

Endocrinology

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

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Selegiline Treatment of Canine Pituitary-Dependent Hyperadrenocorticism

Braddock JA, Church DB, Robertson ID, et al. Inefficacy of selegiline in treatment of canine pituitary-dependent hyperadrenocorticism. *Aust Vet J* 2004;82:272-277.

► INTRODUCTION:

Background: Medical treatment of pituitary-dependent hyperadrenocorticism in dogs has primarily been with mitotane for the last 30 years. Mitotane does not suppress adrenocorticotropic hormone (ACTH) secretion. It is a cytotoxic drug to the adrenal cortex. Iatrogenic hypoadrenocorticism can be an adverse effect to mitotane.

Other medications have been tried, including selegiline, a monoamine oxidase-B inhibitor. Selegiline theoretically decreases ACTH secretion by increasing dopamine concentration in the hypothalamus. Dopamine suppressed ACTH secretion may only occur in the pars intermedia, site of approximately 30% of ACTH-secreting adenomas. Response to selegiline has been considered favorable if alertness and physical activity improved, but one of the metabolites of selegiline is amphetamine. For these reasons and others, there is question as to the efficacy of selegiline in treating most, or any, cases of pituitary-dependent hyperadrenocorticism in dogs.

Objectives: The purpose of this study was to evaluate selegiline as a treatment for pituitary-dependent hyperadrenocorticism in dogs.

✱ SUMMARY:

Methods: Eleven dogs with untreated pituitary-dependent hyperadrenocorticism were treated with selegiline. The diagnosis of pituitary-dependent hyperadrenocorticism was based on patient history, physical examination findings, low-dose dexamethasone suppression, abdominal ultrasonography, endogenous ACTH concentration, and ACTH-stimulation results. Selegiline was administered orally at 2 mg/kg, once daily for 3 months. Rechecks were done at 10, 30, and 90 days after initiating treatment. Rechecks con-

sisted of measuring 24 hour water intake, urine corticoid/creatinine ratio, and an owner questionnaire. The questionnaire included general health, thirst, appetite, activity, panting, and any other abnormal events. Another endogenous ACTH determination and an ACTH-stimulation test was performed at the 90 day recheck.

Results: None of the dogs responded to selegiline on the basis of endogenous ACTH concentration, ACTH stimulation response, urine corticoid/creatinine ratio, or physical examination findings.

However, based on subjective evaluations by owners, 64% believed there had been an overall improvement. When objective data (24-hour water intake estimate) was evaluated, all owners were found to be unreliable. Improved physical activity in the dogs was reported by 45% of owners. No significant adverse effects were observed.

Conclusions: Selegiline is safe, but ineffective in controlling pituitary-dependent hyperadrenocorticism in dogs.



CLINICAL IMPACT:

It is possible, but not likely, that selegiline only has effects in controlling pituitary-dependent hyperadrenocorticism when the cause is a intermediate lobe adenoma and that none of the dogs in this study had an intermediate lobe adenoma. Since there is no reliable, practical means of determining the presence of an intermediate lobe adenoma antemortem, it is more effective to treat all with a drug that has broader effect and greater efficacy. It would have been interesting to have included a placebo and an amphetamine treated group in a blinded trial to compare the subjective evaluations of owners. It is possible that owner perception of improvement from selegiline may have been the same with placebo or amphetamine treatment.

Selegiline is ineffective in controlling pituitary-dependent hyperadrenocorticism in dogs.

- ▶ Selegiline is safe but ineffective in treatment of canine pituitary-dependent hyperadrenocorticism. *Aust Vet J* 2004;82:272-277.
- ▶ Selegiline does not alter the cardiopulmonary effects of medetomidine, oxymorphone, or butorphanol in dogs. *Vet Anaesth Analg* 2004;31:129-137.
- ▶ A somatotroph and corticotroph pituitary adenoma has been reported in a cat with hyperadrenocorticism and secondary diabetes mellitus. *J Comp Path* 2004;130:209-215.
- ▶ Short-term oral budesonide treatment suppresses the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease. *J Am Anim Hosp Assoc* 2004;40:120-123.
- ▶ At peak endurance training, serum thyroid hormone concentrations decrease and thyroid-stimulating hormone concentrations increase in healthy sled dogs. *Am J Vet Res* 2004;65:333-337.
- ▶ Sled dogs may have different reference ranges for serum T_4 , free T_4 , and canine thyroid stimulating hormone concentrations compared to non-sled dogs. *J Am Vet Med Assoc* 2004;224:226-231.
- ▶ Dietary soy increases serum thyroxine concentrations in healthy adult cats. *Am J Vet Res* 2004;65:586-591.
- ▶ Hyperthyroidism causes increased urinary corticoid/creatinine ratios in cats. *J Vet Intern Med* 2004;18:152-155.
- ▶ Commercial canned food may contribute to the risk of hyperthyroidism in cats. *J Am Vet Med Assoc* 2004;224:879-886.
- ▶ Myxedema coma has been reported in a cocker spaniel. *Can Vet J* 2004;45:318-320.
- ▶ Electrolyte disturbances and cardiac arrhythmias may occur in dogs receiving pamidronate for hypercalcemia of malignancy. *J Am Anim Hosp Assoc* 2004;40:75-81.
- ▶ Long-term home monitoring of blood glucose concentrations in cats with diabetes mellitus is feasible for many owners of diabetic cats. *J Am Vet Med Assoc* 2004;225:261-266.
- ▶ There is no advantage to the use of metformin compared to glipizide in the treatment of diabetes mellitus in cats. *J Vet Intern Med* 2004;18:18-24.
- ▶ Xylitol-containing gum is a stimulus to insulin release in dogs and can cause hypoglycemia. *Vet Human Toxicol* 2004;46:87-88.
- ▶ Abdominal ultrasonography should be performed at least two hours before conducting a low-dose dexamethasone suppression test in dogs. *Am J Vet Res* 2004;267-270.
- ▶ Trilostane treatment is moderately successful in treating bilateral adrenal enlargement and excessive sex steroid hormone production in the cat. *J Sm Anim Pract* 2004;45:263-266.
- ▶ Trilostane treatment can cause adrenal necrosis. *J Sm Anim Pract* 2004;45:307-310.
- ▶ Congenital adrenal hyperplasia secondary to 11β -hydroxylase deficiency has been reported in a domestic cat. *J Am Vet Med Assoc* 2004;225:238-241.
- ▶ Trilostane is successful therapy for treatment of pituitary-dependent hyperadrenocorticism in cats. *J Vet Intern Med* 2004;18:160-164.
- ▶ Serum adrenocorticotrophic hormone concentrations increase in dogs with pituitary-dependent hyperadrenocorticism following trilostane therapy. *Vet Rec* 2004;154:399-400.



Selegiline Effects on Responses to Medetomidine, Oxymorphone, or Butorphanol in Dogs

Dodam JR, Cohn LA, Durham HE, et al. Cardiopulmonary effects of medetomidine, oxymorphone, or butorphanol in selegiline-treated dogs. Vet Anaesth Analg 2004;31:129-137.

► INTRODUCTION:

Background: Selegiline is an approved treatment for pituitary-dependent hyperadrenocorticism in dogs, but its efficacy in practice has never reached those of the initial reports on which its approval for treating hyperadrenocorticism was based. Some of the rationale for its use is that it may be efficacious in a small subset of cases, and it is without adverse effects. However, as a monoamine oxidase inhibitor, selegiline has the potential for adverse effects in that it may cause an accumulation of catecholamines: dopamine, norepinephrine, and epinephrine. Catecholamines can cause hypertension, tachycardia, and cardiac dysrhythmia. A metabolite of selegiline is amphetamine which can cause similar adverse effects.

The mean age at which pituitary-dependent hyperadrenocorticism affects dogs is in the geriatric population. This age group is more often subjected to sedation or anesthesia. Dogs on selegiline treatment could therefore be at increased risk of adverse cardiopulmonary effects associated with concurrent administration of medetomidine, oxymorphone, or butorphanol.

Objectives: The goal of this study was to determine if selegiline treatment affects the cardiopulmonary response to medetomidine, oxymorphone, or butorphanol in dogs.

