

# Endocrinology

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

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## Medroxyprogesterone Acetate Effects on Adenohypophyseal Function

*Beijerinck NJ, Bhatti SFM, Okkens AC, et al. Adenohypophyseal function in bitches treated with medroxyprogesterone acetate. Dom Anim Endocrinol 2007;32:63–78.*

### \* INTRODUCTION

**Background:** Medroxyprogesterone acetate (MPA) suppresses the estrous cycle in dogs. It is not known whether the effects are primarily on the hypothalamus, pituitary, or ovary. Prolonged MPA administration can cause adrenocortical suppression in dogs, but effects on other adenohypophyseal functions are unknown or the results of previous studies have been conflicting.

**Objectives:** The purpose of this study was to assess the effects of MPA on adenohypophyseal function in dogs.

### ▲ SUMMARY

**Methods:** Five beagle bitches were administered MPA subcutaneously at 10 mg/kg, every four weeks. A combination of corticotropin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH), gonadotrophin-releasing hormone (GnRH), and thyrotropin-releasing hormone (TRH) was administered before and 2, 5, 8, and 11 months after the initial MPA treatment. Blood samples for determination of plasma concentrations of adrenocorticotropic hormone (ACTH), cortisol, growth hormone (GH), insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin,  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), and thyroid-stimulating hormone (TSH) were collected at -15, 0, 5, 10, 20, 30, and 45 minutes after each administration of combined hypothalamic releasing hormones.

**Results:** MPA administrations stopped the estrous cycle, but did not affect basal and

post-GnRH plasma LH concentrations. Basal plasma FSH concentration was significantly higher at two months after the initial MPA administration than before or other post-stimulation sampling times. Plasma FSH concentrations, before and after stimulation were significantly higher before MPA treatment than afterwards.

Plasma GH concentration did not change during treatment, but IGF-1 concentrations became significantly elevated at eight and 11 months after initiating MPA treatment. Plasma ACTH concentration was not affected during MPA treatment. However, maximal plasma cortisol concentrations after CRH stimulation and the area under the curve were significantly decreased with MPA treatment. MPA treatment did not significantly affect plasma concentrations of prolactin, TSH, and  $\alpha$ -MSH, nor TRH-stimulated plasma prolactin or TSH concentrations.

**Conclusions:** Repeated monthly subcutaneous administration of MPA in dogs can increase plasma FSH concentration, increase IGF-1 secretion, and suppress the hypothalamic-pituitary-adrenal axis.

### ◆ CLINICAL IMPACT

Medroxyprogesterone acetate, a long-acting synthetic progesterone, is not currently approved for use in dogs in the United States. Although it is effective in suppressing the

