

Endocrinology

A COMPENDIUM OF LEADING ARTICLES IN THE FIELD OF VETERINARY ENDOCRINOLOGY SELECTED FOR THE VETERINARY PRACTITIONER

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Syndrome of Inappropriate Secretion of Antidiuretic Hormone in a Dog with Meningoencephalitis

Brofman PJ, Knostman KAB, DiBartola SP. Granulomatous amebic meningoencephalitis cause the syndrome of inappropriate secretion of antidiuretic hormone in a dog. *J Vet Intern Med* 2003;17:230-234.

► INTRODUCTION

Background: The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion is the opposite of diabetes insipidus. SIADH is characterized by (inappropriate) ADH secretion during normal to high blood pressure or low to normal plasma osmolality. Inappropriate ADH leads to water intoxication, disorientation, and hyponatremia. Causes of SIADH include drugs, especially tranquilizers and antineoplastic chemotherapeutics; encephalitis; neoplasia that produce ADH ectopically; and intrathoracic lesions with compromised venous return to the great vessels and pressure receptors. SIADH has rarely been reported in dogs.

Objectives: The purpose of this case report was to describe a dog with SIADH caused by meningoencephalitis.

✦ SUMMARY

Case Report: A 6-month-old, spayed female, German shepherd-mixed breed dog was presented for signs of neurologic disease. The condition had been progressive for the previous two weeks. History included diarrhea, bilateral eye discharge, and vomiting. Laboratory findings included anemia and lymphopenia. Symptomatic and non-specific treatments were unproductive. Two days later, the dog was febrile with a slightly low serum sodium concentration (144 mEq/L). Fluids were administered, and the neurologic signs became more severe and included a changing nystagmus. Upon referral to another hospital, the dog's fever had become worse, hydration was normal, and the serum sodium concentration had fallen to 128 mEq/L. Fluid therapy was continued. Thoracic

radiographic findings were within normal limits. Cerebrospinal fluid (CSF) was collected and analyzed. CSF contained excessive leukocytes (2,925/ μ l) and protein (1,150 mg/dl). The predominant leukocyte was large monocytes (43%). Culture of common bacteria and serology for common protozoa, fungi, and viruses that cause encephalitis in dogs were negative. Fluid therapy was discontinued but access to drinking water was provided. Seizures began, and the owners elected euthanasia. Necropsy revealed amebic (*Acanthamoeba*) meningoencephalitis.

Conclusions: This dog had a rare occurrence of the Syndrome of Inappropriate Antidiuretic Hormone and of *Acanthamoeba* meningoencephalitis.

CLINICAL IMPACT

Although the degree of hyponatremia caused by SIADH can be striking, the incidence of SIADH is probably much greater in dogs than is now appreciated. Most cases are likely to be acute and spontaneously resolve. The important reasons for properly recognizing such cases are to avoid a misdiagnosis of primary hypoadrenocorticism which also causes hyponatremia, avoid fluid administration, restrict water consumption, and discontinue any possible drugs that may be inducing SIADH. Key findings of SIADH are hyponatremia with inappropriate high urine osmolality and natriuresis without edema. Severe or prolonged cases of SIADH should be thoroughly evaluated for encephalitis and for neoplasia. Measurement of plasma ADH does not always correlate with the pathology due to erratic secretion of excessive ADH in some cases and possible ADH hypersensitivity in other cases.

Severe or prolonged cases of SIADH should be thoroughly evaluated for encephalitis and neoplasia

- ▶▶ Granulomatous meningoencephalitis can cause the syndrome of inappropriate secretion of antidiuretic hormone in dogs. *Journal of Veterinary Internal Medicine* 2003;17:230-234.
- ▶▶ Clomipramine administration can significantly decrease serum total and free T₄ concentrations. *Journal of Veterinary Internal Medicine* 2003;17:44-49.
- ▶▶ Anticonvulsant dosage of potassium bromide does not have a significant effect on either thyroid function or morphology in dogs. *Journal of the American Animal Hospital Association* 2003;39:193-202.
- ▶▶ Although the morphology of thyroid follicular cells is unchanged by severe nonthyroidal illness, serum total and free T₄ are often below the ranges for normal. *Journal of the American Veterinary Medical Association* 2003;222:1079-1085.
- ▶▶ Hypothyroidism in dogs has been reported to contribute to aggressive behavior. *Veterinary Record* 2002;151:547-548.
- ▶▶ Goitrous congenital hypothyroidism is an autosomal recessive trait in toy fox terriers. *Journal of Veterinary Internal Medicine* 2003;17:50-57.
- ▶▶ There may be an association between hypothyroidism and myocardial failure in Great Danes. *Journal of the American Animal Hospital Association* 2003;39:133-137.
- ▶▶ A set dose of 4 mCi of radioiodine therapy is considered safe and effective in hyperthyroid cats pretreated with methimazole. *Veterinary Radiology & Ultrasound* 2002;43:587-591.
- ▶▶ Transdermal methimazole is safe and effective treatment for cats with hyperthyroidism. *Journal of Feline Medicine and Surgery* 2003;5:77-82.
- ▶▶ Twice daily administration of methimazole is recommended for medically treating hyperthyroid cats. *Journal of American Veterinary Medical Association* 2003;222:954-958.
- ▶▶ The lowest possible effective dose of radioiodine should be administered to hyperthyroid cats to minimize the duration of post-treatment isolation. *American Journal of Veterinary Research* 2003;64:425-427.
- ▶▶ Parathyroid multinodular hyperplasia is autonomously secreting, as is single parathyroid adenoma in dogs. *Journal of Comparative Pathology* 2003;129:61-69.
- ▶▶ Treatment of diabetic dogs with bovine insulin can lead to anti-insulin antibodies. *Veterinary Immunology and Immunopathology* 2003;91:53-60.
- ▶▶ There are large day-to-day variations of serial blood glucose concentration curves in diabetic dogs being maintained on insulin injections. *Journal of the American Veterinary Medical Association* 2003;222:317-321.
- ▶▶ Diabetic dogs are at risk for recurrent or nonhealing corneal ulcers because of reduced corneal sensitivity. *American Journal of Veterinary Research* 2003;64:7-11.
- ▶▶ Sexually intact male dogs have lower post-ACTH stimulation serum cortisol concentrations than neutered males, intact females, or spayed females. *Domestic Animal Endocrinology* 2003;24:43-57.
- ▶▶ Trilostane has been a successful treatment of functional adrenocortical neoplasia in a dog. *Journal of Small Animal Practice* 2003;44:126-131.
- ▶▶ The most frequent serum steroid hormone elevation in dogs with alopecia, excluding cortisol, is progesterone. *Veterinary Dermatology* 2003;14:91-97.
- ▶▶ Mammary fibroadenomatous hyperplasia has been reported in a young male cat administered the progestogen, megestrol acetate. *Canadian Veterinary Journal* 2003;44:227-229.
- ▶▶ Dogs with feminizing testicular tumors more often have decreased plasma testosterone/estradiol ratio than elevated estradiol-17β concentrations. *Research in Veterinary Science* 2002;73:267-272.



Clomipramine Effects on Thyroid Function

Gulikers KP, Panciera DL. Evaluation of the effects of clomipramine on canine thyroid function tests. *J Vet Intern Med* 2003;17:44-49.

INTRODUCTION

Background: Glucocorticoids, potentiated sulfonamides, anticonvulsants, and many other drugs have been reported to alter thyroid function or plasma protein binding. Among these drugs are tricyclic antidepressants which have been demonstrated to inhibit thyroidal iodine uptake and activity of thyroid peroxidase and may suppress thyroid-stimulating hormone (TSH) release. The tricyclic antidepressant, clomipramine (Clomicalm[®], Novartis Animal Health, Greensboro, NC) has been approved for the treatment of separation anxiety in dogs in the United States. If recommended dosage suppresses thyroid hormone synthesis and release in dogs, it could either be mistakenly diagnosed as hypothyroidism or actually cause clinically significant thyroid hormone insufficiency.

Objectives: The purpose of this study was to evaluate the effect of long-term clomipramine administration on the hypothalamic-pituitary-thyroid axis in healthy dogs.

SUMMARY

Methods: Fourteen healthy dogs were each administered clomipramine 3 mg/kg, orally, twice per day for 112 days. Serum total T₄, free T₄ (fT₄), T₃, reverse T₃ (rT₃), and canine-TSH (c-TSH) were measured, plus thyrotropin-releasing hormone (TRH) response on c-TSH tests, on days 0, 7, 28, 42, 56, and 112.

Results: Serum T₄, fT₄, and rT₃ concentrations were significantly decreased at 28 days

and afterwards compared to day 0 concentrations. The lowest mean for serum T₄ and fT₄ concentrations occurred at day 112, a 35% and 38% decrease, respectively.

Serum concentrations of T₃ declined but were variable. Serum concentrations of c-TSH or post-TRH stimulation c-TSH were not significantly affected. Signs of clinical hypothyroidism were not observed.

Conclusions: Within four months of initiating administration, clomipramine does not cause clinical hypothyroidism in dogs, but it can depress serum concentrations of T₄ and fT₄ into ranges that mimic hypothyroidism.