✦ SUMMARY:

Methods: Twenty-eight, clinically normal, mixed-breed hound dogs were administered selegiline or placebo for at least 44 days prior to the pre-medication drugs: medetomidine, oxymorphone, or butorphanol. Dogs were evaluated before and after one of three different treatments: selegiline and medetomidine, placebo and medetomidine; selegiline and

oxymorphone, placebo and oxymorphone; selegiline and butorphanol, or placebo and butorphanol. Nine dogs were treated with two medications with two weeks washout between treatments. Monitored parameters were arterial blood gas analysis, blood pressure, electrocardiograms, cardiac ultrasound, and behavioral analysis by observers blinded to treatment groups. An intravenous injection of medetomidine (750 µg/m²), oxymorphone (0.1 mg/kg), or butorphanol (0.4 mg/kg) was given, and cardiopulmonary and behavioral data collected at 1, 2, 5, 15, 30, and 60 minutes after injection.

Results: Selegiline did not alter the responses to any of the pre-medication drugs.

Conclusions: Selegiline does not affect responses to medetomidine, oxymorphone, or butorphanol, although these drugs did alter cardiopulmonary and behavioral function.

🌿 CLINICAL IMPACT:

Adverse effects have been reported with the concurrent administration of monoamine oxidase inhibitors and anesthetic drugs. The package insert for selegiline states it is contraindicated to use selegiline with meperidine. This precaution is often extended to avoiding concurrent administration with any opioid. Use of monoamine oxidase inhibitors are recommended to be discontinued at least two weeks before anesthesia.

In this study supported by Pfizer Animal Health, distributor of selegiline, no adverse cardiopulmonary or behavior effects were found after the concurrent administration of selegiline and opioids (oxymorphone and butorphanol) or selegiline and medetomidine, an alpha-2 agonist. Since selegiline did not cause adverse effects, and the same dose used in the previous article did not cause beneficial

effects, perhaps selegiline is relatively ineffective as a monoamine oxidase inhibitor.

Selegiline does not affect responses to medetomidine, oxymorphone, or butorphanol.



Double Pituitary Adenoma Associated With Diabetes Mellitus and Hyperadrenocorticism

Meij BP, van der Vlugt-Meijer RH, van den Ingh TSGAM, et al. Somatotroph and corticotroph pituitary adenoma (double adenoma) in a cat with diabetes mellitus and hyperadrenocorticism. *J Comp Path* 2004;130:209-215.

► INTRODUCTION:

Background: Spontaneous Type II diabetes is the most common form of diabetes mellitus in cats. However, diabetes mellitus can be secondary to the insulin-resistance caused by hyperadrenocorticism or acromegaly. Both hyperadrenocorticism and acromegaly are rare in cats.

Objectives: The reason for this report was to describe a cat with insulin-resistant diabetes mellitus secondary to hyperadrenocorticism and acromegaly.

✦ SUMMARY:

Case Report: A 9-year-old, castrated male, European shorthaired cat weighing 3.5 lb was referred with insulin-resistant diabetes mellitus secondary to pituitary-dependent hyperadrenocorticism based on increased urinary corticoid concentrations that suppressed with dexamethasone administration. Insulin was being administered at 12 U, twice per day, without glycemic control. Additional diagnostic investigations revealed resistance to low-dose dexamethasone suppression based on monitored changes in plasma cortisol, adrenocorticotropic hormone, and α -melanocyte-stimulating hormone. Plasma concentrations of growth hormone and insulin-like growth factor I were also elevated. Dynamic contrast-enhanced computed tomography demonstrated a pituitary adenoma. Pituitary tissue acquired by hypophysectomy contained two adenomas, one acidophilic and the other basophilic. Histopathologic and immunocytochemical examinations identified one adenoma as corticotrophic and the other as somatotrophic. Insulin-resistance resolved after the hypophysectomy, but two weeks later the cat died, possibly from hypoglycemia resulting from an insulin overdose.

Conclusions: This is the first report of double adenomas in the pituitary of an insulin-resistant diabetic cat.



CLINICAL IMPACT:

This case was an oddity, but it demonstrates the need to investigate for insulin-resistance any time that insulin dosage exceeds 1 U/lb/injection without adequate glycemic control. The more common causes of failure to respond to insulin are infections, improper storage or administration of insulin, or use of long-acting insulins when peripheral perfusion is impaired. If these are ruled out or if clinical signs of hyperadrenocorticism or acromegaly are present, insulin resistance secondary to pituitary or adrenal endocrinopathies should be considered.

Pituitary tissue contained two adenomas, one acidophilic and the other basophilic.



Effects of Budesonide on Hypothalamic-Pituitary-Adrenal Axis in Dogs

Tumulty JW, Broussard JD, Steiner JM, et al. Clinical effects of short-term oral budesonide on the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease. J Am Anim Hosp Assoc 2004;40:120-123.

► INTRODUCTION:

Background: Adverse effects of glucocorticoids include clinical signs and metabolic abnormalities associated with iatrogenic hyperadrenocorticism as well as suppression of the pituitary-adrenal axis. In order to avoid these detrimental effects when treating patients with inflammatory bowel disease, new oral glucocorticoid analogs with a high affinity for glucocorticoid receptors and extensive first pass metabolism by the liver have been developed. One of these newer glucocorticoid analogs is budesonide. A relative lack of systemic effects has been found in humans with gastrointestinal disease administered budesonide.

Objectives: The objective of this study was to evaluate the effects of oral budesonide administration in dogs with inflammatory bowel disease on the pituitary-adrenal axis and to cause clinical signs of hyperadrenocorticism.

✕ SUMMARY:

Methods: Six dogs with inflammatory bowel disease diagnosed on intestinal biopsy were administered budesonide, 3 mg/m² body surface area once daily for 30 days. Owners completed a questionnaire regarding water consumption, urination, and appetite before and after treatment. The effect of budesonide administration on the pituitary-adrenal axis was assessed using cortisol response to adrenocorticotropic hormone (ACTH) stimulation and plasma ACTH concentrations before and after 30 days of treatment. In addition, serum alkaline phosphatase activity and urine specific gravity were recorded at each time.

Results: Clinical signs of hyperadrenocorticism were not noted by the owners based on results of the questionnaire. The mean basal cortisol concentration (3.3 µg/dl

pretreatment; 0.8 µg/dl post-treatment), post-ACTH cortisol (12.6 µg/dl pretreatment; 3.0 µg/dl post-treatment), and plasma endogenous ACTH concentration (75 pg/ml pretreatment; 52 pg/ml post-treatment) were significantly less after treatment compared with before budesonide administration. No significant change in alkaline phosphatase activity or urine specific gravity was noted.

Conclusions: Budesonide administration in dogs with inflammatory bowel disease results in significant suppression of the pituitary-adrenal axis, although clinical signs of hyperadrenocorticism do not occur.

Budesonide administration in dogs with inflammatory bowel disease results in significant suppression of the pituitary-adrenal axis.



CLINICAL IMPACT:

While the efficacy of budesonide for treatment of inflammatory bowel disease has not been established, it is desirable to reduce the adverse effects of systemic glucocorticoid therapy when used for their immunosuppressive or anti-inflammatory properties. Unfortunately, marked suppression of cortisol secretion was noted in this study. This suppression could result in adrenal insufficiency in a stressful situation or after withdrawal of the drug if exogenous glucocorticoid were not administered. The duration of suppression of the pituitary-adrenal axis was not determined, but gradual tapering of budesonide might be optimal to avoid signs of iatrogenic hypoadrenocorticism. A study comparing the efficacy and adverse effects of budesonide to other glucocorticoids in the treatment of inflammatory bowel disease is needed before budesonide is determined to be undesirable in treating inflammatory bowel disease in dogs.



Thyroid Hormone Concentrations in Sled Dogs Before and After Athletic Conditioning

Evason MD, Carr AP, Taylor SM, et al. Alterations in thyroid hormone concentrations in healthy sled dogs before and after athletic conditioning. *Am J Vet Res* 2004;65:333-337.

► INTRODUCTION:

Background: Normal sled dogs have been reported to have serum T_4 and T_3 concentrations that are often lower than the typical reference ranges. Although other breeds such as greyhounds also have unique reference ranges for non-sled dogs for some thyroid hormones, it is unclear if the lower hormone concentrations in sled dogs is related to breed characteristics or to the effects associated with preparation for endurance racing.

Objectives: The objective of this study was to determine if athletic conditioning causes a change in thyroid function test results in healthy sled dogs.