*The risk of these adverse effects greatly outweigh the risks of an ovariectomy*

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- ▶ Medroxyprogesterone acetate administration in dogs can increase FSH secretion, activate mammary GH, and suppress the hypothalamic-pituitary-adrenocortical axis. *Dom Anim Endocrinol* 2007;32:63–78.
- ▶ Dogs with the MDR1 mutation that causes increased sensitivity to ivermectin toxicity may also develop adrenal insufficiency during illness or other chronic stresses. *J Vet Emerg Crit Care* 2007;17:61–66.
- ▶ Quantitative measurement of radioactive pertechnetate uptake is the “gold standard” for the diagnosis of hypothyroidism, not the TSH stimulation test. *J Vet Intern Med* 2007;21:25–32.
- ▶ A thyroglossal duct cyst with successful excision has been reported in a cat. *J Am Vet Med Assoc* 2007;230:686–689.
- ▶ Hyperthyroidism has been associated with probable struma cordis, an intracardiac thyroid rest cell tumor, in a young dog. *J Vet Intern Med* 2007;21:332–335.
- ▶ Elevated plasma concentrations of parathyroid hormone-related protein in dogs are specific for hypercalcemia of nonparathyroid malignancy. *Vet Rec* 2006;159:833–838.
- ▶ Primary hyperparathyroidism can be an inherited, autosomal dominant, trait in keeshonden. *J Vet Intern Med* 2007;21:199–203.
- ▶ The success rate for treating primary hyperparathyroidism in dogs is best with parathyroidectomy, poorest with ethanol ablation, and intermediate with heat ablation. *J Am Anim Hosp Assoc* 2007;43:70–77.
- ▶ Considerable day-to-day variability of blood glucose concentration occurs in measurements performed at home in cats with diabetes mellitus. *J Am Vet Med Assoc* 2007;230:1011–1017.
- ▶ Urinary tract infections in cats with hyperthyroidism, diabetes mellitus, and chronic kidney disease are relatively common, and urine bacterial cultures of these patients should be routine. *J Fel Med Surg* 2007;9:124–132.
- ▶ Myelinated nerve pathology in feline and human diabetes mellitus is very similar. *Acta Neuropathol* 2007;113:431–442.
- ▶ Medical management of dogs with insulinoma may be more successful than previously reported. *J Sm Anim Pract* 2007;48:151–156.
- ▶ Paraneoplastic hypoglycemia from an insulin-like growth factor type-II secreting hepatocellular carcinoma has been reported in a dog. *J Vet Intern Med* 2007;21:193–195.
- ▶ Alopecia in Pomeranians and miniature poodles may occur in association with high urinary corticoid:creatinine ratios and resistance to glucocorticoid feedback, suggestive of an atypical hyperadrenocorticism. *Vet Rec* 2007;160:393–397.
- ▶ Profound hypokalemia from hyperadosteronism has caused respiratory failure in a cat. *J Vet Emerg Crit Care* 2007;17:202–207.
- ▶ Trilostane treatment causes diffuse or nodular hyperplasia of the adrenal cortex. *Vet Rec* 2007;160:219–224.
- ▶ A relative lack of adrenocortical response to stress can occur in septic dogs and is associated with systemic hypotension and decreased survival. *J Vet Intern Med* 2007;21:226–231.
- ▶ Up to 24% of dogs with hypoadrenocorticism may be diagnosed with a selective glucocorticoid deficiency. *J Am Vet Med Assoc* 2007;230:1190–1194.
- ▶ Urinary catecholamine- and metanephrine-to-creatinine ratios are increased in dogs stressed from a hospital environment. *J Vet Intern Med* 2007;21:388–393.
- ▶ A single intramuscular injection of methylprednisolone acetate in cats causes significant changes on several serum biochemical parameters, particularly amylase and bicarbonate. *Vet Clin Path* 2007;36:184–187.
- ▶ Fulvestrant, an estrogen receptor antagonist, is not an effective treatment for hair cycle arrest (alopecia X). *Vet Dermatol* 2007;18:63–66.

[ Continued from page 1 ]

estrous cycle in dogs and used in other countries for that purpose, it has the potential for serious adverse effects such as adrenocortical atrophy, diabetes mellitus, acromegaly, and pyometra, among others. The risk of these adverse effects greatly outweighs the risks of an ovariohysterectomy. MPA should not be used to suppress the estrous cycle in dogs.



## Hypothalamic-Pituitary-Adrenal Axis in MDR1-1Δ Mutation Dogs

Mealey KL, Gay JM, Martin LG, et al. Comparison of the hypothalamic-pituitary-adrenal axis in MDR1-1Δ and MDR1 wildtype dogs. *J Vet Emerg Crit Care* 2007;17:61–66.

### \* INTRODUCTION

**Background:** P-glycoprotein (P-gp), an important component of the blood-brain barrier, is the product of the MDR1 gene. P-gp is a drug transporter expressed on brain capillary endothelial cells. Its function is to transport certain substrates from the brain tissue back into the capillary lumen.

P-gp is similar among mammalian species. Drugs that are known substrates for canine P-gp include ivermectin, loperamide, vincristine, vinblastine, and doxorubicin. However, more than 50 drugs are known substrates for human and mouse P-gp. The same drugs are suspected to be substrates for canine P-gp.

Herding dogs are at risk of having an inheritable trait, an MDR1 mutation, that causes a lack of P-gp. P-gp deficiency results in otherwise nontoxic doses of P-gp substrate drugs, such as ivermectin and loperamide being neurotoxic. Therefore, dogs with a MDR1 mutation could have an altered blood-brain barrier to cortisol and corticosterone which would increase the negative feedback on the hypothalamus and pituitary, subsequently increasing the risk of secondary hypoadrenocorticism.

**Objectives:** The purpose of this study was to evaluate the hypothalamic-pituitary-adrenal (HPA) axis in MDR1-1Δ dogs (those with the MDR1 mutation associated with ivermectin sensitivity) and MDR1 wildtype dogs.