Serum concentrations of T₄ and fT₃ are suppressed rapidly by clomipramine



CLINICAL IMPACT

Although signs of hypothyroidism did not develop in healthy dogs administered clomipramine for four months, treatment of dogs with clomipramine for separation anxiety may extend for much longer than four months. It is not known if longer treatment periods or concurrent nonthyroidal illness or other drug administration would induce clinical hypothyroidism signs. Serum concentrations of T₄ and fT₄ are suppressed rapidly by clomipramine which will complicate the investigation of possible primary hypothyroidism in dogs receiving clomipramine.



Potassium Bromide Effects on Thyroid Function and Morphology

Paull LC, Scott-Moncrieff JCR, DeNicola DB, et al. Effect of anticonvulsant dosages of potassium bromide on thyroid function and morphology in dogs. *J Anim Hosp Assoc* 2003;39:193-202.

INTRODUCTION

Background: Numerous drugs, including the anticonvulsant phenobarbital, affect thyroid function tests. Chronic administration of phenobarbital results in suppression of T_4 and free T_4 concentrations. Because bromide is a halide, it is possible that bromide competes with iodide for uptake and synthesis of thyroid hormones.

Objectives: The objective of this study was to determine if acute or chronic administration of potassium bromide to normal dogs affects thyroid function.

SUMMARY

Methods: Ten healthy dogs were administered either potassium bromide (KBr) or water (five dogs in each group) for 180 days. A loading dose of KBr (100 mg/kg, twice per day) was administered for two days followed by a maintenance dose of 30 mg/kg, once per day. The dose of KBr was adjusted after 120 days of treatment in order to achieve a serum bromide concentration of 250-300 mg/dl. Dogs underwent physical examination periodically during treatment and blood samples for measurement of serum biochemistries, T_4 , canine thyroid-stimulating hormone (c-TSH), and bromide (in KBr treatment group) were collected on days 3, 30, 120, and 177 of treatment. Serum free T_4 and thyrotropin-releasing hormone (TRH) stimulation tests were evaluated before treatment and on day 177 of treatment. Unilateral thyroidectomy was performed on day 182 of treatment in all dogs, and the thyroid glands were examined histologically.

Oral administration of KBr for six months does not affect thyroid function tests in dogs

Results: No clinical signs of hypothyroidism or bromism were noted in any dog. Serum biochemical abnormalities were limited to false elevation of chloride due to the bromide. Serum bromide concentrations were within or above the therapeutic range in all dogs from day 30 to the end of the study and within, above, and below the target range in one, one, and three dogs, respectively, on day 177. No differences in serum T_4 , free T_4 , or c-TSH concentrations or T_4 and TSH responses to TRH were noted between the treated and control groups. However, there was a substantial decrease in serum T_4 and free T_4 concentrations and an increase in the post-TRH c-TSH concentration and percent increase in T_4 in both groups at day 177 compared to pretreatment values. No difference in thyroid gland weight or thyroid histopathology was noted between the groups.

Conclusions: Oral administration of KBr for six months does not affect thyroid function tests in dogs.



CLINICAL IMPACT

The lack of effect of KBr administration on thyroid function in this study is in agreement with a previous study of dogs with seizure disorders treated with KBr. Therefore, phenobarbital appears to be the only commonly administered anticonvulsant that affects thyroid function. However, the small number of dogs in this study and the considerable decrease in serum T_4 and fT_4 concentrations over time in both treated and control dogs could have masked any effect of bromide administration.



Morphology and Function of the Thyroid in Severe Sickness

Torres SMF, Feeney DA, Lekcharoensuk C, et al. Comparison of colloid, thyroid follicular epithelium, and thyroid hormone concentrations in healthy and severely sick dogs. *J Am Vet Med Assoc* 2003;222:1079-1085.

INTRODUCTION

Background: Many dogs evaluated for hypothyroidism have an unrelated, nonthyroidal illness. This illness frequently alters thyroid function tests, resulting in a situation that could lead to a misdiagnosis of hypothyroidism. The pathogenesis of the changes in thyroid function tests is multifactorial and complex. Possible causes include decreased secretion or bioactivity of TSH, impaired secretion of thyroid hormones, inhibition of binding to plasma transport proteins, decreased entry into cells, and altered metabolism of thyroid hormones, as well as other mechanisms.

Objectives: The objectives of this study were to evaluate the changes in thyroid function tests and thyroid histology in dogs with severe nonthyroidal illness.

SUMMARY

Methods: Serum concentrations of T_4 , free T_4 (fT_4), and canine thyroid-stimulating hormone (c-TSH) as well as thyroid histology were evaluated in 66 severely ill dogs and compared with 61 dogs (43 beagles, 13 coonhounds, and five mixed breed) that were clinically normal and had normal thyroid function test results. The ill dogs were all euthanized because of the severity of their illness that ranged in duration from 1 to 270 days. Illnesses included neoplasia in 19 dogs, renal disorders in 12, gastrointestinal disorders in nine, infectious disease in seven, heart disease in four, and a number of other conditions in the remaining dogs. Thyroid glands were collected after euthanasia of all dogs and evaluated histologically

by measuring the relative amounts of colloid, follicular epithelium, and interstitium.

Results: The mean serum T_4 and fT_4 concentrations were significantly lower in the ill dogs than the healthy dogs. No significant difference in serum c-TSH was noted between the groups. Serum T_4 was below the normal range in 59%, fT_4 was below normal in 32%, and c-TSH was above normal in 8%. At least one of the hormones measured was outside of the reference range in 43 (65%) of the 61 ill dogs. Of these 43 dogs, only T_4 was below normal in 17, fT_4 alone was below normal in two, and

elevated serum c-TSH concentration was the only abnormality in two. Decreased serum T_4 and fT_4 concentrations were present concurrently in 19 dogs, and three dogs had a combination of decreased serum T_4 and increased c-TSH. Nineteen of the 43 ill dogs with thyroid function tests outside the reference range were receiving drugs that could affect thyroid function tests, primarily corticosteroids and phenobarbital. No difference in the volume of colloid, epithelium, or interstitium was noted on thyroid gland histology between the ill and healthy dogs. In healthy dogs, a positive correlation between the volume of epithelium and both serum T_4 and fT_4 was found, as was a negative correlation between these hormones and the volume of colloid on thyroid histology. In the sick dogs, no correlation between hormone concentrations and thyroid histology measurements was found.

Conclusions: Serum T_4 and fT_4 concentrations are frequently below the normal range in dogs with severe nonthyroidal illness.

Thyroid function testing should be delayed until any nonthyroidal illness that is present is resolved or controlled



CLINICAL IMPACT

This study demonstrates that interpretation of thyroid function tests in dogs with severe illness is difficult at best. While the serum fT_4 concentration was less frequently affected than T_4 concentration, approximately 1/3 of the ill dogs had a serum fT_4 below the reference range. Because none of the dogs in this study were suspected to have hypothyroidism but rather had conditions sufficiently severe to result in euthanasia, it is expected that the accuracy of the thyroid function tests evaluated would be much higher in a population of dogs suspected of hypothyroidism. However, concurrent illness is common in dogs suspected of hypothyroidism, particularly in a referral population. Thyroid function testing should be delayed until any nonthyroidal illness that is present is resolved or controlled.



Aggression and Hypothyroidism

Fatjo J, Stub C, Manteca X. Four cases of aggression and hypothyroidism in dogs. *Vet Rec* 2002;151:547-548.

► INTRODUCTION

Background: Aggressive behavior in dogs has been attributed to hypothyroidism in a small number of cases. Clinical signs of hypothyroidism have reportedly been absent in most cases. Because aggression can be a difficult behavior to effectively manage, identification of any underlying cause might allow more successful treatment.

Objectives: The objective of this report was to describe thyroid function test results and response to treatment in four dogs with aggression.

✦ SUMMARY

Methods: Three dogs with findings consistent with dominance-related aggression toward family members and one with fear aggression toward strangers were evaluated using a behavioral history, physical and neurological examinations, complete blood count, serum biochemistries, and serum concentrations of T_4 and canine thyroid-stimulating hormone (c-TSH). All dogs were treated with levothyroxine at 0.02 mg/kg, twice per day, and owners were instructed to avoid situations that might trigger aggressive behavior in their dog.

Results: No abnormalities were found on physical and neurological examinations, hemogram, or serum biochemistries with the exception of two dogs having a slight increase in body weight. The aggressive behavior had been present for “a long time” in all dogs. It had increased in frequency or intensity in two dogs for 2 and 18 months.

Aggression appears to be an uncommon manifestation of the disease (hypothyroidism)

Two other dogs had recent single severe episodes of aggression as the reason for presentation. Serum T_4 concentration was below and serum c-TSH concentration was above the reference range in all dogs. Aggression decreased but did not completely resolve in all four dogs after eight months of levothyroxine treatment, although one of the four “responded poorly to treatment” with less improvement than other dogs.

Conclusions: Hypothyroidism can reduce the threshold for aggressive behavior.