✕ SUMMARY:

Methods: Nineteen healthy sled dogs housed outdoors in northern Saskatchewan were studied. Blood samples for measurement of serum T_4 , free (f) T_4 by equilibrium dialysis, T_3 , f T_3 , thyroid-stimulating hormone (TSH), and thyroglobulin autoantibodies were collected in the late summer when dogs were in an untrained state and approximately four months later in December during peak training. During training, dogs ran a mean of 174 km/wk over 4 to 5 days each week. The diet during training consisted of approximately 40% protein, 40-45% fat, and 10-15% carbohydrate while that during the summer comprised approximately 50% protein, 25-30% fat, and 20-25% carbohydrate. The mean temperature at the time of sampling during the untrained state was 19°C, while that during peak training was 16°C.

Results: Compared with the untrained state, serum T_4 and f T_4 concentrations were significantly decreased, and TSH concentrations were significantly increased during peak

training. There were no differences in serum T_3 , f T_3 , or thyroglobulin autoantibodies between the sampling times. Serum T_4 and f T_4 concentrations were less than the reference range at the time of peak training in 11 and 8 dogs, respectively. At the time of sampling during the summer, serum T_4 and f T_4 were greater than the reference range in 3 and 9 dogs, respectively, and below the reference range in 2 and 1 dog, respectively.

Conclusions: Endurance training with weight resistance consistently decreases serum T_4 and f T_4 concentrations in sled dogs.

Endurance training with weight resistance consistently decreases serum T_4 and f T_4 concentrations.

🌐 CLINICAL IMPACT:

The frequent finding of serum T_4 and f T_4 concentrations below the normal range in dogs undergoing strenuous endurance training could lead to a misdiagnosis of hypothyroidism. Therefore, veterinarians should take into account factors associated with training when evaluating thyroid function in sled dogs. In addition to running long distances during training, much lower ambient temperatures and feeding a high fat diet were factors that differed between sedentary and training states. Training does not decrease the already low serum thyroid hormone concentrations found in greyhounds, but training of sled dogs is more intensive.



Racing and Lack of Training Effects on Plasma Thyroid Hormone Concentrations in Sled Dogs

Lee JA, Hinchcliff KW, Piercy RJ, et al. Effects of racing and nontraining on plasma thyroid hormone concentrations in sled dogs. *J Am Vet Med Assoc* 2004;224:226-231.

► INTRODUCTION:

Background: Sled dogs competing in endurance races undergo extremes of exercise, energy expenditure, and environmental conditions.

Serum T_4 and T_3 concentrations have been shown to decrease in dogs after a long-distance race, but other thyroid function tests have not been evaluated. In addition, sled dogs have been reported to frequently have lower normal concentrations of serum thyroid hormones than the reference ranges established by most laboratories for the general canine population.

Objectives: The objective of this study was to evaluate thyroid function tests in sled dogs during training for a race, immediately following an endurance race, and 3 months after racing and training ceased.

✕ SUMMARY:

Methods: Thyroid function tests, including T_4 , free (f) T_4 , thyroid-stimulating hormone (TSH), and thyroglobulin autoantibodies were evaluated in 122 sled dogs before, immediately following, and three months after competition in the Iditarod Trail Sled Dog Race of approximately 1,100 miles.

Results: Eighty-four dogs completed the race and 38 withdrew prior to finishing. Prior to the race, plasma T_4 or f T_4 concentration was less than the reference range in 26% and 18% of dogs, respectively, while plasma TSH was above the reference range in 6%. Plasma T_4 concentration was significantly lower after the race compared with values before the race in dogs that did and did not complete the race. Free T_4 and TSH concentrations were significantly lower after the race in dogs that finished, but not in those that withdrew. Dogs that completed the race had significantly lower T_4 and f T_4 concentrations than those

that retired before completion. After running, serum T_4 and f T_4 concentrations were below the reference range in 82% and 37% of dogs, respectively, that withdrew early and in 95% and 44% of dogs, respectively, that completed the race. Serum T_4 , f T_4 , TSH and thyroglobulin autoantibodies were not significantly different 3 months after racing compared with values before racing. Serum T_4 and f T_4 were below the reference range in 25% and 26% of dogs, respectively, 3 months after racing.

Conclusions: Serum T_4 , f T_4 , and TSH concentrations decrease after endurance racing in sled dogs, and serum T_4 and f T_4 are frequently below reference range in sled dogs in the untrained state.

🌀 CLINICAL IMPACT:

Thyroid function tests are unlikely to be performed in sled dogs immediately after racing, even in dogs removed from the race early due to health problems. These elite canine athletes must be euthyroid to perform well in a long distance endurance with weight resistance race. However, hypothyroidism might be erroneously diagnosed in the approximately 20 to 25% of healthy sled dogs either before racing in the trained state and in the untrained state. The lack of difference between the trained and untrained state is different from the previous studies reviewed in this issue. The primary difference between the studies is that the sample representing the untrained state was obtained 3 months after stopping training in this study and after several more months in the untrained state in the former study.

Hypothyroidism might be erroneously diagnosed in the approximately 20 to 25% of healthy sled dogs.



Dietary Soy Effects on Serum Thyroid Hormone Concentrations in Adult Cats

White HL, Freeman LM, Mahony O, et al. Effect of dietary soy on serum thyroid hormone concentrations in healthy adult cats. *Am J Vet Res* 2004;65:586-591.

► INTRODUCTION:

Background: Many veterinary endocrinologists believe that hyperthyroidism in cats is a new disease. Prior to 1978, it was unreported. By 1990, it was considered the most commonly diagnosed endocrinopathy in cats. Epidemiologic studies have pointed more consistently to the diet as a factor in the incidence of hyperthyroidism than any other evaluated parameter. Dietary iodine has been implicated as a goitrogen that is highly variable in commercial feline diets and affects thyroid function when in low or high dietary concentrations.

Soy, a high quality vegetable protein used in commercial cat foods, is another goitrogen. No studies have been reported on the role that dietary soy may play in the incidence of hyperthyroidism in cats.

Objectives: The purpose of this study was to determine the effects of dietary soy on thyroid function.

✕ SUMMARY:

Methods: Eighteen adult cats were randomly assigned to custom manufacturer diets with and without soy for three months. Iodine was added at three times minimum the recommended concentrations. Two of the original 20 cats selected for the investigation were unable to complete the study. Groups were crossed over at the first three months and another three months of feeding trials performed. Diet identity was blinded to the investigators and cat owners. Blood was collected at six week intervals for hemograms, serum biochemistries, and serum thyroid hormone analysis: T_4 , free (f-) T_4 , and T_3 . Isoflavone concentrations were determined in urine at the beginning of the study and after the completion of each dietary trial.

Results: Serum T_4 and f- T_4 concentrations

were significantly higher after cats were on the soy containing diet compared to when on the soy-free diet, although the change was small (8-14%). Serum T_3 concentrations did not change with the soy-containing and soy-free diets. Serum T_3 /f- T_4 ratio was significantly lower after cats were on the soy-containing diet. There were no other significant changes in measured parameters. Genistein, a soy isoflavone, was detected in the urine of 10 of 18 prior to the dietary trials and in all cats on either trial. Urinary isoflavone was much higher in concentration in cats on the soy-containing trials.

Short term consumption of soy in the diet has a modest effect of increasing serum T_4 concentration.

Conclusions: Short term consumption of soy in the diet of cats has a modest effect of increasing serum T_4 concentration.

🌀 CLINICAL IMPACT:

This study of the effects of dietary soy on thyroid function was small in size, short in duration, and yielded small changes in serum thyroid hormone concentrations. The accuracy and significance of this change associated with dietary soy compared to a diet that was soy-free is unknown.

The authors correctly state in their discussion that chronic low-level hyperstimulation of the thyroid gland for months or years may induce autonomous thyroid adenomas or multinodular hyperplasia. However, it is more probable that a dietary constituent such as excessive dietary iodine that suppresses thyroid function and causes persistent hypersecretion of thyroid-stimulating hormone induces adenomas rather than soy-containing diets that may lead to mild increase in serum T_4 concentrations.



Urinary Corticoid/Creatinine Ratios in Hyperthyroid Cats

de Lange MS, Galac S, Trip MRJ, et al. High urinary corticoid/creatinine ratios in cats with hyperthyroidism. J Vet Intern Med 2004;18:152-155.

► INTRODUCTION:

Background: Confirming a diagnosis of hyperadrenocorticism in cats is difficult because typical clinical signs may not be apparent until the disease is advanced, and results of adrenocorticotrophic hormone (ACTH) response and dexamethasone suppression tests are variable. Urine corticoid/creatinine (UCCR) ratio may be a useful tool in diagnosis of feline hyperadrenocorticism provided stress is avoided during the collection process, i.e. samples are obtained at home and reflects the plasma free cortisol concentration over the hours that glomerular filtration occurred to produce the urine tested.