### ▲ SUMMARY

**Methods:** MDR1 genotyping was used for assigning seven healthy collie dogs to either the group homozygous for the MDR1 wildtype or the group homozygous for the MDR1 mutation. Blood samples were collected for the determination of cortisol and adrenocor-

ticotrophic hormone (ACTH) concentrations under basal conditions, before and after ACTH administration, and before and after dexamethasone administration.

**Results:** Plasma cortisol concentrations before and after ACTH administration were significantly lower in MDR1 mutant dogs as compared to MDR1 wildtype dogs. Plasma ACTH concentrations after dexamethasone administration were significantly lower in MDR1 mutant dogs as compared with MDR1 wildtype dogs.

**Conclusions:** P-gp plays a role in the regulation of the HPA axis. Deficiency of P-gp results in ease of cortisol access to the brain and exaggerated hypothalamic and pituitary suppression leading to secondary hypoadrenocorticism. Dogs with the MDR1 mutation may have impaired recovery from stress.

**One of the reasons for a favorable response to administered corticosteroids in stress is explained by the results of this study**

### ◆ CLINICAL IMPACT

Administering corticosteroids to dogs in shock has variable results. In some cases, the response to corticosteroids can be beneficial while in others, it is detrimental. One of the reasons for a favorable response to administered corticosteroids in stress is explained by the results of this study. Increased permeability of the blood-brain barrier to cortisol can down regulate ACTH production and cause secondary hypoadrenocorticism with impaired ability to produce sufficient cortisol during periods of stress. The MDR1 mutation, most common in herding dogs, is at least one cause for an altered blood-brain barrier which can cause secondary hypoadrenocorticism.



## Assessment of Thyroid Function with Low Plasma Thyroxine Concentration

*Diaz Espineira MM, Mol JA, Peeters ME, et al. Assessment of thyroid function in dogs with low plasma thyroxine concentration. J Vet Intern Med 2007;21:25–32.*

### \* INTRODUCTION

**Background:** When testing dogs for hypothyroidism, serum  $T_4$  concentration is a fairly sensitive measure. However, lack of specificity reduces the reliability of a single measurement of  $T_4$ . This is particularly true in dogs with nonthyroidal illness that frequently causes a test result to be below the reference range. No true noninvasive “gold standard” of assessing thyroid function has been identified in the dog.

**Objectives:** The purpose of this study was to determine the accuracy of commonly performed blood tests for hypothyroidism with results of thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH) stimulation tests and technetium uptake in dogs suspected of having hypothyroidism.

### ▲ SUMMARY

**Methods:** Thirty dogs with clinical signs consistent with hypothyroidism that had a plasma  $T_4$  concentration below the reference range were measured. Primary hypothyroidism was confirmed by histopathology of thyroid gland biopsy demonstrating severe destruction or atrophy in 14 dogs, while thyroid gland histology was normal in 13 dogs. Two other dogs had secondary hypothyroidism and the remaining dog had thyroid carcinoma. These last three dogs were not included in the statistical evaluation. Plasma  $T_4$ , free  $T_4$  ( $fT_4$ ), TSH, and thyroglobulin autoantibodies were measured in all dogs. Thyroid scintigraphy with technetium perchlorate ( $^{99m}TcO_4$ ) was performed to determine technetium uptake. A TSH stimulation test was performed by measuring  $T_4$  in plasma samples collected before and four hours after intravenous administration of 5 IU of bovine TSH. One to three weeks later,

serum TSH was measured before and after the administration of TRH.

**Results:** The total  $T_4$  concentration was significantly lower in the hypothyroid group (median 2 nmol/L; range 2–4 nmol/L) than the nonthyroidal illness group (median 8 nmol/L; range 2–18 nmol/L). Serum  $fT_4$  was below the limit of detection (1.9 pmol/L) in 11 of the 12 hypothyroid dogs tested and was within the reference range in the remaining dog. Dogs with nonthyroidal illness had a median  $fT_4$  of 9.3 nmol/L, although one dog had a  $fT_4$  below the detectable limit.

