at 8 hours
Urine cortisol:creatinine ratio	Cortisol:creatinine ratio elevated
Computed tomography (CT) or MRI of head	Pituitary mass

Images:

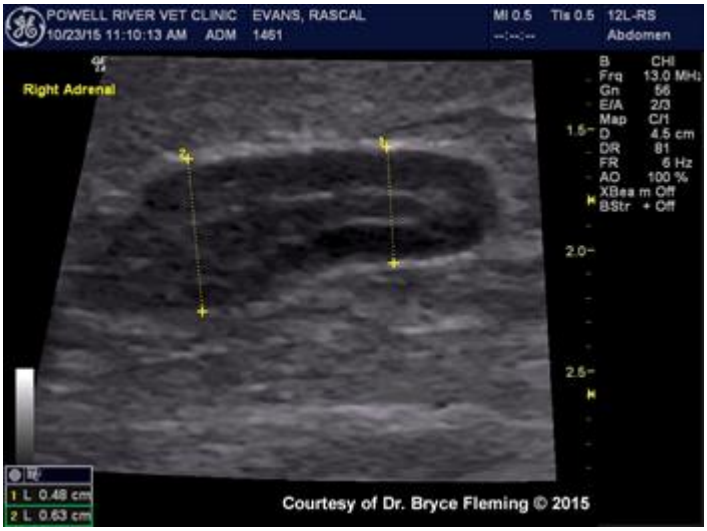
Click on each image to see a larger view

Figure 1. Normal adrenal gland (ultrasound)



Appearance of normal adrenal gland showing normal tissue layering.
Click here to see board discussion

Figure 2. Adrenal gland with changes consistent with Cushing's disease (ultrasound)



If you look at the layering ratios in that adrenal gland from the hypoechoic layering, which is part of the cortex, to that of the hyperechoic medulla, it is over 3:1 which is expected with hyperadrenocorticism.
Click here to see board discussion

URL: http://www.vin.com/doc/?id=7102771

Treatment/Management/Prevention:
Several options are available for treatment of PDH in dogs. A debate exists amongst veterinarians as to when to start therapy. Many clinicians do not treat PDH if clinical signs are absent or minimal.[2,4] Other clinicians argue in favor of therapy even if clinical signs are minimal in an effort to help control some of the complications associated with PDH. Such complications include UTIs, thromboembolic disease, hypertension, proteinuria, chronic pyoderma, calcium urolithiasis, biliary mucoceles, blindness (e.g. retinal detachment from hypertension, SARD, optic chiasm compression from macroadenoma), and diabetes mellitus.[4] Cost of therapy, side effects, frequency of follow-up evaluations, severity of disease, and presence of concurrent disorders should all be taken into account when determining appropriate therapy for PDH.[2] See the Medical FAQ on Decisions about Treating Hyperadrenocorticism.

SPECIFIC MEDICAL THERAPY

Trilostane

Trilostane is a synthetic, hormonally-inactive analogue that is a competitive inhibitor of the 3 β-hydroxysteroid dehydrogenase system. It blocks production of several adrenal steroids (e.g. cortisol) and aldosterone (to a lesser extent).[10,11,23] Trilostane is rapidly absorbed after oral administration, with peak concentrations occurring within 90 minutes. Duration of cortisol suppression varies but cortisol concentrations return to baseline levels within 10-18 hours.[2]

Current recommended starting doses of trilostane range from 1-2.5 mg/kg PO q 24 hrs, which is lower than the manufacturer's recommended starting dose.[2] Most patients require an increase in either dosage or frequency over time. Dosage adjustments should be based on clinical signs and results of ACTH stimulation testing. Although good clinical control can occur with once daily administration, some patients require twice daily administration.[12] Several studies suggest that administration of trilostane twice daily at low doses (0.5-1 mg/kg PO q 12 hrs) may provide superior clinical control and cause fewer side effects compared to higher, once daily dosing.[4,10,12,13] In addition, dogs weighing >30 kg (and possibly >15 kg) may require smaller amounts of trilostane per dose or per day than small dogs.[23]

Trilostane appears to be well tolerated in dogs. Side effects have been reported in 4-17% of treated patients.[4,3] Side effects include anorexia, vomiting, diarrhea, lethargy, shaking, and weight loss. Hypocortisolemia, hyperkalemia, and hypoaldosteronism can also occur. In one study of 13 dogs that developed iatrogenic hypoadrenocorticism secondary to trilostane, the mean dosage used was 4.75 mg/kg/day. Three of 13 dogs developed mineralocorticoid deficiency and four dogs developed permanent hypoadrenocorticism.[14] Acute adrenal necrosis has been reported in patients receiving trilostane. Although this is a rare, it is a very serious complication.[4] See the Medical FAQ on Trilostane.