CLINICAL IMPACT

While the thyroid function tests in these cases are supportive of hypothyroidism, the lack of clinical signs other than worsening of aggressive behavior makes the diagnosis suspect but not impossible. The response to treatment was not well described, and the contribution of levothyroxine treatment to reduction of aggression might be difficult to determine as owners were instructed concurrently to avoid situations that might trigger the aggression. While a small number other cases of aggression appear to have been induced or worsened by hypothyroidism, it appears to be an uncommon manifestation of the disease.



Congenital Hypothyroidism in Toy Fox Terriers

Fyfe JC, Kampschmidt K, Dang V, et al. Congenital hypothyroidism with goiter in toy fox terriers. *J Vet Intern Med* 2003;17:50-57.

INTRODUCTION

Background: Congenital hypothyroidism, cretinism, is usually caused by agenesis of the thyroid (nongoitrous) or an inherited defect in thyroid hormone synthesis (goitrous). Goitrous congenital hypothyroidism can also be caused by deficient or excessive dietary iodine ingested by the gestating mother or a newborn. Dietary acquired congenital hypothyroidism is more rare and less severe than inherited forms of congenital hypothyroidism.

Thyroid dysmorphogenesis is most often a defect in organification, the bonding of iodine to thyroglobulin in the thyroid follicular colloid which is mediated by thyroid peroxidase and oxidase. A mixed-breed dog has been reported with goitrous congenital hypothyroidism with results of a radioiodine uptake and perchlorate discharge test consistent with thyroid peroxidase deficiency. Breeders of toy fox terriers have reported anecdotal incidences of mentally impaired nursing puppies which have been euthanized in the first three weeks of life and not been assessed for congenital hypothyroidism.

Objectives: The purpose of this study was to identify the molecular defect that causes thyroid dysmorphogenesis in toy fox terriers and develop a carrier detection test.

SUMMARY

Case Reports: Two clusters of toy fox terrier puppies were evaluated for suspected goitrous congenital hypothyroidism. Both male and female puppies were affected. Goiter was detected by palpation of the

ventral aspect of the neck by one week of age. Within three weeks of birth, affected puppies exhibited thick short necks, inactivity, short fluffy hair coats, and reluctance to nurse well. Opening of the ear canals and palpebral fissures was delayed. Brainstem auditory evoked response test results were within normal limits. Serum thyroid hormone concentrations (T_4 and free T_4) were low; serum canine-thyroid stimulating hormone (c-TSH) concentrations were high.

Histologic examination of the goiter tissue revealed small, irregular shaped colloid follicles with cuboidal to columnar follicular cells. Near normal growth rate was achieved with thyroid hormone administration. Radioiodine uptake and perchlorate discharge tests done at 8 weeks of age confirmed an organification defect in the thyroid. Biochemical analysis of the goitrous thyroids demonstrated a peroxidase deficiency. Thyroid peroxidase canine DNA sequence was determined and the mutation in genomic DNA was identified. The occurrence within family lines was consistent with an autosomal recessive trait.

Conclusions: Goitrous congenital hypothyroidism occurs as an autosomal recessive trait in some families of toy fox terriers. The genetic mutation results in a deficiency of thyroid peroxidase. This is the first report of an identified gene mutation causing an endocrinopathy in dogs.



CLINICAL IMPACT

Few toy fox terriers or other dogs with congenital hypothyroidism either live or are allowed to live to weaning. The most common presentation is a puppy whose

eyes and ear canals have not opened by three weeks of age with palpable goiter. It may also be possible to detect mental depression and stunted growth in relation to its more active litter mates. Approximately one in four puppies in the litter may be affected.

If the puppies live a few months, other features typical of congenital hypothyroidism will become apparent. These include macroglossia, lateral strabismus, short-legged disproportionate dwarfism, delayed permanent dentition, prognathism, and anemia. Radiographs of the ends of long bones will show epiphyseal dysgenesis.

The retardation of growth can be incompletely corrected by thyroid hormone supplementation, but mental retardation will be permanent if replacement hormone therapy is not begun within the first week of life.

Subsequent to the original work on this paper, a DNA-based carrier test has been made available to toy fox terrier breeders. In the cohort tested, the incidence of carriers was 31%.

The most common presentation is a puppy whose eyes and ear canals have not opened by three weeks of age with palpable goiter



Hypothyroidism and Heart Failure in Great Danes

Phillips DE, Harkin KR. Hypothyroidism and myocardial failure in two Great Danes. *J Am Anim Hosp Assoc* 2003;39:133-137.

INTRODUCTION

Background: Hypothyroidism can cause impaired cardiovascular function in dogs. Impaired electrical conductivity can result in bradycardia, first degree atrioventricular block, and low-voltage electrocardiographic (ECG) complexes. Hypothyroidism also causes impaired myocardial contractility and relaxation, decrease myocardial beta-adrenergic receptors, decreased vascular volume, and increased systemic vascular resistance. This usually results in mild clinical changes manifested as lower-than-expected heart rate or overt bradycardia, weak peripheral pulses, and mild reductions of myocardial contractility documented by echocardiography. While rare cases of myocardial failure secondary to hypothyroidism have been documented in humans, it has not been reported in dogs.

Objectives: The objective of this report is to describe clinical findings in two dogs with hypothyroidism and concurrent myocardial failure.

SUMMARY

Case Reports: Two Great Dane dogs (2 and 4 years of age) were evaluated for clinical signs related to congestive heart failure. Tachypnea, tachycardia, atrial fibrillation, and radiographic evidence of cardiomegaly and pulmonary edema were found in both cases.

Case 1 had thickened skin consistent with myxedema and hypercholesterolemia as evidence of hypothyroidism. Serum T_4 , free (f) T_4 , and T_3 were markedly below the reference range, and the antithyroglobulin

antibody was elevated. Serum canine thyroid-stimulating hormone (c-TSH) concentration was normal. Echocardiographic findings consistent with dilated cardiomyopathy included a fractional shortening of 8% and enlarged left ventricle and left atrium. Treatment included digoxin, diltiazem, furosemide, lisinopril, and levothyroxine (0.02 mg/kg, twice per day).

It would seem appropriate to limit evaluation of thyroid function in dogs with heart failure to those with concurrent clinical evidence of hypothyroidism

Four weeks after initiating treatment, the dog was reported to have been doing well, was no longer tachypneic or tachycardic, had lost 10.8 kg, and no longer appeared to have myxedema. On electrocardiogram, atrial fibrillation with a ventricular rate of 60

beats per minute (bpm) was present. Prior to treatment the ventricular rate had been 160 bpm. The hypercholesterolemia had resolved. Fractional shortening had increased to 27%, and the diastolic diameters of the left ventricle and left atrium had decreased slightly from those recorded prior to treatment. After an additional 30 days of treatment (without furosemide), atrial fibrillation with a ventricular rate of 70 bpm, a fractional shortening of 37%, and further reduction in size of the left ventricle and atrium were noted. All treatment was discontinued except levothyroxine and diltiazem. Six weeks later, atrial fibrillation with a ventricular rate of 84 bpm was found, the fractional shortening continued to be normal (36%), and the left atrium was still enlarged. The dog remained clinically normal for 38 months after initial evaluation, although further assessment of cardiac function was not made.

The dog in Case 2 had documented congestive heart failure and dilated cardiomyopathy as well as hypothyroidism.

The response to treatment was incomplete and less convincingly associated with levothyroxine treatment. However, the dog remained free of clinical signs of heart disease, had a fractional shortening of 24% (compared with 10% at initial presentation), and continued atrial fibrillation but with a ventricular rate of 92 bpm while receiving only levothyroxine and diltiazem.

Conclusions: Hypothyroidism can cause severe myocardial dysfunction leading to congestive heart failure, and the myocardial changes are largely reversible with levothyroxine administration.

CLINICAL IMPACT

Hypothyroidism is occasionally documented in dogs with dilated cardiomyopathy. This finding is usually the result of concurrent but unlinked hypothyroidism and idiopathic or breed-related cardiomyopathy rather than hypothyroidism-induced cardiac dysfunction. Some breeds with a high prevalence of myocardial disease, such as Doberman pinschers and boxers, also are predisposed to develop hypothyroidism. Myocardial disease would be expected to resolve with levothyroxine supplementation if due entirely to hypothyroidism. Because nonthyroidal illness can suppress serum T_4 and fT_4 concentrations, the effects of heart failure on thyroid function tests can result in a misdiagnosis of hypothyroidism. Both cases described in this report had clinical findings suggestive of hypothyroidism other than myocardial dysfunction that resolved with levothyroxine treatment. It would seem appropriate to limit evaluation of thyroid function in dogs with heart failure to those with concurrent clinical evidence of hypothyroidism.



Predictors of Response to Radioiodine Therapy

Chun R, Garrett LD, Sargeant J, et al. Predictors of response to radioiodine therapy in hyperthyroid cats. *Vet Radiol Ultrasound* 2002;43:587-591.

INTRODUCTION

Background: The safest and most effective treatment for feline hyperthyroidism is radioiodine administration. Treatment is generally administered by a single subcutaneous injection of ^{131}I . Some studies have suggested that cats with higher pretreatment serum T_4 concentrations, larger thyroid glands, and more severe clinical signs are more likely to have persistent hyperthyroidism.

Objectives: The objective of this study was to evaluate factors that affect the outcome of radioiodine treatment in hyperthyroid cats.