Plasma TSH concentration was elevated in eight of 14 hypothyroid dogs and one dog with nonthyroidal illness. All hypothyroid dogs had a plasma  $T_4$  concentration after TSH stimulation of less than 9 nmol/L and a change in  $T_4$  of less than 6 nmol/L. The post-TSH plasma  $T_4$  concentration in dogs with nonthyroidal illness was not reported, but the median increment in  $T_4$  during the test was 16 nmol/L, with one dog having no increase in  $T_4$  in response to TSH. The increase in  $T_4$  in the TSH stimulation test was significantly higher in the nonthyroidal illness group than the hypothyroid group. TRH stimulation of hypothyroid dogs resulted in minimal change in TSH in six dogs in the hypothyroid group and only one in the nonthyroidal illness group. The increment of change in TSH after TRH stimulation was significantly higher in the nonthyroidal illness group. Thyroglobulin autoantibodies were detected in four of five hypothyroid and was negative in all six nonthyroidal illness dogs. Thyroid scintigraphy demonstrated no overlap in uptake of technetium by the thyroid gland between the groups. Hypothyroid dogs have lower technetium uptake than dogs with nonthyroidal illness.

**Conclusions:** Thyroid uptake of technetium is the most effective test for differentiating hypothyroidism from nonthyroidal illness.

### ◆ CLINICAL IMPACT

A low total  $T_4$  is not specific for hypothyroidism, as demonstrated in this study where all dogs in the nonthyroidal illness group had a low  $T_4$ . This selection resulted in the study of only the most difficult cases to diagnose, and all tests would have performed better if all dogs suspected of hypothyroidism had been included. A low serum  $fT_4$  concentration is more specific than total  $T_4$  for a diagnosis of hypothyroidism, but some dogs with nonthyroidal illness will have a  $fT_4$  below the reference range and some dogs with mild hypothyroidism will have a  $fT_4$  within the reference range. Measurement of plasma canine (c)-TSH concentration helps confirm hypothyroidism if it is elevated, but the assay sensitivity for c-TSH is low and occasionally a dog with nonthyroidal illness has an elevated c-TSH concentration. Use of thyroid scintigraphy for assessment of technetium uptake or even TSH stimulation testing is generally impractical for most clinical environments. Finding a subnormal  $T_4$  and  $fT_4$  with or without an elevated c-TSH in a dog with clinical signs consistent with hypothyroidism justifies a clinical trial of treatment with levothyroxine.

**Hypothyroid dogs have lower technetium uptake than dogs with nonthyroidal illness**





## Thyroglossal Duct Cyst in a Cat

Giles JT, Rochat MC, Snider TA. Surgical management of a thyroglossal duct cyst in a cat. *J Am Vet Med Assoc* 2007;230:686–689.

### \* INTRODUCTION

**Background:** The thyroid gland is the first of the endocrine glands to develop in the embryo. It begins as a bilobed bud on the ventral aspect of the primitive pharynx between the first and second brachial (pharyngeal) pouches. The bud is attached to the brachial pouch epithelium by a stalk, the thyroglossal duct. As the thyroid bud develops, it normally detaches from the pharynx by involution of the thyroglossal duct. Failure of the duct to involute can create a congenital cyst in the neck.

**Objectives:** The aim of this report was to describe the diagnosis and surgical treatment of a thyroglossal duct cyst in a cat.

### ▲ SUMMARY

**Case Report:** A 14 year-old, castrated male, domestic shorthair cat was presented with a ventral cervical swelling of six weeks duration, mild dysphagia, and lethargy. The referring veterinarian had previously aspirated about 50 ml of bacteriologically sterile, acellular fluid from the swelling. Physical examination revealed a 13 cm mass on the ventral side of the neck, extending from the first cervical vertebra to the manubrium of the sternum. A hemogram and routine serum chemistries were within normal limits. A radiograph of the swelling demonstrated dorsal and lateral deviation of the trachea and esophagus. A contrast-enhanced computed tomograph revealed that the swelling was cystic and filled with fluid. It did not appear to be associated with the thyroid gland. An incisional biopsy was performed and 60 ml of clear fluid was removed. The histopathologic findings were consistent with a thyroglossal

duct cyst. The cyst was successfully excised four weeks later without complications.

**Conclusions:** Thyroglossal duct cysts are rare in cats, but they should be considered as a possible cause of swellings on the ventral aspect of the neck.

**Thyroglossal duct cysts in cats should be considered as a possible cause of swellings on the ventral aspect of the neck**

### ◆ CLINICAL IMPACT

The thyroglossal cyst in this cat was much larger than the typical cyst in humans. Although this is just the second thyroglossal cyst reported in a cat, the large size of the cyst that attracted attention suggests that smaller cysts in cats probably go unnoticed.