Objectives: The objective of this study was to assess the effect of hyperthyroidism on urine corticoid/creatinine ratio in cats.

✕ SUMMARY:

Methods: Two urine samples were collected at home for measurement of corticoid and creatinine on consecutive mornings from 32 cats with hyperthyroidism and 45 healthy cats 7 to 17 years of age. Cats were determined to be healthy based on history and physical examination, but no further testing was reported. UCCR was measured in seven cats after treatment of hyperthyroidism for 3 months by administration of methimazole (five cats) or by thyroidectomy (two cats). Clinical signs consistent with hyperadrenocorticism were not present in any cat in this study, but specific testing was not performed.

Results: The reference range for UCCR in healthy cats was determined to be 8×10^{-6} to 42×10^{-6} . The UCCR in hyperthyroid cats were significantly higher in hyperthyroid cats than healthy cats. Fifteen hyperthyroid cats had a UCCR that was above the reference range. After treatment of hyper-

thyroidism in seven cats, the UCCR were significantly lower than prior to treatment.

Conclusions: Hyperthyroidism should be ruled out in all cats that undergo testing of adrenocortical function with UCCR for hyperadrenocorticism.



CLINICAL IMPACT:

Excessive cortisol secretion occurs in hyperthyroidism as a result of either enhanced metabolic clearance of cortisol or stress associated with the hyperthyroid state. Because clinical signs of hyperthyroidism are much different than those of hyperadrenocorticism, evaluation of thyroid function is not routine in cats suspected of hyperadrenocorticism. However, because hyperthyroidism is such a common disease in older cats and because this study showed that hyperthyroidism can affect adrenal function tests, all cats suspected of hyperadrenocorticism should be evaluated for hyperthyroidism. Failure to do so may result in a false positive UCCR.

UCCR in hyperthyroid cats were significantly higher in hyperthyroid cats than healthy cats.



Consumption of Commercial Canned Food and Risk of Hyperthyroidism in Cats

Edinboro CH, Scott-Moncrieff JC, Janovitz E, et al. Epidemiologic study of relationships between consumption of commercial canned food and risk of hyperthyroidism in cats. *J Am Vet Med Assoc* 2004;224:879-886.

► INTRODUCTION:

Background: The consumption of canned cat food has been implicated in three epidemiologic studies on factors associated with the incidence of feline hyperthyroidism. In each the duration and exclusiveness of consumption of canned cat food was not reported.

Objectives: The main objective of this study was to determine if there is an association between consumption of canned food over a lifetime and development of hyperthyroidism and if the increased incidence of hyperthyroidism is due to an aging cat population.

✦ SUMMARY:

Methods: A database of medical records information from nine veterinary teaching hospitals spanning 20 years (1978 to 1997) was used to determine the prevalence of hyperthyroidism and the age distribution of cats with and without hyperthyroidism. The prevalence of feline hyperthyroidism was compared with other common diseases (diabetes mellitus and renal insufficiency) in this database as well. A separate study using a case-control design was developed to investigate the effect of diet on hyperthyroidism using medical records from a single veterinary teaching hospital. Medical records of cats admitted over 20.5 month period beginning in 1998 that had a serum T_4 concentration measured were reviewed. Records of cats at least 6 years of age that did not have a previous diagnosis of hyperthyroidism were reviewed for history and physical examination findings. Owners of these cats were contacted by mail and telephone with a request to answer a questionnaire regarding dietary intake over the lifetime of the cat and a medical history. Dietary information requested included food type (canned, dry, or semimoist), the specific brand of food, and

any home-cooked foods over the life of the cat. Cats with a diagnosis of hyperthyroidism based on one or more clinical signs and a serum T_4 concentration 5.0 $\mu\text{g}/\text{dl}$, or more (reference range 2.4 B 4.6 $\mu\text{g}/\text{dl}$) were compared with cats without hyperthyroidism (serum T_4 of 3.5 $\mu\text{g}/\text{dl}$, or less) for risk factors related to dietary intake. The effect of consuming less than 50%, 50%, or more than 50% canned food in the diet was evaluated as was the effect of feeding canned food from cans with easy open, “pop top” lids compared to those requiring a can opener to open.

Results: The prevalence of hyperthyroidism increased significantly from 0.61/1000 hospital visits from 1978–1982 to 29.6/1000 visits from 1993–1997. The prevalence of diabetes mellitus and renal insufficiency also increased over the same time period, but at significantly lesser rates than the increase of hyperthyroidism. In the case control study, 313 of 535 owners returned questionnaires. Of these 313 cats, 109 were hyperthyroid, and 173 were controls. Hyperthyroid cats were significantly more likely to be female than controls (62 vs 45%, respectively) and older than controls (13.1 vs 11.4 yrs, respectively). There was no significant difference in age, breed, body condition, or body weight between the hyperthyroid and control cats. Cats consuming a diet containing any canned food were at increased risk for development of hyperthyroidism, with the highest risk occurring in cats consuming 50% canned cat food. The relative risk for cats consuming 50%, or more than 50%, canned food over a lifetime were 3 to 3.5 times more likely to develop hyperthyroidism than a cat consuming only dry food. The risk of hyperthyroidism increased with longer length of time a cat consumed a canned diet. Cats fed canned food from pop top cans had a higher risk of hyper-

thyroidism than those consuming food that was not definitely from pop top cans. Feeding baby food as a kitten also increased the relative risk of hyperthyroidism by 4.7 times.

Conclusions: Consumption of some canned foods play a role in the development of hyperthyroidism in cats.

CLINICAL IMPACT:

This study is consistent with other investigations of risk factors associated with hyperthyroidism that also found canned food to be associated with development of the disease. The finding that consuming food from pop top cans has a stronger association with hyperthyroidism than conventional cans led the authors to speculate that coatings used in these cans may leach into the food and affect thyroid function. One possible substance used in canning that can impair thyroid function and potential contribute to hyperthyroidism is bisphenol-A-diglycidyl ether. However, 23% of the hyperthyroid cats were fed only dry food and many other factors were not evaluated in this study, so other causes are likely to be involved in the development of hyperthyroidism, such as iodine excess and other goitrogens. Epidemiologic surveys such as this study are useful in identifying areas that require further investigation, but are not intended to prove a specific causal relationship.

Some canned foods play a role in the development of hyperthyroidism in cats.



Myxedema Coma With Respiratory Depression

Atkinson K, Auber I. Myxedema coma leading to respiratory depression in a dog. *Can Vet J* 2004;45:318-320.

► INTRODUCTION:

Background: Myxedema coma is the most severe stage of primary hypothyroidism. It is characterized by mild to moderate clinical signs of hypothyroidism until a stressful precipitating event occurs such as exposure to cold ambient temperatures, infection, or dehydration, plus other hypotensive causes including the administration of anesthesia, tranquilizers, or diuretics. As myxedema coma develops there is hypothermia without shivering, lethargy, respiratory depression, bradycardia, and stupor progressing to coma. Successful treatment of myxedema coma requires early presumptive diagnosis and treatment with levothyroxine and judicious supportive treatment.

Objectives: The purpose of this report was to describe respiratory depression in a cocker spaniel with myxedema coma.

✕ SUMMARY:

Case Report: A 10-year-old, male, cocker spaniel was presented with lethargy for the past 2 weeks. A tentative diagnosis had been made previously and furosemide and enalapril had been prescribed. Laboratory findings prior to referral were non-regenerative anemia and hypercholesterolemia.

Significant physical examination findings at presentation were hypothermia (36.3°C), bradycardia (66 bpm), systemic arterial hypotension (92/54 mmHg), melena, and severe dehydration. Laboratory findings were non-regenerative anemia, venous metabolic acidosis, hypercapnea, hyponatremia, hyperkalemia, azotemia, and urine specific of 1.014. Thoracic radiographs were consistent with right-sided cardiomegaly.

Initial supportive treatment included intravenous crystalloid solution and boluses

of 50% dextrose, ampicillin, and dexamethasone. Hours later a tentative diagnosis of myxedema coma was made and levothyroxine was administered orally. The next day hypercarbia and hypoxemia were present. The respiratory rate was 12/minute and shallow. Intravenous levothyroxine was administered, but hypercarbia became worse. Mechanical assisted ventilation was recommended, but the owners requested that the dog be euthanized. Necropsy revealed small thyroid glands with lymphoplasmacytic infiltration.