SUMMARY

Methods: Medical records of 193 cats diagnosed with hyperthyroidism based on elevated serum T_4 concentration or abnormal technetium thyroid scans that were treated with radioiodine were evaluated retrospectively. Serum T_4 was measured before and on at least two occasions; 1 week, and 1, 3, 6, 12 months after radioiodine treatment. A favorable response to treatment was defined as resolution of clinical signs of hyperthyroidism and a serum T_4 concentration in the normal range. All cats underwent thyroid scintigraphy as well. Clinical findings, previous treatment with methimazole, serum T_4 concentration, and scintigraphic findings were evaluated for relationship to response to radioiodine treatment.

Results: Of all the parameters evaluated, only pretreatment serum T_4 concentration

and thyroid to salivary gland scintigraphic ratio were found to be significantly associated with outcome of radioiodine treatment. Higher pretreatment serum T_4 was associated with a higher post-treatment serum T_4 , but the T_4 was in the normal range in most cats. Only two cats required a second radioiodine treatment, and no cat evaluated had an elevated serum T_4 concentration six or 12 months after treatment. The thyroid-to-salivary gland scintigraphic ratio was associated with a higher post-treatment serum T_4 concentration only at one week after treatment. The median serum T_4 concentration was significantly lower in cats

where treatment with methimazole was discontinued five or more days before radioiodine compared with those where treatment was discontinued less than five days before radioiodine administration. There was no relationship between methimazole administration and post-treatment serum T_4 concentration.

Conclusions: There is no relationship between pretreatment serum T_4 concentration or scintigraphic findings and persistent hyperthyroidism or hypothyroidism in cats following treatment with 4 mCi of radioiodine.

CLINICAL IMPACT

This study shows that there is no indication for thyroid scintigraphy in treatment of hyperthyroidism as the results have no relationship with final outcome of treatment. A fixed dose of radioiodine appears to be

effective, and no other factors that would provide guidance to different dosages were identified.

This study also confirms that methimazole treatment prior to radioiodine does not affect the outcome of controlling hyperthyroidism. However, 9% of treated cats were diagnosed with post-treatment hypothyroidism and administered replacement therapy. How many of the post-radioiodine treatment hypothyroid cats were pretreated with methimazole was not mentioned in the study. Recent treatment with methimazole will increase thyroid-stimulation hormone release and could increase radioiodine uptake in normal thyroid tissue, increasing the risk of post-treatment hypothyroidism. Whether is theory is true cannot be confirmed or disregarded as yet.

There is no indication for thyroid scintigraphy in treatment of hyperthyroidism



Transdermal Administration of Methimazole

Hoffmann G, Marks SL, Taboada J, et al. Transdermal methimazole treatment in cats with hyperthyroidism. *J Feline Med Surg* 2003;5:77-82.

► INTRODUCTION

Background: The primary disadvantage to medical management of hyperthyroidism is owner compliance with oral administration of methimazole. Percutaneous administration would simplify treatment and allow more cats to be treated successfully with methimazole. Absorption of a drug percutaneously is enhanced by the vehicle. A pleuronic lecithin organogel is used as a vehicle for percutaneous drug delivery in animals and humans.

Objectives: The objectives of this study were to evaluate the clinical response and serum T_4 concentrations in hyperthyroid cats administered methimazole in a pleuronic lecithin organogel.

✦ SUMMARY

Methods: Thirteen cats with hyperthyroidism were treated with methimazole that was formulated by a compounding pharmacy in a pleuronic lecithin organogel at a concentration of 5 mg/0.1 ml. Eleven cats had not been treated with any anti-thyroid medication prior to transdermal methimazole, while two had been treated with methimazole orally. The two that were treated previously had been administered methimazole orally and had vomiting as an adverse effect that necessitated discontinuing treatment. Dosage ranged from 2.5 mg, once per day, to 10 mg, twice per day. Owners were instructed to clean off any material on the pinna and to apply the gel to the inner pinna of an ear by rubbing the compound gently while wearing gloves. Ten of the cats were evaluated after a mean of 4.3 weeks of treatment and eight of the cats

at 5.4 months after initiating treatment for evaluation of response to treatment, adverse effects, serum T_4 , and in some cases complete blood count, serum chemistries, and urinalysis.

Results: All cats showed improvement or resolution of clinical signs of hyperthyroidism according to owners. The mild liver enzyme elevations noted prior to treatment resolved in three of four cats. At the initial recheck, serum T_4 concentration had decreased in nine of 10 cats and was within or below the normal range in seven cats. The three cats that had little or no decrease in serum T_4 concentration received relatively low doses of methimazole (2.5 mg, every 24-48 hr; 5 mg, once per day; and 3.75 mg, twice per day). In addition, poor compliance with treatment was noted in two of these cases, and one of the cats was euthanized because of difficulty in consistent treatment. The only one of these three cats rechecked at the second time period had a serum T_4 concentration below normal after a dosage adjustment. At the second recheck, seven of eight cats had normal or below normal serum T_4 concentrations. Adverse effects were not noted in any cat, including the two cats that vomited while receiving methimazole orally. Overall, there was a significant decrease in the mean serum T_4 concentration at both treatment times compared with that prior to treatment.

Conclusions: Methimazole can be used transdermally to successfully control hyperthyroidism in cats.



CLINICAL IMPACT

Use of transdermal methimazole will allow effective medical management by many cat owners that are not able to administer the drug orally. Transdermal administration is simple and apparently effective in this study, confirming clinical impressions of many veterinarians using the preparation routinely. The positive effects occur despite a previous study in healthy cats demonstrating unreliable and generally poor absorption of a single transdermal dose of methimazole. It is likely that repeated treatment or dermal changes with hyperthyroidism enhances absorption. No vomiting was noted following transdermal methimazole in the two cats that vomited after receiving oral methimazole. Because vomiting and anorexia are the most common adverse effects of oral methimazole, transdermal treatment may offer an alternative that minimizes this problem. Because the preparation utilized in this study was compounded by a pharmacy, variation in the lecithin organogel or compounding process could lead to less effective or inconsistent results.

Transdermal administration is simple and apparently effective



Frequency of Administration of Methimazole

Trepanier LA, Hoffman SB, Kroll M, et al. Efficacy and safety of once versus twice daily administration of methimazole in cats with hyperthyroidism. *J Am Vet Med Assoc* 2003;222:954-958.

INTRODUCTION

Background: Methimazole is concentrated in the thyroid and inhibits the synthesis of thyroid hormones. It is used to pharmacologically control hyperthyroidism in cats. Potential adverse effects most often are vomiting and anorexia, but occasionally serious blood dyscrasias, facial swelling and pruritus, and hepatopathy can occur.

The plasma half-life is 2 to 6 hours. Therefore, it is usually recommended to be administered two to three times per day at least initially. However, the biological effects may be much longer than the plasma half-life, especially since it is concentrated in the thyroid.

Objectives: The goal of this study was to determine whether once daily administration of methimazole is as efficacious and safe in hyperthyroid cats as twice daily administration of methimazole.

SUMMARY

Methods: Forty cats with newly diagnosed hyperthyroidism were randomly assigned to either receive 5 mg of methimazole, by mouth, once daily (25 cats) or 2.5 mg, twice daily (15 cats). Physical examination, hemogram, serum biochemistries and T₄ concentration, urinalysis, and blood pressure were evaluated at 0, 2, and 4 weeks of treatment in each cat.

Results: Serum T₄ concentrations were significantly higher in cats receiving methimazole once daily compared to those receiving it twice per day after two and four weeks of administration. After two weeks of administration, 87% of the cats receiving the drug

twice per day had serum T₄ concentrations in euthyroid range, whereas only 54% of the cats receiving once daily treatment had euthyroid serum T₄ concentrations. After four weeks of treatment, 92% of cats treated twice daily had normal serum T₄ concentrations, while only 71% of those treated once daily had normal T₄ concentrations. There was no significant difference in the incidence of adverse effects.

Conclusions: Once daily administration of methimazole is not as effective as twice daily administration.



CLINICAL IMPACT

The dosage of methimazole used in this study was not as high as is typically recommended for initial treatment of hyperthyroidism in cats. Plus, the rate of decline of serum T₄ concentration was not as rapid as in cats treated at higher dosage. Still, the incidence of adverse effects were higher than expected: 44% overall, 10% with hepatopathy, and 15% with facial excoriations.

There are at least two possible explanations for the apparent high incidence of adverse effects. First, the cats of this study may have been more closely monitored and had more sensitive thresholds for the declaration an adverse effect. Second, giving higher initial doses of methimazole may produce a tachyphylaxis that reduces the incidence of immunologically mediated adverse effects. Additional studies are needed with higher initial dosages of methimazole administered transdermally.

The incidence of adverse effects were higher than expected



Duration of Isolation for Radioiodine Therapy

Weichselbaum RC, Feeney DA, Jessen CR. Evaluation of relationships between pretreatment patient variables and duration of isolation for radioiodine-treated hyperthyroid cat. *Am J Vet Res* 2003;64:425-427.