The age of the cat at the time a thyroglossal cyst was first diagnosed might be considered unusual. However, developmental cysts often are subclinical until aggravated by trauma or infection and then enlarge to the point of attracting attention later in life.

Brachial (pharyngeal) pouch cysts also cause ventral cervical swellings, but they occur off the midline. A midline cyst that occurs anywhere from the base of the tongue to the normal location of the thyroid just caudal to the larynx should be considered a thyroglossal cyst until proven otherwise. It should also be noted that the risk of ectopic thyroid tissue is higher in patients with thyroglossal cysts.



## Hyperthyroidism and Struma Cordis

Olson EE, Bulmer BJ, Heaney AM. Hyperthyroidism associated with probable struma cordis in a young dog. *J Vet Intern Med* 2007; 21:332–335.

### \* INTRODUCTION

**Background:** In dogs, hyperthyroidism usually results from a primary neoplasm of the thyroid gland, typically a carcinoma. Thyroid tumors causing hyperthyroidism are typically palpable in the ventral cervical area. However, thyroid tissue originates during embryogenesis from a midline evagination of the pharyngeal epithelium, migrating caudally as the heart descends. Thus, remnants of thyroid tissue may occur at any location from the tongue to the heart. Struma cordis is ectopic, benign thyroid tissue in the heart.

**Objectives:** The purpose of this report was to describe the clinical findings of a dog with ectopic thyroid tissue in the heart that caused hyperthyroidism.

### ▲ SUMMARY

**Case Report:** A 2-year-old, mixed breed, dog was presented for routine examination without a complaint of illness. Mild hyperthermia, a slightly thin body condition, dull hair coat, mild seborrhea sicca, and an irregular cardiac rhythm were identified on examination. A normal sinus rhythm with left anterior fascicular block was present on electrocardiogram. An echocardiogram demonstrated normal cardiac chamber size and function but also the presence of a 1.4 cm diameter mass arising from the right infundibular ventricular surface just proximal to the pulmonic valve. Serum  $T_4$ ,  $fT_4$ , and  $T_3$  were elevated. Thyroid scintigraphy with technetium pertechnetate showed uptake in the cardiac mass but not in the thyroid glands. The dog was administered 0.58 mCi/kg  $^{131}I$  for treatment of the presumed thyroid tissue in the heart.

Two months later, the cardiac mass remained the same size but the serum  $T_4$  concentration decreased into the reference

range. The mass decreased slightly in size at 10 months, and at 12 months after treatment the mass had decreased further in size but was still clearly present. Uptake of technetium was noted in the thyroid glands but not in the cardiac mass on repeat scintigraphy 10 months after radioiodine. The dog was reported to be normal two years after treatment.

**Conclusions:** The cardiac mass was consistent with intracardiac thyroid tissue, similar to that found with struma cordis.

### ◆ CLINICAL IMPACT

The thyroid and heart have proximal origins. The heart can incorporate thyroid tissue, or during migration into the chest the heart can drag thyroid tissue. Heart base and intracardiac tumors in dogs can therefore be of thyroid origin.

The cardiac mass described in this case was not biopsied, so it is not clear if the thyroid tissue was normal, hyperplastic, or neoplastic. Because hyperthyroidism was found in this dog, it seems likely that the thyroid tissue in the heart was abnormal, possibly an adenoma or carcinoma. Since administration of a relatively low dose of radioiodine compared with that given as treatment for thyroid carcinoma was effective in resolving the hyperthyroidism and reducing the size of the cardiac mass, a benign process seems likely. While extremely rare, struma cordis in humans often causes clinical signs due to right ventricular outflow tract obstruction, and hyperthyroidism is not reported.

The cardiac mass was consistent with intracardiac thyroid tissue



## Plasma Parathyroid Hormone-Related Protein in Dogs

*Mellanby RJ, Craig R, Evans H, et al. Plasma concentrations of parathyroid hormone-related protein in dogs with potential disorders of calcium metabolism. Vet Rec 2006;159:833–838.*

### \* INTRODUCTION

**Background:** Hypercalcemia in dogs can be caused by malignancy, hypoadrenocorticism, renal failure, primary hyperparathyroidism, hypervitaminosis D, granulomatous diseases, and non-malignant skeletal lesions. The most common cause is malignancy, and the mediator is usually parathyroid hormone-related protein or peptide (PTHrp). The plasma concentrations of PTHrp that should be expected in other causes of hypercalcemia in dogs are not well known.