Mitotane (Lysodren)

Mitotane has direct cytotoxic effects on the adrenal cortex (i.e. adrenocorticolytic), resulting in adrenocortical necrosis and atrophy. Mitotane causes selective necrosis of the zona fasciculate and zona reticularis layers of the adrenal cortex. At high doses, it can also cause necrosis of the zona glomerulosa layer (site of mineralocorticoid production).[2]

Mitotane is started at an induction dose of 30-50 mg/kg/day PO for up to 7-10 days or until clinical signs suggestive of hypoadrenocorticism develop (e.g. vomiting, diarrhea, decreased appetite, depression). An ACTH stimulation test is then performed. Prednisone at low doses (i.e. 0.1-0.2 mg/kg/day PO) is initiated in patients showing signs of hypoadrenocorticism during the induction phase of mitotane therapy.[10] Maintenance therapy of 50 mg/kg PO q 7-10 days is begun once the ACTH stimulation test shows adequate cortisol suppression (pre- and post-ACTH cortisol measurements in the normal resting range) and prednisone supplementation is successfully discontinued.[10] The maintenance dose of 50 mg/kg q 7-10 days may be divided into 2-4 equal doses.[2] Supplementation with prednisone is typically not needed during maintenance therapy but may be required during periods of stress or illness.[2] See the Medical FAQ on Lysodren Protocols.

Side effects are common with mitotane therapy. Lethargy, weakness, vomiting, diarrhea, decreased appetite, and ataxia are the most common signs. Side effects have been reported in up to 25% of dogs undergoing induction with mitotane and in approximately 30% of patients during maintenance therapy.[4] Complete adrenal necrosis leading to Addison's disease occurs in 2-5% of treated dogs.[2,4]

Nonselective adrenocorticolysis has been done in patients with PDH. The objective of this protocol is to completely destroy all three layers of the adrenal cortex, resulting in permanent Addison's disease (hypoadrenocorticism). Some clinicians feel that it is easier to treat Addison's disease long term than PDH.[4] Mitotane is given at 50-75 mg/kg/day PO divided into 2-4 small doses with food. Therapy is continued for 25 days. Lifelong therapy with fludrocortisone at 0.01 mg/kg/day PO and prednisone at 0.2 mg/kg/day PO is started on Day 3.[2] Side effects are very common with this nonselective protocol, and may require temporary or complete cessation of mitotane therapy. Death can occur in up to 40% of patients treated with this regimen. In one study of dogs undergoing nonselective mitotane therapy, 15/129 patients died during treatment.[4] Nonselective adrenocorticolysis is not universally recommended.[4] See the Medical FAQ on Chemical Adrenalectomy using the Utrecht Protocol.

Ketoconazole
Ketoconazole inhibits glucocorticoid synthesis while having minimal effects on mineralocorticoid synthesis. A starting dosage of 5 mg/kg PO q 12 hrs is given for one week. If this dose is well tolerated, it is increased to 10 mg/kg PO q 12 hours for 2 weeks. An ACTH stimulation test is then performed to determine cortisol levels. If cortisol levels remain above the reference range, the dose of ketoconazole is increased to 15 mg/kg PO q 12 hrs.[2] Therapy with ketoconazole is not recommended as a first choice therapy for PDH because it is effective in only about 50% of patients.[2]

Selegiline
Selegiline may down regulate ACTH secretion by increasing dopamine levels. However, it's effectiveness for PDH is questionable and its use is controversial.[2]

Cabergoline
Cabergoline (Cbg) is a D2 dopamine agonist that may be helpful for PDH. Dopamine may inhibit the corticotrophic cells of the pars distalis. In one study, 40 dogs with PDH were treated with Cbg at 0.07 mg/kg/week PO divided into 3 doses given q 48 hrs. In the study, 17 dogs responded to therapy.[4] Endogenous ACTH levels and pituitary tumor size were decreased after a year of therapy, and average survival time was 3 years.[4] Further studies are needed to evaluate cabergoline as an option for PDH.

SPECIFIC SURGICAL THERAPY
Transsphenoidal hypophysectomy is the treatment of choice for people with PDH and has also been successfully performed in dogs. Pituitary surgery is performed in tertiary referral institutions. Possible complications include diabetes insipidus, hypothyroidism, hypernatremia, decreased tear production, incomplete hypophysectomy, and procedure-related mortality.[2]

MONITORING
Patients undergoing therapy for PDH require close monitoring. The ACTH stimulation test is the most common test used for monitoring medical therapy.

Monitoring Cortisol Levels on Trilostane Therapy
For dogs undergoing trilostane therapy, evaluations are done at 10 days, 1 month, 3 months, and q 3 months thereafter. An ACTH stimulation test is performed approximately 2-4 hours after administration of trilostane for optimal results.[11] It is important to perform the ACTH test at about the same time after administration each time it is performed.[24] The first ACTH stimulation test at 10 days after starting therapy is mostly done to confirm that post-treatment cortisol levels have not decreased to below normal. If post-ACTH cortisol levels are still elevated at Day 10, the same dosage is continued.