INTRODUCTION

Background: Radioiodine is a common treatment for hyperthyroidism, the most frequently diagnosed endocrinopathy of cats. Radioiodine emits gamma rays and is eliminated in all body secretions which are a potential beta-ray risk to handlers if ingested. Treated cats are kept in radioisotope isolation units until reasonable risk to the owner has dissipated based on repeated monitoring with a Geiger-Mueller counter. However, isolation is stressful to the cat and its owner. A pretreatment predictor of the required duration of isolation would be helpful in explaining the treatment for an individual cat to its owner and estimating the overall treatment expense.

Objectives: The purpose of this study was to evaluate the possible correlation between selected pretreatment clinical findings and the required duration of isolation of hyperthyroid cats treated with radioiodine.

able that correlated with the duration of required isolation.

Conclusions: Radioiodine treatment dose should be as low as possible to reduce the duration of isolation.



CLINICAL IMPACT

There is no universal method of determining the dosage of radioiodine to hyperthyroid cats. In addition, the safety level for cats treated with radioiodine for hyperthyroidism to be released to their owners varies among States, and subcutaneous injection of radioiodine is more convenient to administer and reliable in delivering a specific dose than oral administration, as used in this study. Despite these difficulties in the direct application of the methods used in this investigation, the finding that radioiodine dosage correlates with the length of time for isolation probably is true to a given safety level within any State's requirements.

Radioiodine treatment dose should be as low as possible to reduce the duration of isolation

SUMMARY

Methods: One hundred and forty-nine cats with hyperthyroidism were treated orally with 2.9 to 6.04 mCi of radioiodine. Possible predictors of isolation duration were evaluated and included serum creatinine and T_4 concentrations, body weight, age, radioiodine dose, and concurrent cardiac medications. Gamma radiation at dismissal from isolation was less than 2.0 mR/h at the skin surface over the thyroid area.

Results: The mean duration of isolation required was 16.7 days. The dose of radioiodine was the only pretreatment vari-



Parathyroid Hormone Histochemistry: Adenoma or Hyperplasia

van Vonderen IK, Kooistra HS, Peeters ME, et al. Parathyroid hormone immunohistochemistry in dogs with primary and secondary hyperparathyroidism: the question of adenoma and primary hyperplasia. *J Comp Path* 2003;129:61-69.

INTRODUCTION

Background: Hyperparathyroidism can be primary or secondary. Primary hyperthyroidism is less common than secondary hyperthyroidism. The great majority of primary hyperthyroidism cases are caused by autonomous solitary parathyroid adenoma. Uncommon causes are parathyroid carcinoma or autonomous primary (nodular) hyperplasia of the parathyroids.

Objectives: The purpose of this investigation was to describe the histology of parathyroid gland abnormalities and parathyroid hormone immunohistochemistry in healthy dogs and dogs with primary parathyroid gland hyperplasia, parathyroid adenoma, and secondary parathyroid gland hyperplasia caused by chronic renal failure.

SUMMARY

Methods: The clinical findings, histologic findings, and parathyroid hormone immunohistochemistry were evaluated in five dogs with primary hyperparathyroidism, three dogs with secondary hyperparathyroidism from chronic renal failure, and eight control dogs that had received hypophysectomies 10 weeks earlier.

Results: Among the five dogs with primary hyperparathyroidism, two dogs had nodular hyperplasia of the parathyroids, and an adenoma was present in each of the other three dogs. Non-nodular (diffuse) hyperplasia was present in the parathyroids of all three dogs with chronic renal failure. Both hyperplastic and adenomatous parathyroid tissue had diffuse cytoplasmic parathyroid hormone immunohistochemistry staining

while healthy parathyroid tissue did not. Localized paranuclear parathyroid hormone labeling of normal, hyperplastic, and adenomatous parathyroid tissue was present and therefore, nonspecific for functional status.

Conclusions: Primary multinodular hyperplasia is the existence of multiple adenomas rather than hyperplasia.



CLINICAL IMPACT

Solitary and multiple adenomas (“multinodular hyperplasia”) of the parathyroids are functionally and immunochemically identical. However, their origins or cause may be different. Solitary adenomas are more likely to be the result of acquired insults or cell aging changes while multinodular adenomas are more likely to be familial in origin or the result of chronic stimulation of the parathyroids. The conversion of secondary hyperplasia of the parathyroids to autonomous multinodular change is referred to as tertiary hyperparathyroidism.

Patients diagnosed with primary hyperparathyroidism that have multinodular lesions of the parathyroids should be evaluated for familial tendency for hyperparathyroidism or multiple endocrine neoplasias. They should also be evaluated for concurrent diseases which may have originally caused secondary hyperparathyroidism and progressed to tertiary hyperparathyroidism, especially chronic renal failure.

Primary multinodular hyperplasia is the existence of multiple adenomas rather than hyperplasia



Anti-insulin Antibodies in Dogs

Davison LJ, Ristic JME, Heritage ME, et al. Anti-insulin antibodies in dogs with naturally occurring diabetes mellitus. Vet Immunol Immunopathol 2003;91:53-60.

► INTRODUCTION

Background: Insulin treatment of dogs is performed with another species' insulin such as bovine, porcine, or recombinant origin human insulin. Insulin is a poor antigen due to its small molecular size, but if combined with another protein such as C-peptide of proinsulin, significant antibodies may form and bind insulin prior to its binding insulin receptors and effecting post-receptor, insulin-mediated cellular events. The incidence of anti-insulin antibodies in diabetic dogs is not known.

Objectives: The purpose of this study was to determine the incidence of anti-insulin antibodies in dogs treated with bovine insulin to what species insulin and subunit were antibodies directed against.

None of the dogs of this report were adversely affected by the anti-insulin antibodies

dogs compared to control dogs. Twenty of the 30 diabetic dogs were considered to have significant anti-insulin antibody production. However, there was no significant difference in the occurrence of canine distemper virus or anti-thyroglobulin antibodies between diabetic dogs and control dogs. The presence of anti-bovine insulin antibodies correlated well with the presence of anti-porcine insulin antibodies. Anti-insulin antibodies were primarily directed against the B chain, but greater levels of antibodies were generated against the entire insulin molecule than just the B chain.

Conclusions: Treatment of diabetic dogs with bovine insulin can lead to the production of anti-insulin antibodies.

✕ SUMMARY

Methods: Serum was collected from 30 diabetic dogs being treated with lente (28 dogs) or protamine zinc bovine insulin (two dogs) for at least one month and from 30 nondiabetic dogs with neoplasia, gastrointestinal disorders, and renal or respiratory disease. The diabetic dogs were 14 females and 16 males with an average age of 9.6 years and a median duration of insulin treatment of one year. The control group consisted of 12 females and 18 males with an average age of 5.2 years. All dogs were vaccinated against canine distemper virus. Serum from six dogs with anti-insulin antibodies was analyzed to determine the portion of the insulin molecule the antibodies were directed against.

Results: Anti-insulin antibodies were detected significantly more often in diabetic



CLINICAL IMPACT

Treatment of diabetic dogs with heterologous insulin (bovine-origin) can cause the production of anti-insulin antibodies which can cross-react with porcine insulin and therefore canine insulin which is homologous with porcine insulin. As ominous as this seems, the amount and affinity of anti-insulin antibodies produced is critical to clinical significance. Pure insulin is a small molecule with weak antigenicity. Older forms of insulin contained traces of proinsulin which were more capable of inducing anti-insulin antibodies of sufficient amount to interfere with insulin action or cause injection site local reactions. None of the dogs of this report were adversely affected by the anti-insulin antibodies produced by long-term injection of commercially available, purified bovine insulin.



Day-to-Day Variability of Blood Glucose Concentrations in Diabetic Dogs

Freeman LM, Rand JS. Evaluation of day-to-day variability of serial blood glucose concentration curves in diabetic dogs. *J Am Vet Med Assoc* 2003;222:317-321.

INTRODUCTION

Background: Some clinicians assume that if a diabetic dog is fed a consistent meal at a consistent time, receives the same amount of exercise each day, and is administered the same dose of insulin at the same time every day, there will not be any significant variation in daily blood glucose concentration curves. This assumption is often proven false. Other factors that can cause day-to-day variations in blood glucose curves are the efficiency in agitating insulin solution, measurement of very small volumes of insulin, and vascularity and perfusion of the subcutaneous injection sites.

Objectives: The purpose of this study was to investigate day-to-day variability of serial blood glucose concentrations in diabetic dogs.

SUMMARY

Methods: Ten diabetic dogs that had been previously started on insulin therapy three weeks to three years earlier were selected for an outpatient study. All dogs were administered porcine insulin subcutaneously, twice per day, in dosages required to meet individual needs. Each dog had paired 12 hour serial blood glucose curves assessed on two consecutive days on three separate occasions with at least two weeks between the testing occasions. Meals and administered insulin were the same each of the two consecutive days. Blood samples were collected every two hours during the test days.

Blood glucose curves based on samples taken every two hours are not accurate predictors of blood glucose control for the next day

Results of Day 1 curve and Day 2 curve were evaluated and compared. Parameters recorded were blood glucose concentrations just prior to the twice daily insulin injections, maximum and minimum blood glucose concentrations, time from insulin injection to minimum blood glucose level, difference between blood glucose concentration just prior to the morning insulin injection and the minimum level, the area under the blood glucose curve, mean blood glucose concentration during 12 hours between insulin injections, the standard deviations, and J-index.