Conclusions: This was a case of myxedema coma with respiratory depression. Dogs with hypothermia without shivering, depression, non-pitting edema, and bradycardia should be presumed to have myxedema coma and treatment with levothyroxine should begin without delay.



CLINICAL IMPACT:

Myxedema coma does not occur without respiratory depression. The unique aspects of this report is the breed affected, a cocker spaniel, and the probable precipitating cause, inappropriate diuretic therapy. Hypothyroidism is more common in large breed dogs. Most canine myxedema coma cases have been reported in Doberman pinschers.

This case is a good reminder however of the need to treat presumed myxedema coma prior to confirmation by serum T₄ levels. Key findings that should lead to a presumptive diagnosis of myxedema coma are hypothermia without shivering, bradycardia, and respiratory depression. Diuretics should be used judiciously, if at all, in dogs with possible or confirmed myxedema stupor or coma.

Diuretics should be used judiciously, if at all, in dogs with myxedema stupor or coma.



Adverse Effects of Treatment for Hypercalcemia of Malignancy

Kadar E, Rush JE, Wetmore L, et al. Electrolyte disturbances and cardiac arrhythmias in a dog following pamidronate, calcitonin, and furosemide administration for hypercalcemia of malignancy. J Am Anim Hosp Assoc 2004;40:75-81.

► INTRODUCTION:

Background: Hypercalcemia of malignancy is definitively treated by resolving the primary neoplasm. However, hypercalcemia has detrimental effects and often has to be treated prior to therapy directed at the malignancy. Fluid diuresis is effective alone in many cases. If not effective, administration of furosemide, calcitonin, bisphosphonates, or a combination of serum calcium lowering agents is recommended. Hypercalcemia can impair renal function, resulting in electrolyte loss. Because treatments for hypercalcemia often affect other electrolytes as well, various electrolyte disturbances can occur during management of hypercalcemia of malignancy.

Objectives: The purpose of this report was to describe cardiac arrhythmias in a dog treated with multiple agents for hypercalcemia of malignancy.

✕ SUMMARY:

Case Report: A 13-year-old, neutered male, mixed breed dog was evaluated for hypercalcemia and a perianal mass. The dog had a four month history of episodic urinary incontinence and difficulty rising and climbing stairs. Physical examination revealed a thin dog that was weak, unable to rise or support weight on the hind limbs. It was dehydrated and had bilateral perianal masses. At presentation, hypercalcemia (17.2 mg/dl) and azotemia (BUN 66 mg/dl, creatinine 5.0 mg/dl) were present. Other electrolytes, including phosphorus, magnesium, ionized magnesium, potassium, sodium, and chloride were normal. Urine specific gravity was 1.013. Initial treatment consisted of IV administration of isotonic sterile saline, furosemide, cimetidine, and calcitonin. Because of persistent hypercalcemia after 21 hours of treatment, a single dose of pamidronate was administered and furosemide was discontinued. Apocrine gland adenocarci-

noma was diagnosed on cytology of a fine needle aspirate of the perianal masses. Total and ionized calcium decreased considerably over the first 4 days of treatment, and hypomagnesemia and hypophosphatemia were noted. The dog was anesthetized and the tumor was removed surgically. Hypotension developed during anesthesia and dopamine was administered. Soon after initiation of the dopamine infusion, cardiac arrhythmias, including an accelerated ventricular rhythm, first and second degree atrioventricular block, sinus bradycardia, atrial fibrillation, and atrial flutter were noted. A normal sinus rhythm was established when surgery was completed and inhalation anesthesia was discontinued. Further arrhythmias were not noted during hospitalization. Mild hypocalcemia, hypophosphatemia, and hypomagnesemia were still present 3 days after surgery, but the dog appeared fully recovered and was discharged. One week later, mild hypomagnesemia and azotemia were the only laboratory abnormalities.

Conclusions: Electrolyte abnormalities can occur after administration of pamidronate and that induced hypomagnesemia may contribute to the development of cardiac arrhythmias.

🌀 CLINICAL IMPACT:

Multiple factors are likely responsible for the cardiac arrhythmias noted in this dog, including anesthetic agents, hypotension, dopamine, and electrolyte disturbances. The authors propose that hypomagnesemia played a large role in the arrhythmias of this case, but because the arrhythmia resolved without correction of the hypomagnesemia, other factors contributed. The aggressive treatment of the hypercalcemia likely caused the electrolyte abnormalities. All the agents used alter calcium, magnesium, and phosphate homeostasis, so it is likely that the combination of treatments caused the abnormalities rather than pamidronate

alone. When managing hypercalcemia of malignancy, it is prudent to closely monitor all electrolytes and to proceed with caution when making additions to treatment.



Home Monitoring of Blood Glucose Concentrations in Diabetic Cats

Kley S, Casella M, Reusch CE. Evaluation of long-term home monitoring of blood glucose concentrations in cats with diabetes mellitus: 26 cases (1999-2002). J Am Vet Med Assoc 2004;225:261-266.

► INTRODUCTION:

Background: The dose and duration of insulin varies with individuals, but most are controlled well with 0.5 to 1.0 U/lb, twice per day, of intermediate acting insulin subcutaneously. In those who require atypical doses or atypical frequency of administration, blood glucose curves are appropriate and justifiable. However, in-hospital blood glucose curves based on sampling every 2 hours for one day are often not representative of the curves at home. In selected cases it could be advantageous to improve glycemic control by having owners collect capillary blood from a diabetic pet's ear at home and use a portable reflectance colorimeter to determine blood glucose concentrations.

Objectives: The purpose of this study was to assess owner compliance with long-term home monitoring of blood glucose concentrations in their diabetic cats and to determine if the frequency of needed in-hospital re-evaluation is changed by routine home monitoring.

✕ SUMMARY:

Methods: The medical records of 26 diabetic cats were reviewed and owners were contacted by phone. Parameters assessed were signalment, laboratory test results, insulin treatment regimen, home glucose monitoring details, clinical signs during treatment, frequency of in-hospital re-evaluations, and survival time. Monitoring began within the first 12 weeks after initial examination.

Results: Eight owners were unable to perform the monitoring procedure. One cat was euthanized after 1 week. The duration of monitoring was 4.8 to 46 months in 17 cats. Six cats died after 7 to 18 months. Home monitoring was successfully performed by 14 owners every 2 to 4 weeks. Eleven cats were

still being monitored at the completion of the study. Four of 17 monitored cats became non-insulin dependent for up to one year.

Higher doses of insulin were required by cats that were home monitored than those that were not monitored at home. The frequency of in-hospital re-evaluation was not affected by home monitoring.

Conclusions: Some owners can satisfactorily monitor the blood glucose concentration in their diabetic cat, but the frequency of in-hospital re-evaluation is not affected by home monitoring.

Home blood glucose monitoring is far superior to attempting to collect urine and drawing any accurate conclusions about glycemic control.



CLINICAL IMPACT:

The true percentage of owners of diabetic cats that will attempt and successfully perform home monitoring of blood glucose levels is over represented by this study. Only the number of owners who would attempt monitoring was given and not all of those were successful. Still, for the highly motivated client with a diabetic cat, this should be considered. Home blood glucose monitoring is far superior to attempting to collect urine and drawing any accurate conclusions about glycemic control.

If owners do perform home monitoring, they should not adjust insulin doses based on a single reading or without consulting their veterinarian. Many factors can lead to transient or spurious hyperglycemia readings. Insulin dosage should be adjusted based on trends, not single readings.



Effects of Metformin in Normal and Diabetic Cats

Nelson R, Spann D, Elliot D, et al. Evaluation of the oral antihyperglycemic drug metformin in normal and diabetic cats. J Vet Intern Med 2004;18:18-24.

► INTRODUCTION:

Background: Metformin is an oral hypoglycemic in the biguanide family with a method of action that is primarily inhibition of hepatic gluconeogenesis and glycogenolysis. Its most serious adverse effect is to cause metabolic acidosis from lactic acid production, and it was previously removed from the U.S. market for this adverse effect. Metformin was re-released in the United States because the incidence of metabolic acidosis in humans was later found to be acceptably low. However, it is still contraindicated if renal or hepatic disease is present with diabetes mellitus or any condition that is associated with tissue hypoxia.

Objectives: The purpose of this study was to evaluate metformin as a treatment for diabetes mellitus in cats.