**Objectives:** The purpose of this study was to measure the plasma concentrations of total calcium, ionized calcium, albumin, PTH, and PTHrp protein in dogs with lymphoma, primary hyperparathyroidism, and apocrine gland adenocarcinoma of the anal sac.

### ▲ SUMMARY

**Methods:** The plasma concentrations of total calcium, ionized calcium, albumin, PTH, and PTHrp were measured in 25 dogs with lymphoma, nine dogs with primary hyperparathyroidism, and seven dogs with apocrine gland adenocarcinoma of the anal sac. The plasma concentrations of total calcium, ionized calcium, albumin, and PTHrp were measured in 18 healthy control dogs. PTHrp concentrations were determined by an immunoradiometric two-site assay.

**Results:** Twelve of 14 dogs with hypercalcemia from a malignancy had elevated plasma PTHrp concentrations. Plasma PTHrp concentrations were within reference range in control dogs, 17 dogs with lymphoma and normal plasma calcium concentrations, and seven dogs with parathyroid adenomas that produced hypercalcemia.

**Conclusions:** Most dogs with hypercalcemia and malignancy, particularly lymphoma or anal sac adenocarcinoma or parathyroid carcinoma have elevated plasma concentrations of PTHrp in excess of 1.5 pmol/l. Normocalcemic dogs or dogs with hypercalcemia from parathyroid gland adenomas have plasma concentrations of PTHrp of less than 1.5 pmol/l.

### ◆ CLINICAL IMPACT

Measurement of PTHrp concentrations by an immunoradiometric two-site assay usually provides evidence of hypercalcemia of malignancy when the malignancy is a solid tumor. However, not all malignancies associated with hypercalcemia are mediated by PTHrp. Other mediators are believed to be osteoclast-activating factor, prostaglandins, interleukin-6, tumor necrosis factor, or hydroxyvitamin D products of tumors.

Plasma PTHrp concentrations should be measured in all dogs with hypercalcemia where the cause is unknown. Those with plasma PTHrp concentrations in excess of 1.5 pmol/l should be suspected of having a solid malignancy. Careful examination for lymphoma or anal sac adenocarcinoma should be the first tumors to consider. Normal plasma PTHrp concentration does not entirely eliminate the possibility of hypercalcemia of malignancy however.

**Plasma PTHrp concentrations should be measured in all dogs with hypercalcemia where the cause is unknown**



## Primary Hyperparathyroidism in Keeshonden

Goldstein RE, Atwater DZ, Cazolli DM, et al. Inheritance, mode of inheritance, and candidate genes for primary hyperparathyroidism in keeshonden. *J Vet Intern Med* 2007;21:199–203.

### \* INTRODUCTION

**Background:** Keeshonden are predisposed to development of primary hyperparathyroidism, and make up at least 25% of the population of dogs diagnosed with this disorder. It is diagnosed by finding an elevated or inappropriately normal serum PTH concentration in a dog with an elevated ionized calcium. Numerous gene mutations have been identified to cause familial hypercalcemia in humans.

**Objectives:** This study was designed to determine the mode of inheritance of primary hyperparathyroidism in the keeshond breed and to investigate several genes for potential causes of the disorder.

### ▲ SUMMARY

**Methods:** Blood samples from 176 keeshonden, including 34 with primary hyperparathyroidism were used to establish a DNA bank for the breed. Information regarding the parathyroid status of the dogs and a five generation ancestry of the dogs was used to construct a pedigree. This information was used to predict the mode of inheritance. DNA from 4–12 keeshonden with primary hyperparathyroidism and 2–8 without the disease was analyzed for one of four genes where mutations in humans have been shown to cause inherited primary hyperparathyroidism. A parathyroid tumor from a keeshond with primary hyperparathyroidism and a normal parathyroid gland from a mixed breed dog had mRNA isolated and amplified with primers associated with genes known to cause primary hyperparathyroidism in humans.

**Results:** The mean age at diagnosis of primary hyperparathyroidism was 9.8 years, with a range of 6.2–13.7 years. Pedigree analysis showed that the incomplete dominant mode of inheritance was most likely, and that all affected dogs were heterozygous for the pri-

mary hyperparathyroidism trait. Screening of DNA for mutations of candidate genes for primary hyperparathyroidism failed to identify an abnormality. Similarly, no mutation in four genes that cause primary hyperparathyroidism in people were identified in the parathyroid tumor from a keeshond.