If post-ACTH levels are still elevated at the 1 month evaluation and clinical signs of PDH are present, then a dosage increase may be needed. Alternatively, some patients may respond better to twice daily dosing instead of once daily dosing.[12,13] The dose is typically increased by 25-50% and an ACTH stimulation test is re-evaluated in 2-4 weeks.[2] If post-ACTH cortisol levels are low but the patient is clinically tolerating the drug, trilostane should be stopped for 5-7 days and restarted at a 25-50% reduction in dose. More than 50% of patients on trilostane therapy require dosing adjustments.[2]

Because ACTH response tests are expensive to run, baseline cortisol concentration, endogenous ACTH, and baseline cortisol/ACTH ratios have been evaluated as potential monitoring tools during trilostane therapy.[25,26] In one study, all three parameters were found to be inferior to the ACTH response test.[25] In another study, a single baseline cortisol value appeared to be a viable tool for making dosing change decisions.[26]

Monitoring Cortisol Levels on Mitotane Therapy
Patients undergoing induction therapy with mitotane are evaluated via an ACTH stimulation test 7-10 days after initiation of therapy or if any adverse events occur during therapy. The goal of induction therapy is to achieve pre-ACTH cortisol levels within the normal reference range, with little to no increase in post-ACTH cortisol levels. If cortisol levels are subnormal, mitotane is stopped and glucocorticoids are given until pre-ACTH cortisol levels return to normal. If cortisol levels are found to still be too high, induction therapy continues, with weekly ACTH stimulation tests until the desired pre-ACTH cortisol level is achieved. Induction therapy can take from a few days to 2 months, depending on the individual.[2]

Patients in the maintenance phase of therapy have ACTH stimulation tests done q 3-6 months. Approximately 50% of dogs have a relapse within 12 months of treatment initiation. Return of clinical signs or pre- and/or post-ACTH cortisol levels higher than desired can occur. If a relapse occurs, induction therapy is instituted again for 5-7 days, and an ACTH stimulation test is done. If cortisol levels have returned to the reference range, maintenance therapy consisting of a dosage 50% higher than the original maintenance dose can be started.[2]

Other Monitoring
Patients with PDH require frequent physical exams, with a CBC, biochemistry panel, and urinalysis. Hyperkalemia is a possible (but uncommon) adverse event with trilostane therapy. Electrolytes should be monitored in dogs on trilostane.[2,11] Patients with PDH, even if treated, are at risk for several concurrent diseases. These include hypertension, pyelonephritis, urinary calculi, diabetes mellitus, thromboembolic disease, chronic pyoderma, vacuolar hepatopathy, biliary mucocele, and chronic UTIs.[4,6] Other common monitoring tests include urine culture and blood pressure measurement.

PROGNOSIS
In one study of dogs with PDH treated with either mitotane or trilostane, median survival time for the mitotane group was 708 days and 662 days for the trilostane group.[10] In another study of dogs treated with trilostane, median survival time for patients treated with lower dose trilostane BID was 900 days.[2] In a study of 200 dogs treated with the typical mitotane induction protocol, mean survival time was 2.2 years, with 27% alive after 4 years and 8% alive after 6 years.[4] Another study of 1500 dogs treated with mitotane reported an average survival time of 32 months. [4] In a study of 150 dogs undergoing transsphenoidal hypophysectomy, the 1, 2, 3 and 4 year survival rates were 84%, 76%, 72%, and 68%, respectively.[4]

CONCURRENT DISEASES AND COMPLICATIONS
Concurrent diseases are common with PDH, especially if PDH is poorly controlled or left untreated. These diseases can have negative prognostic effects and decrease survival time. Approximately 15-20% of dogs with PDH develop neurologic signs related to expansion of their pituitary tumor. Pulmonary thromboembolism is a rare but potentially fatal complication of HAC. Hypertension is one of the most common concurrent abnormalities. One report found 86% of dogs with untreated HAC were hypertensive compared to 40% of dogs with well-controlled PDH.[2,6] Hypertension and proteinuria do not always resolve with treatment, so affected dogs may be at risk for renal dysfunction.[27] Diabetes mellitus develops in 5-10% of dogs with HAC.[2]

Special considerations:
Other Resources:
Recent VIN Message Board discussions on treatment of PDH
Recent VIN Message Board discussions on trilostane dosing
Recent VIN Message Board discussions on atypical HAC
VIN Message Board discussions on switching from mitotane to trilostane or trilostane to mitotane
Medical FAQ on diagnosing HAC
Medical FAQ on PU/PD
HAC simulator
Client Handouts on Cushing's disease
Client Handout on pituitary macroadenoma
Associate chapter on pituitary functional adenoma
VIN Rounds pertaining to HAC
Proceedings articles on pituitary-dependent HAC
Slide show entitled Diagnosing Adrenal Gland Disease by Dr. Luther

Differential Diagnosis:
Cholangiohepatitis, cholangitis

Diabetes insipidus, central
Diabetes insipidus, nephrogenic
Diabetes mellitus
Hyperadrenocorticism, adrenal-dependent
Other causes of vacuolar hepatopathy
Other causes of PU/PD
Pancreatitis
Pyelonephritis
Urinary tract infection

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