✦ SUMMARY:

Methods: There were three phases of the study. Phase 1 was a dose evaluation study performed on five, young, neutered male cats. Six doses of metformin (50 to 750 mg) were administered and plasma metformin concentrations were analyzed to determine the dose that would yield human therapeutic plasma concentrations.

Eight, young, neutered cats were used for Phase 2 which was a three week long period of administration of the oral dose of metformin determined to yield therapeutic plasma concentrations. Phase 3 involved the administration of the previously determined dose of metformin to five diabetic cats.

Results: The dose of 50 mg/cat, twice per day was found to yield plasma concentrations of 0.5 to 2.0 µg/ml, considered to be therapeutic in humans. The three week trial with metformin resulted in lethargy, inappetence, vomiting, and weight loss. Results

of hemograms, serum biochemistries, plasma lactate concentrations, and urinalyses remained within normal reference ranges during metformin treatment. Eight weeks of treatment in five diabetic cats resulted in one cat having euglycemia, three did not, and one cat died after 11 days of metformin administration. The cat that responded had serum insulin levels within or above normal range. The cats which did not respond had low serum insulin levels.

Metformin is not recommended as the sole treatment for diabetes mellitus in cats.

Conclusions: Metformin may be effective in diabetic cats if they are insufficient but not deficient in endogenous insulin, but it is not recommended as the sole treatment for diabetes mellitus in cats.

🌀 CLINICAL IMPACT:

Although lactic acidosis was not documented in this study, the incidence of adverse effects was high when doses required to achieve therapeutic serum concentrations were repeatedly administered. Metformin is eliminated unchanged by the kidneys. Reduced renal function will cause accumulated toxic doses of the active drug.

The single cat that responded to metformin in this study also had the highest endogenous insulin secretion which increased after metformin. Metformin administration causes weight loss which can increase insulin receptors. Whether the response to metformin in the single cat was due to its effects on gluconeogenesis or glycogenolysis, or to a recovery from glucose toxicity, or to adverse gastrointestinal effects and weight loss is not known. The results of this study provide insufficient reason to consider metformin for control of diabetes mellitus in cats.



Hypoglycemia Resulting from Ingestion of Gum Containing Xylitol

Dunayer EK. Hypoglycemia following canine ingestion of xylitol-containing gum. *Vet Human Toxicol* 2004;46:87-88.

► INTRODUCTION:

Background: Hypoglycemia in adult dogs is most often the result of insulinoma, non-islet cell neoplasia, insulin overdose, sepsis, hepatic failure, hypoadrenocorticism, pregnancy, or polycythemia. Xylitol, an artificial sweetener used in sugar-free candies and chewing gums, is a more potent inducer of insulin release than glucose when given orally to dogs, but not humans. The insulin excess in the absence of glucose intake can cause hypoglycemia.

Objectives: This report describes the clinical course of a dog that developed hypoglycemia after consuming a large amount of chewing gum containing xylitol.

History-taking on cases of hypoglycemia in dogs should include inquiries regarding ingestion of xylitol products.



CLINICAL IMPACT:

Blood glucose should be evaluated upon presentation of any dog that is seizing. History-taking on cases of hypoglycemia in dogs should include inquiries regarding ingestion of sugar-free products that might contain xylitol. The hypoglycemia induced by xylitol can occur within 10 to 30 minutes of ingestion, and while the duration of effect has been reported to be short in experimental studies, it was prolonged in this dog perhaps because of slow release from the gum ingested. In one study, an oral dose of 1 g/kg xylitol resulted in a glucose concentration of about 50 mg/dl. Vomiting should be induced if ingestion was recent and signs of hypoglycemia are not present.

✕ SUMMARY:

Case Report: A 9-month-old, neutered male, Labrador retriever was evaluated for acute onset of seizures that began approximately 1 hour after ingestion of 100 pieces of sugar-free gum. The total dose of xylitol was estimated to be 2.96 g/kg. The serum glucose was 37 mg/dl. A rapid response was noted following administration of intravenous boluses of dextrose and intravenous (IV) fluid therapy. Blood glucose was below normal or in the lower end of the reference range for 11 hours despite supplementation of dextrose (5%) in IV fluids given as a constant rate infusion and frequent feeding. Hypokalemia and hypophosphatemia were also present when the dog was admitted. The dog was considered bright and alert with a good appetite when released from the emergency clinic the following morning. Further follow-up was not reported.

Conclusions: Sugar-free gum containing xylitol can cause severe, symptomatic hypoglycemia in dogs if ingested in sufficient quantity.



Effects of Ultrasonography on Low-Dose Dexamethasone Suppression Testing in Dogs

May ER, Frank LA, Hnilica KA, et al. Effects of a mock ultrasonographic procedure on cortisol concentrations during low-dose dexamethasone suppression testing in clinically normal adult dogs. *Am J Vet Res* 2004;267-270.

► INTRODUCTION:

Background: The low dose dexamethasone suppression test (LDDST) is a sensitive test for diagnosis of hyperadrenocorticism in dogs. Its advantages over the ACTH response test include higher sensitivity, lower cost, and the ability to differentiate pituitary-dependent from adrenal-dependent hyperadrenocorticism in about 50% of cases. Unfortunately, the LDDST is less specific than the ACTH stimulation test, as stressful nonadrenal illness is frequently associated with abnormal LDDST results.

Objectives: The objective of this study is to evaluate the effects of abdominal ultrasound on serum cortisol concentrations when performed during the LDDST.

✦ SUMMARY:

Methods: Six healthy client-owned dogs were studied. During the initial testing, LDDSTs were performed weekly in each dog. The LDDST was performed by obtaining blood samples for measurement of serum cortisol before and 2, 4, 6, and 8 hours after intravenous administration of 0.01 mg/kg dexamethasone. A mock ultrasound procedure, consisting of placing the dog in dorsal recumbency, clipping hair off the abdomen, and placing an ultrasound probe on the abdomen for approximately 20 minutes in a dark room. The first LDDST was performed without interruption by an ultrasound procedure and was used as a baseline for comparison of other tests. During the four subsequent LDDSTs, dogs had a mock ultrasound performed prior to one of the sampling times, and the blood sample was obtained within 5 minutes of completing the procedure. Dogs were randomized regarding sampling times and each dog had a mock ultrasound performed before

each sampling time at weekly intervals. During the second part of the experiment, 1 to 4 months after the initial testing, dogs underwent an identical mock ultrasound procedure and had blood samples obtained for serum cortisol determination at the same times as the initial study, but dexamethasone was not administered.

Any potentially stressful procedures should be performed at least 2 hours prior to the LDDST.

Results: The median serum cortisol concentration was not significantly different when results during the mock ultrasound tests were compared with those when the ultrasound was not performed. One dog had serum cortisol concentrations above the reference range on two occasions (4 and 6 hours after mock ultrasound) during the LDDST. Results of all other time periods were normal for this dog. All samples at all times were within the reference range for the remaining five dogs. During the second part of the study, all dogs had significant increases in serum cortisol concentration immediately after the mock ultrasound procedure, with median cortisol concentrations of 38.9 and 88.8 nmol/L before and after the ultrasound, respectively.

Conclusions: Abdominal ultrasound procedure does not alter results of LDDST in most dogs, but it does significantly increase serum cortisol concentrations in normal dogs and could affect test results of the LDDST.



CLINICAL IMPACT:

The increase in serum cortisol noted in untreated normal dogs following the mock ultrasound procedure here was suppressed in most dogs during the LDDST. However, serum cortisol was above the reference range in 1 of the 6 dogs immediately after the ultrasound procedure. Because cortisol returned to normal during subsequent samples, any potentially stressful procedures should be

performed at least 2 hours prior to obtaining blood samples during the LDDST. Failure to do so could result in a false positive test and an erroneous diagnosis of hyperadrenocorticism.



Trilostane Treatment of Bilateral Adrenal Enlargement in a Cat

Boag AK, Neiger R, Church DB. Trilostane treatment of bilateral adrenal enlargement and excessive sex steroid hormone production in a cat. *J Sm Anim Pract* 2004;45:263-266.

► INTRODUCTION:

Background: Hyperadrenocorticism in cats is usually pituitary-dependent and causes Cushing's syndrome (effects and signs of hypercortisolemia). The adrenal cortex also produces sex hormones, primarily weak androgens such as dihydroepiandrosterone. Adrenocortical tumors may possess the enzymes to produce androgens more than the enzymes to produce cortisol, a condition called adrenal virilism. Bilateral adrenal hyperplasia less commonly can cause adrenal virilism.