Results: Significant differences existed between blood glucose concentrations on Day 1 and Day 2. Insulin dosage changes were believed warranted between Day 1 and Day 2 in 27% of occasions. Desire to change insulin dosage on Day 2 was greatest (40% of occasions) when the blood glucose nadir was less than 180 mg/dl.

Conclusions: Blood glucose concentration curves in diabetic dogs vary significantly on consecutive days despite consistent insulin dose and meals.



CLINICAL IMPACT

Although the differences in consecutive blood glucose curves were significant in this study that used medium- to large-sized diabetic dogs, smaller diabetic dogs would probably have had greater differences between blood glucose curves on consecutive days. Smaller dogs require smaller vol-

umes of insulin which are more difficult to measure accurately and to reproduce the same degree of dispersal into solution. The small volumes of insulin to inject are also more susceptible to variation in absorption due to injection site vascularity and perfusion.

The results of this study provide evidence that blood glucose curves based on samples taken every two hours are not accurate predictors of blood glucose control for the next day and certainly not for longer periods into the future. Less frequent blood glucose determinations are sufficient to determine initial doses required for stabilization. Subsequent dosage adjustments are best based on changes in body weight, attitude, appetite, 24-hour water consumption, presence or absence of ketonuria, and serum fructosamine or glycohemoglobin concentrations rather than, or in addition to, glucose curves.

This study also support the value of careful agitation and volume measurement of insulin. Dilutions of insulin should be considered on dogs under 20 lbs in weight and cats to increase volume for accurate measurement and reliability of consistent rate of absorption. Dilutions of insulin should be prepared under sterile conditions in small quantity. Careful agitation is still a requirement prior to aspiration into the dose syringe.



Corneal Sensitivity in Diabetic Dogs

Good KL, Maggs DJ, Hollingsworth SR, et al. Corneal sensitivity in dogs with diabetes mellitus. *Am J Vet Res* 2003;64:7-11.

► INTRODUCTION

Background: The most common ocular complication of diabetes mellitus is cataract formation. Because most diabetic dogs develop cataracts, lensectomy is frequently performed. Corneal abnormalities have also been documented in diabetic dogs, and may in part be the result of a neuropathy involving the corneal nerves. Impaired corneal healing may result, increasing complications following surgery for cataracts.

Objectives: The objective of this study was to determine if corneal sensitivity is reduced in dogs with diabetes mellitus.

of diabetes mellitus to evaluation in the 23 dogs was eight months. The corneal touch threshold was significantly higher, thus corneal sensitivity was lower in the diabetic dogs compared with control dogs in all regions of the cornea. There was no correlation of corneal touch threshold with duration of diabetes mellitus, serum fructosamine, or glycosylated hemoglobin concentration. In diabetic and control dogs, the presence of cataracts did not appear to affect corneal touch threshold.

Conclusions: Reduced corneal sensitivity is present in diabetic dogs, and duration and control of the diabetes does not alter impaired sensitivity.

✦ SUMMARY

Methods: Corneal sensitivity was assessed in both eyes of 23 diabetic and 29 nondiabetic dogs. All dogs were determined to be free of ocular disease based on history and complete ophthalmic examination with the exception of cataracts. Control of hyperglycemia in diabetic dogs was determined by measurement of serum fructosamine and glycosylated hemoglobin concentrations at the time of examination. Corneal sensitivity was assessed in five regions of the cornea using a Choquet-Bonnet aesthesiometer. This instrument evaluates corneal sensitivity by touching a monofilament fiber of variable stiffness to the cornea. The fiber stiffness, and thus pressure on the cornea, was gradually increased until the dog had a blink response.

Results: The median time from diagnosis

Reduced corneal sensitivity is present in diabetic dogs



CLINICAL IMPACT

The reduction in corneal sensitivity is probably the result of a neuropathy induced by the diabetes mellitus. It is likely that this is at least in part responsible for the high incidence of corneal ulcers following cataract surgery in diabetics. This can be a substantial complication that leads to prolonged recovery and treatment failure. The lack of correlation between glycated proteins and corneal sensitivity does not necessarily indicate that adequate control of diabetes would not improve the sensitivity. The study consisted of a relatively small number of dogs and the values for glycated proteins and other measures of control of the diabetes were not reported.



Steroid Hormone Concentrations Before and After ACTH-Stimulation

Frank LA, Rohrbach BW, Bailey EM, et al. Steroid hormone concentration profiles in healthy intact and neutered dogs before and after cosyntropin administration. *Dom Anim Endocrinol* 2003;24:43-57.

INTRODUCTION

Background: Steroid hormones in serum other than cortisol are infrequently measured in dogs for diagnostic purposes. Estradiol or progesterone may be helpful in diagnosing the presence of ovarian tissue in a dog without a history of being spayed or when ovarian tissue may be remaining after an attempted spay operation. Serum testosterone concentration has been used to investigate the possibility of cryptorchid testes. In dogs with atypical hyperadrenocorticism, serum 17-hydroxyprogesterone determination may be of aid in confirming hyperactivity of the adrenal cortices when cortisol levels are within normal limits.

Objectives: The purpose of this study was to determine serum steroid hormone concentrations before and after adrenocorticotrophic hormone (ACTH)-stimulation in healthy intact and neutered male and female dogs.

SUMMARY

Methods: Seventeen intact female, 20 intact male, 30 spayed female, and 30 castrated male dogs were sampled for serum steroid hormone determinations before and one-hour after ACTH stimulation. Steroid hormones assayed were cortisol, progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone, and estradiol.

Results: Concentrations of serum DHEAS, androstenedione, and testosterone were higher in intact male dogs. Intact female dogs had higher concentrations of progesterone. Intact male dogs had lower

responses in plasma cortisol and no responses in plasma testosterone and DHEAS to ACTH stimulation. Other groups had slightly higher increases in testosterone and DHEAS concentrations after ACTH stimulation. Serum estradiol concentrations were similar in all groups and did not increase in response to ACTH stimulation. Intact dogs had significantly greater 17-hydroxyprogesterone before and after ACTH stimulation than did neutered dogs. All groups had significantly higher serum progesterone concentrations after ACTH stimulation.

Conclusions: Serum estradiol concentrations should not be used to differentiate intact from spayed female dogs. Serum cortisol concentrations after ACTH stimulation are lower in neutered males.

Serum estradiol concentrations do not aid in differentiating sex or neutered status in dogs.



CLINICAL IMPACT

More reports of expected serum estradiol levels in healthy intact and neutered dogs, as well as dogs with adrenocortical or gonadal disorders are needed. Based on this report, serum estradiol concentrations do not aid in differentiating sex or neutered status in dogs.

The other primary finding of this study was that serum cortisol concentrations after ACTH are lower in neutered male dogs compared to females or intact males. A castrated male dog with hyperadrenocorticism could therefore have an exaggerated response to ACTH stimulation, but when the response is evaluated by standard reference ranges, it could fall within the limits of normal. However, this is unlikely and would only occur in early or mild hyperadrenocorticism.



Trilostane Treatment for Adrenocortical Neoplasia

Eastwood JM, Elwood CM, Hurley KJ. Trilostane treatment of a dog with functional adrenocortical neoplasia. J Sm Anim Pract 2003;44:126-131.

INTRODUCTION

Background: Trilostane is an adrenal steroid enzyme antagonist that has been used successfully in the management of canine pituitary-dependent hyperadrenocorticism (PDH). Few adverse effects have been noted, although hypoadrenocorticism can occur during trilostane administration. The consistent efficacy and relatively low incidence of serious adverse effects makes trilostane an attractive alternative to mitotane for treatment of PDH.

Objectives: The objective of this report was to describe the results of trilostane treatment in a dog with hyperadrenocorticism caused by a functional adrenal mass.

SUMMARY

Case Report: A 13-year-old, spayed female, mixed breed dog was diagnosed with hyperadrenocorticism based on compatible clinical findings and elevated basal and post-ACTH stimulation plasma cortisol concentrations. Abdominal radiographs and ultrasound examination revealed a mineralized mass in the area of the left adrenal gland. The right adrenal gland was not visualized. Trilostane was administered at 60 mg (4.4 mg/kg), once daily. A clinical response consisting of improved appetite and strength, decreased water consumption, and resolution of isosthenuria was noted within 10 days of initiating treatment with trilostane. Based on results of adrenocorticotrophic hormone (ACTH) response tests, the dosage of trilostane

was gradually increased to 240 mg, once daily, to maintain the post-ACTH plasma cortisol concentration below 110 nmol/L (4.0 µg/dl). Clinical signs and biochemical changes including elevated alkaline phosphatase and alanine transferase (ALT) largely resolved with treatment.

Plasma aldosterone concentrations before and after ACTH administration were not suppressed by trilostane administration. No adverse effects attributable to trilostane were noted during the 19 months the case was followed.

The effect of trilostane is limited to reducing clinical signs of hyperadrenocorticism

Conclusions: Trilostane is effective for treatment of hyperadrenocorticism caused by an adrenal tumor in the dog.