**Conclusions:** Primary hyperparathyroidism is a genetic disease and is transmitted in an autosomal dominant mode in keeshonden.

**Primary hyperparathyroidism is a genetic disease in keeshonden**

### ◆ CLINICAL IMPACT

Because of the prevalence of primary hyperparathyroidism in keeshonden, a genetic basis to the disease has been known for many years. This study confirmed the genetic basis and showed its mode of inheritance. Because only heterozygotes were identified, it is likely that the homozygous state is lethal. Although none of the genes tested identified the mutation that causes primary hyperparathyroidism, further evaluation has recently resulted in the development of a screening test that can be used to eliminate the disease from the keeshond breed.





## Evaluation of Treatments for Primary Hyperparathyroidism

Rasor L, Pollard R, Feldman EC. Retrospective evaluation of three treatment methods for primary hyperparathyroidism in dogs. *J Am Anim Hosp Assoc* 2007;43:70–77.

### \* INTRODUCTION

**Background:** Primary hyperparathyroidism is usually caused by a parathyroid adenoma in one of the four parathyroid glands.

Surgical excision has been the standard treatment for adenomas, but less invasive techniques have recently been introduced. Destruction of the parathyroid gland using ultrasound to guide a needle into the affected gland for injection of ethanol or application of heat have been successful in some reports.

**Objectives:** This study compares the efficacy of surgery, ethanol ablation, and heat ablation for treatment of primary hyperparathyroidism in dogs.

### ▲ SUMMARY

**Methods:** Records of 110 dogs with primary hyperparathyroidism that were treated with surgical excision, ultrasound guided ethanol ablation, or ultrasound guided radiofrequency heat ablation were evaluated retrospectively. Ethanol ablation was performed with dogs under general anesthesia by injection of 96% ethanol into the parathyroid gland using a 27 gauge needle directed using ultrasound. Similarly, radiofrequency heat ablation was accomplished in anesthetized dogs using ultrasound to guide a catheter into the parathyroid gland to apply radiofrequency energy to the gland.

**Results:** A single, unilateral parathyroid mass was found on cervical ultrasound in 96 dogs, while two masses were noted in 14 dogs. Parathyroidectomy was performed in 47 dogs, ethanol ablation in 15, and radiofrequency heat ablation in 48 dogs. Parathyroidectomy was successful in 44 of 47 dogs, ethanol ablation in 12 of 15 dogs, and heat ablation in 43 of 48 dogs. Of the three dogs where parathyroidectomy failed, one had resolution of

hypercalcemia with a second surgery. Neither of the remaining two dogs was treated again, but no parathyroid tissue was identified on histopathology of tissue excised at surgery.

The outcome of parathyroidectomy was significantly better than that of ethanol ablation, but not heat ablation. Hypercalcemia resolved more slowly in dogs undergoing heat ablation compared with either parathyroidectomy or ethanol ablation. However, all dogs that responded to heat ablation had resolution of hypercalcemia within six days of the procedure.

Hypocalcemia was the most common complication after each procedure, occurring in 18 of 47, seven of 15, and 16 of 48 dogs with parathyroidectomy, ethanol ablation, and heat ablation, respectively. Symptomatic hypocalcemia occurred in only 12 of the 41 dogs that became hypocalcemic after the procedures. Cough or change in bark occurred after ethanol ablation in three dogs, these complications or Horners syndrome occurred in one dog each in the heat ablation group.

**Conclusions:** Parathyroidectomy is the most effective treatment for primary hyperparathyroidism with the fewest complications, but radiofrequency heat ablation is an effective alternative.

### ◆ CLINICAL IMPACT

Parathyroidectomy performed by an experienced surgeon is nearly always effective treatment for primary hyperparathyroidism. However, care must be taken to properly identify the enlarged parathyroid gland or glands as cervical ultrasound does not always correctly identify the affected gland. Unaffected parathyroid glands should be atrophied in a chronically hypercalcemic dog. The use of less invasive techniques, particularly heat ablation, is an alternative to surgery, but success is, in part, dependent on experience. The reason

for an alternative to parathyroidectomy that is less effective and more difficult for most veterinarians to perform safely than parathyroidectomy is not apparent.

**Parathyroidectomy is the most effective treatment for primary hyperparathyroidism with the fewest complications**



## Variability of Home-Measured Daily Blood Glucose Concentrations in Diabetic Cats

Alt N, Kley S, Haessig M, et al. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc* 2007;230:1011–1017.