Adrenal hyperplasia in dogs is usually treated with mitotane, a cytotoxic chlorinated hydrocarbon. Trilostane, an 3β -hydroxysteroid dehydrogenase inhibitor, decreases serum cortisol, estradiol, and testosterone concentrations in dogs and possibly cats.

Objectives: This case was reported to describe the results of treating a cat with bilateral adrenal enlargement and excessive sex steroid production with trilostane.

✕ SUMMARY:

Case Report: A 14-year-old, spayed female, domestic short hair cat was presented with a history of recent aggressiveness to other animals and urine spraying. The urine had a tom cat odor.

Physical examination revealed aggressive responses to restraint, marked vulval hyperplasia, unkempt hair coat, and skin thickening. Hemogram and serum chemistries were unremarkable. The urinalysis demonstrated mild hematuria. Urine culture for bacteria was negative. Thoracic radiographs were within normal limits, but abdominal radiographs revealed radio-opaque cystic calculi. Abdominal ultrasonography also identified bilateral adrenal enlargement.

Adrenocorticotrophic hormone (ACTH)

stimulation was performed and serum was collected from the patient and a normal spayed female cat for cortisol (baseline and post-ACTH at 30 and 60 minutes), testosterone, 17α -hydroxyprogesterone, estradiol, progesterone, and dehydroepiandrosterone assay. Magnetic resonance imaging of the cranium was normal.

A cystotomy was performed to remove the urinary calculi. Analysis showed them to be composed of calcium oxalate. Serum cortisol concentrations were within normal reference ranges. Serum testosterone, 17α -hydroxyprogesterone, estradiol, and progesterone were elevated.

Treatment of the excessive adrenal sex hormone production was attempted with 30 mg of trilostane, once per day. Serum was collected six hours after the administration of trilostane on treatment days 7, 28, and 84 for cortisol, testosterone, 17α -hydroxyprogesterone, estradiol, progesterone, and dehydroepiandrosterone assay. All hormone concentrations at each re-examination day were increased compared to pretreatment concentrations.

At treatment day 84 the urine odor, spraying, and aggressiveness were reduced. Soon after being re-examined on treatment day 174, aggressiveness and urine odor were returning. Euthanasia was performed and necropsy was not permitted.

Conclusions: This was a spayed female cat with adrenal virilism that was moderately responsive to trilostane treatment.

🌀 CLINICAL IMPACT:

Subjective assessment of this cat's behavior, frequency of urine spraying, and urine odor suggest that it was successfully managed by trilostane treatment. However, the more objective serum hormone assays did not agree. Conversely, the serum hormone elevations became worse with trilostane treatment.

The benefit of trilostane treatment for adrenal virilism in cats is unclear.

The authors speculate that the hormone results may have been spurious, but that is unlikely since four separate assays were used for the four hormones that rose in concentration with trilostane treatment. Some of the hormones measured were evaluated in comparison with a normal spayed cat. However, the patient was 14 years old, and the age of the control cat was not given. Adrenal androgens are among many hormones that normally decrease in serum concentration with aging. Interpretations of the hormone values in the patient may have been different with a better matched control cat or with normal ranges based on multiple cats.

The description of an apparent case of adrenal virilism in a cat is interesting. It is unfortunate that the cause was not confirmed by necropsy. The benefit of trilostane treatment for adrenal virilism in cats at the dose used in this case report is unclear.



Adrenal Necrosis Associated with Trilostane Treatment

Chapman PS, Kelly DF, Archer J, et al. Adrenal necrosis in a dog receiving trilostane for the treatment of hyperadrenocorticism. *J Sm Anim Pract* 2004;45:307-310.

► INTRODUCTION:

Background: Mitotane is the most commonly used medical treatment for pituitary-dependent hyperadrenocorticism in dogs. It is cytotoxic to the adrenal cortex. Trilostane is now also being used to treat hyperadrenocorticism. Its method of action is to inhibit the 3β -hydroxysteroid dehydrogenase enzyme and impede the production of cortisol and other steroid hormones. Because trilostane is not considered cytotoxic and its effects are short-lived, it is considered to have a wider margin of safety than does mitotane. However, recent cases of hypoadrenocorticism have been reported with the use of trilostane.

Objectives: The purpose of this report was to describe a dog with hyperadrenocorticism that developed adrenocortical necrosis associated with trilostane administration.

✕ SUMMARY:

Case Report: A 10-year-old, 17 kg, castrated male, Staffordshire bull terrier was diagnosed with pituitary-dependent hyperadrenocorticism based on consistent history, physical findings, serum chemistries, and endocrine tests. Treatment was begun with 120 mg of trilostane, once daily. Clinical response was noted within two weeks. Baseline and post-adrenocorticotropic hormone (ACTH) stimulation serum cortisol concentrations were within normal ranges.

At three weeks of treatment, the dog had depression, inappetence, and diarrhea. Pre- and post-ACTH stimulation serum cortisol concentrations were below normal ranges. Serum sodium was decreased and serum potassium was increased. Primary hypoadrenocorticism was suspected and trilostane was discontinued. Intravenous fluids, fludrocortisone, and prednisone were administered.

At 34 days after treatment began and a

week after the discontinuation of trilostane administration, clinical signs included muscle tremors, polydipsia, depression, and pot-belly appearance. Abdominal ultrasound revealed an enlarged liver and bilaterally enlarged adrenal glands. Fludrocortisone and prednisone were discontinued and at day 38, baseline and post-ACTH stimulation serum cortisol concentrations were subnormal.

On day 42 an exploratory laparotomy and biopsy of the left adrenal gland was done. Histopathologic examination of the adrenal gland showed marked neutrophil infiltration and coagulative necrosis. Post-surgically, the dog was stabilized on fludrocortisone and prednisolone. Three months after discharge the signs of hyperadrenocorticism were resolving.

Conclusions: Trilostane can cause adrenal necrosis and iatrogenic primary hypoadrenocorticism in dogs.

🌀 CLINICAL IMPACT:

Any clinician who has treated many cases of canine hyperadrenocorticism knows that mitotane can cause either a dose-related or an inexplicable hypoadrenocorticism. Dose-related hypoadrenocorticism can be prevented by careful management. However, what causes the inexplicable type, or how to prevent it, is not known.

Trilostane can also cause inexplicable hypoadrenocorticism in some dogs being treated for hyperadrenocorticism. The authors of this report speculate the cause could be related to hypercoagulability and thrombus formation, adrenocortical venous vasoconstriction with thrombus formation, or high or suddenly increased plasma ACTH concentrations.

Other cases of trilostane-induced hypoadrenocorticism have been reported, including

an addendum to this report. The pathogenesis is still unknown. The theories involving thrombi were not substantiated by this report. No thrombosis was found. The theory of increased plasma ACTH concentrations somehow being at fault is not supported by acute increase in plasma ACTH concentration from stimulation testing or chronic increases of ACTH concentration with recovery from corticosteroid administration. Adrenal necrosis is not associated with either of these situations. However, there may be contributing factors in certain atypical forms of bilateral adrenocortical hyperplasia that makes the cells undergo necrosis when exposed to sudden increases in ACTH concentration.

Trilostane can cause adrenal necrosis in dogs.



Congenital Adrenal Hyperplasia Secondary to 11 β -Hydroxylase Deficiency in a Cat

Knighton EL. Congenital adrenal hyperplasia secondary to 11 β -hydroxylase deficiency in a domestic cat. *J Am Vet Med Assoc* 2004;225:238-241.

► INTRODUCTION:

Background: The congenital deficiency of an enzyme in the steroidogenesis pathways of the adrenal cortex can cause a deficiency of hormones normally created by the enzyme. At the same time, there is an excess production of other hormones caused by the increase in substrates, i.e. backed up precursors that can go through an alternate pathway for another end-product. The most common congenital adrenocortical enzyme deficiency in humans results in low or low normal serum cortisol, compensatory increased adrenocorticotropic hormone (ACTH), and higher than normal adrenal androgen production. Mineralocorticoid (aldosterone and deoxycorticosterone) production may be increased or decreased depending on the enzyme that is deficient.

Objectives: The purpose of this report was to describe the first reported case of congenital adrenal hyperplasia in a cat.