CLINICAL IMPACT

Trilostane is being used more frequently in treatment of hyperadrenocorticism, even in North America where it is not approved for use in animals or humans. Because 50% of adrenal tumors are malignant, surgery remains the treatment of choice in many cases, although serious perioperative complications are common. Mitotane has advantages over trilostane in treatment of functional adrenal tumors as it can induce remission of the adrenal tumor and prevent local complications such as invasion of surrounding vasculature. The effect of trilostane is limited to reducing clinical signs of hyperadrenocorticism, and has no effect on tumor growth or metastasis. Therefore, mitotane is the preferred medical treatment for functional adrenocortical tumors and hyperadrenocorticism.



Sex Hormone Concentrations in Dogs with Alopecia

Frank LA, Hnilica KA, Rohrbach BW, et al. Retrospective evaluation of sex hormones and steroid hormone intermediates in dogs with alopecia. *Vet Dermatol* 2003;14:91-97.

►INTRODUCTION

Background: Alopecia is a common clinical finding in dogs with a variety of endocrine diseases. An uncommon syndrome known variously as adrenal hyperplasia-like syndrome, alopecia X, growth hormone responsive dermatosis, castration responsive dermatosis, as well as other names, has been hypothesized to be the result of an adrenal steroid hormone abnormality. It occurs most frequently in plush-coated breeds and poodles. Loss of guard hairs followed by complete alopecia is found, usually sparing the limbs. The cause and most appropriate treatment remain unknown.

Objectives: The objectives of this study were to evaluate the serum concentrations of a number of steroid hormones before and after adrenocorticotrophic hormone (ACTH) stimulation testing in dogs with an unknown cause of alopecia.

✕SUMMARY

Methods: This retrospective study evaluated serum concentrations of progesterone, 17-OH progesterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, estradiol, and cortisol during ACTH stimulation testing. All dogs had alopecia, normal serum T₄ and canine-TSH concentrations or a lack of response to thyroid supplementation and a post-ACTH cortisol concentration less than 200 ng/ml. Further clinical information was apparently not provided.

Results: Samples from 276 dogs over a period of seven years were included in the study. Breeds most frequently evaluated included Pomeranian, poodle, chow chow, Keeshond, Samoyed, Alaskan Malamute,

American Eskimo, Siberian husky, and cocker spaniel. At least one basal or post-ACTH stimulation steroid hormone was above the normal range in 73% of dogs. The post-stimulation progesterone concentration was the most common abnormality, with 58% of samples having an elevation. Basal and post-ACTH stimulation concentrations of estradiol, progesterone, 17-OH progesterone, and DHEAS were significantly different among breeds and in some cases compared with normal dogs. Basal and post-ACTH serum cortisol concentrations of progesterone and 17-OH progesterone as well as basal androstenedione concentration was significantly correlated with cortisol concentrations.

Conclusions: There is no consistent steroid hormone abnormality associated with alopecia not due to hypothyroidism or excessive cortisol secretion. A hormone imbalance may not be the cause of alopecia in many cases.



CLINICAL IMPACT

While this study includes a large number of dogs, the final diagnosis of the cause of alopecia was not clearly established in individual dogs. In addition, a reference range of hormone concentrations for normal dogs of specific breeds was not established, and it is very possible that the normal range may vary among breeds. It has been shown that dogs with hyperadrenocorticism resulting in excessive cortisol secretion frequently have excessive secretion of other steroid hormones including progesterone and 17-OH progesterone. In addition, all the clinical abnormalities associated with

Cushing's syndrome have been described in dogs with normal plasma cortisol, but elevated progesterone or 17-OH progesterone concentrations on ACTH stimulation testing. Non-endocrine causes of alopecia were not ruled out in all cases of alopecia in the dogs studied. Without information regarding other clinical findings in the dogs with alopecia in this study, the importance of the hormone abnormalities noted in this study are unclear.



Mammary Fibroadenomatous Hyperplasia Associated with Megestrol Acetate

MacDougall LD. Mammary fibroadenomatous hyperplasia in a young cat attributed to treatment with megestrol acetate. *Can Vet J* 2003;44:227-229.

INTRODUCTION

Background: Mammary gland neoplasia in older cats has a very poor prognosis. Approximately 90% are adenocarcinomas and have metastasized by the time of diagnosis.

The most common mammary tumor of younger cats is however a progesterone-dependent ductal hyperplasia termed mammary fibroadenomatous hyperplasia. It is benign and can spontaneously regress. Regression coincides with removal of progesterone influence which may be ovariectomy if the source is the corpus luteum, use of a progesterone antagonist such as aglepristone, or withdrawal of the administration of a progesterone.

The most commonly used progesterone in cats is megestrol acetate. Use of the drug in cats is off-label. It is administered as an anti-inflammatory, immune-modulating agent.

Objectives: The purpose of this case report is to describe mammary fibroadenomatous hyperplasia in a castrated male cat.

SUMMARY

Case Report: A 1.5-year-old, castrated male, cat was presented for a pruritic dermatitis of the chin. Systemic antibiotic and glucocorticoid treatment in conjunction with topical cleansing was administered without resulting improvement in the dermatitis. One month after the initial presentation, megestrol acetate was prescribed

at 1 mg/kg, once per day, for five days and then 0.5 mg/kg, twice per week, for three weeks. The prescription was refilled and administered for 18 additional days. Nearly two months after beginning megestrol acetate, the cat was reluctant to walk and had acute, asymmetrical mammary gland enlargement. Physical examination of the mammary glands revealed a particularly enlarged right inguinal gland that was warm, edematous, and hyperemic. Thoracic radiographs, hemogram, and serum chemistries were within normal limits. A mastectomy and regional lymph node excision were performed. Biopsy revealed fibroadenomatous hyperplasia with secondary mastitis. Most mammary glands regressed in size by 10 to 15 days after the surgery, but persistent mastitis and dermatitis of the chin led the owners to request euthanasia for their cat. Necropsy was not performed.

Conclusions: The administration of a progesterone such as megestrol acetate can induce mammary fibroadenomatous hyperplasia in cats of both genders and the risk is not directly dose dependent.

Conclusions: The administration of a progesterone such as megestrol acetate can induce mammary fibroadenomatous hyperplasia in cats of both genders and the risk is not directly dose dependent.

CLINICAL IMPACT

Cats under 5 years of age with acute, asymmetrical mammary gland enlargement should first be suspected of having mammary gland fibroadenomatous hyperplasia. Most are young females that are pregnant or spontaneously ovulated and have an active corpus luteum. Ovariectomy or eventual luteolysis with progression of the estrous cycle will result in regression of the

mammary gland enlargement.

Administered progesterones can cause fibroadenomatous hyperplasia of the mammary glands in either males or females at any age. The logical and effective treatment is withdrawal of progesterone administration. However, regression may require 4 to 6 weeks to be evident.

Administered progesterones can cause fibroadenomatous hyperplasia of the mammary glands in either males or females



Sex Hormone Concentrations in Dogs with Testicular Diseases

Mischke R, Meurer D, Hopen HO, et al. Blood plasma concentrations of oestradiol-17 β , testosterone and testosterone/oestradiol ratio in dogs with neoplastic and degenerative testicular diseases. *Res Vet Sci* 2002;73:267-272.

INTRODUCTION

Background: The standard rule-outs for bilateral alopecia in older male dogs include hypothyroidism, typical and atypical hyperadrenocorticism, and feminizing testicular tumors. The most common testicular tumor associated with bilateral alopecia is Sertoli-cell tumor. However, Leydig-cell tumors can cause a feminizing syndrome with alopecia.

Objectives: The purpose of this study was to assess the plasma estradiol-17 β and testosterone concentrations in dogs with testicular tumors, cryptorchidism, and degenerate testicular disease.

Feminization in male dogs is more often associated with decreased plasma testosterone/estradiol ratio than with elevated estradiol concentrations

SUMMARY

Methods: Among 93 male dogs that were castrated and had their testes examined histologically, 20 dogs had Leydig-cell tumors, six had Sertoli-cell tumors, nine had seminomas, seven had bilateral inguinal cryptorchid testes, nine had abdominal cryptorchid testes, six had degenerate testes, and 20 had histologically normal scrotal testes. Plasma estradiol-17 β and testosterone concentrations were determined in each dog prior to castration. Dogs with a unilateral cryptorchid testicle that was normal based on ultrasonography were not castrated if owners declined permission. Dogs with mixed tumors, testicular cysts, orchitis, and other abnormalities were excluded from the study.

Results: Dogs with Sertoli-cell tumors had significantly higher than normal average

plasma estradiol concentrations (29 pg/ml; normal, 18 pg/ml) and lower than average plasma testosterone concentrations (0.08 ng/ml; normal, 1.95 mg/ml) compared to normal dogs. The highest plasma estradiol concentrations occurred in dogs with intra-abdominal Sertoli-cell tumors.

Plasma testosterone/estradiol ratio was significantly lower (0.32; normal, 9.5) than in normal dogs. Dogs with seminomas had significantly lower plasma estradiol concentrations than normal dogs (12.0 pg/ml; normal, 18 pg/ml).