✦ SUMMARY:

Case Report: A 6-month-old, calico-colored kitten phenotypic male was presented with possible cryptorchidism. Exploratory laparotomy revealed apparent female gonads and internal genitalia: bilateral ovaries and uterine horns. Histologic examination of the removed internal genitalia showed ovaries, oviducts, uterus, vas deferens, and epididymis. Chromosomal analysis on leukocytes revealed a normal female feline karyotype (38, XX). Based on a female karyotype and masculinized external genitalia, a diagnosis of female pseudohermaphroditism was made.

At 10-months of age, the cat was presented with a history of inappropriate urination, polyuria, and polydipsia. The hemogram revealed lymphocytosis. A urinalysis was normal with a low normal specific gravity. At 14-months

of age, the cat's penis had barbs, suggesting that excessive androgens were being secreted. Serum testosterone concentration was slightly in excess of that appropriate for sexually intact male cat (1,040 pg/ml), ACTH concentration was markedly high (313 pmol/L), and aldosterone concentration was subnormal. No testes nor enlarged adrenal glands were observed on abdominal ultrasonography. ACTH administration did not normally stimulate the production of cortisol. Serum steroid hormone concentrations that were

elevated in addition to testosterone included 11-deoxycortisol, deoxycorticosterone, androstenedione, progesterone, and 17-hydroxyprogesterone. Serum estradiol was within normal range for a spayed female cat. Congenital adrenal virilism was based on the endocrine concentrations and clinical findings.

Prednisone given orally at 0.65 mg/kg, once per day, resulted in incomplete improvement in clinical signs and return of affected steroid hormones to normal concentrations.

Conclusions: This was a case of congenital adrenal hyperplasia in a cat caused by a deficiency in the 11 β -hydroxylase enzyme.

🌀 CLINICAL IMPACT:

This is an excellent case report of congenital adrenal hyperplasia with virilism in cat. Congenital adrenal hyperplasia syndromes are due to autosomal recessive traits. The irony is that this condition is far more likely in purebred dogs who have concentrated recessive genes than in more genetically diverse domestic short hair cats. However, no case in a dog has been so well described as this cat.

Most cases of female pseudohermaphroditism in humans are caused by congenital adrenal hyperplasia. All cases of ambiguous genitalia should be evaluated for congenital adrenal hyperplasia and should have

This is an excellent case report of congenital adrenal hyperplasia with virilism in cat.

plasma ACTH, cortisol, aldosterone, and 17-hydroxyprogesterone levels measured to screen for congenital adrenal hyperplasia.

This case was only partially controlled by prednisone to replace cortisol and suppress ACTH production. More frequent administration than once per day may have been more successful. Cats are also known to be more refractory to the feedback effects of low-dose dexamethasone testing than in dogs, so a higher dose of prednisone may also be necessary to control congenital adrenal hyperplasia in cats.



Trilostane Treatment of Pituitary-Dependent Hyperadrenocorticism in Cats

Neiger R, Witt AL, Noble A, et al. Trilostane therapy for treatment of pituitary-dependent hyperadrenocorticism in 5 cats. J Vet Intern Med 2004;18:160-164.

► INTRODUCTION:

Background: Hyperadrenocorticism is a rare disease in cats, and a consistently effective medical treatment is not available. Bilateral adrenalectomy is currently the recommended treatment for pituitary-dependent hyperadrenocorticism. Unfortunately, poor wound healing and increased susceptibility to infection and thromboembolism make cats with hyperadrenocorticism poor surgical candidates. In addition, cats must be supplemented with mineralocorticoids and glucocorticoids for their lifetimes following bilateral adrenalectomy.

Objectives: The objective of this study was to report results of trilostane administration to cats with pituitary-dependent hyperadrenocorticism.

✕ SUMMARY:

Methods: Five cats with pituitary-dependent hyperadrenocorticism confirmed by a majority of consistent clinical signs, abnormal adrenocorticotropic hormone (ACTH) response tests, and bilateral adrenomegaly were administered trilostane for treatment. Monitoring included assessment of clinical response, and ACTH response tests and urine cortisol:creatinine ratio in some cats.

Results: Clinical signs varied, but consisted of thin skin, poor hair coat, pendulous abdomen, fragile skin, and hepatomegaly. Diabetes mellitus was present in 3 cats. Four cats were initially administered trilostane orally at 30 mg once daily and one cat was treated with 20 mg once daily. Improvement in clinical signs was noted in all cats after 7–14 days of treatment. The cortisol response to ACTH decreased to the reference range in all three cats tested, while one cat had a marked reduction in urine cortisol:creatinine ratio. One cat

died 16 days after initiating trilostane treatment apparently of renal failure. Azotemia and a urine specific gravity of 1.018 were present prior to treatment with trilostane. A second cat died 140 days after initiation of trilostane treatment. This cat had concurrent diabetes mellitus that was poorly controlled during treatment and relatively high

Further study is necessary to determine the pharmacokinetics of trilostane including route of excretion.

post-ACTH cortisol concentrations (335–406 nmol/L on three tests). Necropsy revealed hepatic congestion and thickening of the adrenal cortices, but the cause of death was not determined.

One cat experienced weight loss while on trilostane treatment, but it resolved after decreasing the dosage from 30 to 15 mg, once daily.

Clinical response was good in 3 cats, with complete or partial resolution of polydipsia, polyphagia, cutaneous abnormalities, and improvement in control of diabetes mellitus (two cats). Final dosage in the three cats still alive after 6 to 20 months of trilostane treatment ranged from 15 mg to 60 mg per day.

Conclusions: Trilostane is effective in controlling clinical signs of hyperadrenocorticism, but further study is necessary to determine the pharmacokinetics of trilostane including route of excretion.

🌀 CLINICAL IMPACT:

Trilostane may be a viable treatment for feline hyperadrenocorticism as it was effective at improving clinical signs and controlling excessive cortisol secretion in most cats in this study. However, two cats died during treatment. Although details were not given, the cat that died of apparent renal failure deteriorated after 10 days on trilostane. If the drug undergoes renal excretion, trilostane could have accumulated and contributed to the death of this cat. The cause of death

in the second cat was undetermined, but trilostane should be used with caution in cats until its use is investigated further.



Adrenocorticotrophic Hormone Concentrations After Treatment with Trilostane for Pituitary-Dependent Hyperadrenocorticism

Witt AL, Neiger R. Adrenocorticotrophic hormone levels in dogs with pituitary-dependent hyperadrenocorticism following trilostane therapy. *Vet Rec* 2004;154:399-400.

► INTRODUCTION:

Background: Trilostane inhibits cortisol secretion from the adrenal glands by inhibiting 3- β hydroxysteroid dehydrogenase and is an effective treatment of hyperadrenocorticism in dogs. Dogs treated with trilostane for hyperadrenocorticism developed further adenomegaly and when treated for one year or longer were found to have nodular changes of unknown significance. Secretion of adrenocorticotrophic hormone (ACTH) would be expected to increase during trilostane treatment due to loss of negative feedback of cortisol on the pituitary gland.

Objectives: The objective of this study was to evaluate plasma ACTH concentrations in response to chronic trilostane administration in dogs with hyperadrenocorticism.

✕ SUMMARY:

Methods: Seventeen dogs with pituitary-dependent hyperadrenocorticism were treated with trilostane at unspecified dosages. Plasma samples for ACTH determination were obtained before and at least 6 months after initiating treatment. Samples were obtained 3 to 20 hours after the previous trilostane treatment.

Results: The median plasma ACTH concentration before treatment was 102 pg/ml and after treatment was 246 pg/ml. The post-treatment plasma ACTH concentration was significantly higher than that prior to treatment. There was significant correlation between the number of hours after trilostane the sample was collected and the plasma ACTH, with the highest ACTH concentrations found in dogs most recently treated.

Conclusions: Trilostane increases plasma ACTH concentration in dogs with pituitary-dependent hyperadrenocorticism.



CLINICAL IMPACT:

These results are consistent with the inhibitory effect of trilostane on cortisol secretion and the relatively short duration of action of the drug. Trilostane lowers basal cortisol concentrations for only a few hours, so its effect on cortisol secretion should be evaluated within 6 to 8 hours after drug administration. This short duration of effect is reflected in the higher ACTH concentrations in dogs tested soon after trilostane administration. It is possible that twice daily trilostane administration would better control hypercortisolemia and clinical signs than once daily dosing. Adrenal ultrasound was not performed so no assessment of the size and shape of the adrenal could be made.

Trilostane increases plasma ACTH concentration in dogs.

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 adenohypophysis 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

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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

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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.