Five of the six dogs with Sertoli-cell tumors and one of the dogs with a Leydig-cell tumor had signs of feminization, gynecomastia, hyperpigmentation, and bilaterally symmetrical alopecia. The dog with feminization associated with a Leydig-cell tumor had the highest testosterone/estradiol ratio.

Conclusions: Feminization in male dogs is more often associated with decreased plasma testosterone/estradiol ratio than with elevated estradiol concentrations. Plasma testosterone/estradiol ratio is a better diagnostic tool for feminizing testicular tumors than are individual hormone concentrations.



CLINICAL IMPACT

At least one-third of Sertoli-cell tumors are capable of producing estrogenic substances and causing signs of feminization and alopecia. The size of the tumor or being located intra-abdominally, or both,

may be correlated with the production of estrogenic substances, particularly estradiol-17 β . Estradiol inhibits luteinizing hormone production and subsequent testosterone production from the Leydig cells. Male dogs with alopecia and asymmetrical scrotal or prescrotal testes or intra-abdominal testes should be castrated. However, if physical findings are equivocal for the presence of a feminizing Sertoli-cell tumor, a decreased testosterone/estradiol ratio may be diagnostic.

Leydig-cell tumors are capable of producing testosterone in relative excess. Dogs with Leydig-cell tumors are at higher than average risk for developing androgen-dependent problems such as perineal hernia and perianal gland adenomas. Feminization has also been previously associated with some Leydig-cell tumors, as occurred in a dog of this report. Androgens may be aromatized to estrogens at target cells resulting in feminization. The present case demonstrated an elevated testosterone/estradiol ratio but not an absolute elevation of plasma testosterone concentration. Leydig-cell tumor is the most common testicular tumor that may not be palpated and its incidence is not increased with cryptorchidism. Monitoring male dogs with alopecia for an elevated testosterone/estradiol ratio to search for a feminizing Leydig-cell tumor holds promise for more clinical use than testosterone/estradiol ratio in dogs with Sertoli-cell tumors.

Thyro-Tabs[®]

(levothyroxine sodium tablets, USP)

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

Each Thyro-Tabs[®] tablet provides synthetic crystalline levothyroxine sodium (L-thyroxine).

Indications:

For use in dogs for correction of conditions associated with low circulating thyroid hormone (hypothyroidism). Low serum circulating T-4 concentrations, coupled with clinical signs, are suggestive of hypothyroidism. The following T-4 concentrations in canine serum have been established:

Normal (euthyroid) – 18 to 32 ng/mL (18 to 32 µg/dL)

Possible hypothyroid - 10 to 18 ng/mL (10 to 18 µg/dL)

Hypothyroid – less than 10 ng/mL (10 µg/dL)

Hypothyroidism is unlikely with a resting serum T-4 concentration of 18 ng/mL or above. A dog exhibiting signs of hypothyroidism with a T-4 below 18 ng/mL should be considered for levothyroxine replacement therapy. Confirmation of the diagnosis could include withdrawal of therapy after which a recurrence of clinical signs further supports the diagnosis. Correct diagnosis of hypothyroidism is important, since such a diagnosis normally commits an animal to life-long replacement therapy. The principle objective of levothyroxine sodium administration is to achieve and maintain normal metabolism in the animal's normal physiologic range. Animal adaptation may necessitate regular monitoring of serum T-4 concentrations during the first several months of treatment to establish maintenance doses. TSH testing may be used to provide a definitive diagnosis in dogs with borderline resting T-4 values.

Mode of actions:

Levothyroxine sodium provided by Thyro-Tabs cannot be distinguished from that endogenously secreted by the thyroid gland. The primary regulator of thyroid function is thyroid stimulating hormone (TSH) which is synthesized and secreted by the pars distalis of the adenopophys (anterior pituitary). The mediator from the hypothalamus which exerts a continuous

influence over the release of TSH is thyrotropin-releasing hormone (TRH).

Hypothyroidism in the dog:

Hypothyroidism usually occurs in middle-aged and older dogs although the condition will sometimes be seen in younger dogs of the larger breeds. Neutered animals of either sex are also frequently affected, regardless of age. The condition is primary failure of the thyroid gland because of lymphocytic thyroiditis or other loss of follicular epithelium and resulting atrophy of the gland. Secondary hypothyroidism is rare and usually due to a destructive pituitary tumor.

Clinical signs:

The following list of clinical signs and laboratory findings may vary depending upon the degree of thyroid dysfunction:

Nerve and muscle function: lethargy, lack of endurance, increased sleeping, reduced alertness and interest with dulled mental attitude, hypotonus, stiff, slow movements, dragging of forelimbs, head tilt, disturbed balance, unilateral facial paralysis.

Metabolism: decreased oxygen consumption and lower metabolic rate, sensitivity and intolerance to cold, low body temperature, cool skin, heat seeking, increased body weight, constipation, poor exercise tolerance, slow heart rate, weak pulse, weak apex heart beat and low voltage on ECG.

Reproduction: reproductive failure, abortion, stillbirth, live birth of weak young, delayed puberty, reduced libido, impaired spermatogenesis, irregular estrus and anestrus, galactorrhea.

Skin and hair: myxedema of face, blepharoptosis, atrophy of epidermis, thickening of the dermis, surface and follicular hyperkeratosis, hyperpigmentation, coarse and sparse coat, dry, dull and brittle hair, slow regrowth and retarded turnover of hair, bilateral alopecia.

Laboratory findings: low serum T-4 concentrations, hypercholesterolemia, hypertriglyceridemia, elevated serum creatine kinase, normochromic, normocytic anemia.

Contraindications:

Therapy is contraindicated in thyrotoxicosis, acute myocardial infarction, and uncorrected adrenal insufficiency. Other conditions in which the use of therapy should be used with caution include

primary hypertension, euthyroidism, and pregnancy.

Precautions:

The administration of levothyroxine sodium to dogs to be used for breeding purposes or in pregnant bitches has not been evaluated. There is evidence that administration to pregnant bitches may affect the normal development of the thyroid gland in the unborn pups. The clinical effects of therapy are slow in being manifested. Overdosage may produce the signs of thyrotoxicosis including but not limited to: polydipsia, polyuria, polyphagia, reduced heat tolerance and hyperactivity or personality change. Thyro-Tabs 0.1 mg and 0.7 mg tablets contain FD&C yellow #5 (tartrazine) which has been associated with allergic-type reactions (including bronchial asthma) in susceptible humans. It is unknown if such a reaction could also occur in dogs.

Adverse reactions:

There are no specific adverse reactions associated with therapy at the recommended dosages. Overdosage will result in thyrotoxicosis.

Dosages:

The initial recommended daily dose is 0.1 to 0.2 mg/10 pounds (4.5 kg) body weight in single or divided doses. Dosage is adjusted by monitoring T-4 blood levels of the dog every four weeks until a maintenance dose is established. The usual daily maintenance dose is 0.1 mg/10 pounds (4.5kg). A maximum of 0.8 to 1.0 mg total daily dose will be sufficient in many dogs over 80 pounds in body weight.

Administration:

Thyro-Tabs may be administered orally or placed in the food.

How supplied:

Available as scored, color-coded caplets in 8 concentrations: 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg and 0.8 mg in bottles of 120 and 1,000.

Storage:

Store at controlled room temperature; 15°-30°C (59°-86°F) and protect from light.

References: See package insert.



For more information call
1-800-831-0004
Revised September 2003

Journals examined by the editors for article inclusion:

American Journal of Veterinary Research
 Australian Veterinary Journal
 Canadian Journal of Veterinary Research
 Canadian Veterinary Journal
 Domestic Animal Endocrinology
 Endocrinology
 European Journal of Endocrinology
 Journal of Veterinary Internal Medicine
 Journal of the American Animal Hospital Association
 Journal of Small Animal Practice
 Journal of the American Veterinary Medical Association
 Journal of Veterinary Diagnostic Investigation
 Journal of Veterinary Medical Science
 Journal of Veterinary Medicine, Series A
 Journal of Comparative Pathology
 Journal of Veterinary Pharmacology and Therapeutics
 New Zealand Veterinary Journal
 Research in Veterinary Science
 Veterinary Journal
 Veterinary Pathology
 Veterinary Record
 Veterinary Radiology & Ultrasound
and more than 20 others

Small Animal Clinical

Endocrinology

Volume 14 • Issue 1, 2004

Editors

C. B. Chastain, DVM, MS

Dip ACVIM (Internal Medicine)
 Professor, Companion Animal Medicine
 Department of Veterinary
 Medicine and Surgery
 College of Veterinary Medicine
 University of Missouri
 Columbia, MO 65211

Dave Panciera, DVM, MS

Dip ACVIM (Internal Medicine)
 Professor, Small Animal Medicine
 Department of Small Animal
 Clinical Sciences
 Virginia-Maryland Regional College
 of Veterinary Medicine
 Blacksburg, VA 24061



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Small Animal Clinical Endocrinology

Department of Veterinary Medicine and Surgery

College of Veterinary Medicine

University of Missouri

Columbia, MO 65211-5110

A professional service provided by:



P.O. Box 130
Shenandoah, IA 51601-0130 U.S.A.