### \* INTRODUCTION

**Background:** One of the shortcomings of blood glucose curves is that the stress associated with blood collection during hospitalization can alter the blood glucose measurements. At home monitoring of blood glucose can be effectively accomplished by many owners that have been trained in the use of lancets and hand held glucometers. Results of blood glucose curves obtained during hospitalization are often different than those obtained by owners at home in diabetic cats, and the glucose concentrations are often lower measured by the in-hospital measurements.

**Objectives:** This study was performed to assess the variability of blood glucose curves performed at home compared with those obtained in hospital.

### ▲ SUMMARY

**Methods:** Seven cats with diabetes mellitus had blood glucose curves performed at home on two consecutive days and again in the hospital on one day within a week of the at home measurements. This protocol was repeated a minimum of four weeks later after any adjustment in insulin dosage had been made. All owners had been trained in the proper technique to measure blood glucose. Blood samples were obtained every two hours for 12 hours beginning immediately before an insulin injection. History, physical examination, and serum fructosamine concentration were also evaluated at the time of the blood glucose curves. Based on clinical evaluation and serum fructosamine, cats glycemic control was determined to be well controlled or poorly controlled. Comparison of the pre-treatment, nadir, maximum, mean, and fasting minus nadir blood glucose concentrations as well as the time to nadir glucose and area-

under-the-curve of blood glucose during the blood glucose curve were compared between the various times.

**Results:** The variability between blood glucose curves was quite large, with coefficients of variations of the parameters measured ranging from 69–101%. There was no difference in the variability between in-hospital and home glucose curves. The fasting, maximum, and mean blood glucose concentrations as well as the area-under-the-curve were lower in the first vs. the second home curve. The clinic glucose curve had higher fasting and maximum blood glucose concentrations than the first, but not the second home glucose curve.

When theoretical recommendations for altering insulin dosage were applied to the individual blood glucose curves from all sequential home measurements, only six of 14 paired curves would have resulted in the same treatment recommendation. When comparisons were made between home and clinic glucose curves, agreement on treatment decisions occurred 50% of the time. Cats that had good glycemic control were somewhat more likely to have agreement between glucose curves than those that were poorly controlled.

**Conclusions:** There is considerable variability in blood glucose curves performed in the home environment.

### ◆ CLINICAL IMPACT

The variability of results noted in blood glucose curves when obtained in the home environment indicates that stress is unlikely to be the only factor causing inconsistencies in blood glucose. Potential reasons for the variability include differences in absorption of insulin from specific sites of injection, exercise, food intake, and small errors in dos-

age. The lack of repeatability in blood glucose curves can be frustrating and confusing.

Once diabetes mellitus is well controlled by insulin administration, glucose curves should not be performed unless there is a specific reason to do so as owner assessment of clinical signs and physical examination may better reflect the response to treatment. Serum fructosamine can be useful, although it can be misleading if used alone as there is considerable overlap in fructosamine in well and poorly controlled diabetics. While the glucose curves of cats that were well controlled were more consistent between dates, this has not been shown in other studies. The optimal method of assessing treatment probably lies in some combination of the above tests.

*Stress is unlikely to be the only factor causing inconsistencies in blood glucose in the home environment*



## Urinary Tract Infections in Cats with Hyperthyroidism or Diabetes Mellitus

Mayer-Roenne B, Goldstein RE, Erb HN. Urinary tract infections in cats with hyperthyroidism, diabetes mellitus and chronic kidney disease. *J Fel Med Surg* 2007;9:124–132.

### \* INTRODUCTION

**Background:** Diabetes mellitus and chronic renal failure predispose affected individuals of many species to infection of the urinary tract (UTI). While the prevalence of UTI in cats with diabetes mellitus and chronic renal failure has been reported to be 10–13% and 17–19%, respectively, studies evaluating hyperthyroid cats for urinary infections are scarce. Because many dogs with UTI and diabetes mellitus are asymptomatic, it is important to determine if the same is true for cats.

**Objectives:** The purpose of the study was to determine the prevalence of UTI in cats with diabetes mellitus, chronic kidney disease, and hyperthyroidism.

### ▲ SUMMARY

**Methods:** Medical records of cats with a diagnosis of hyperthyroidism, diabetes mellitus, or chronic renal failure that had a urine culture performed were retrospectively reviewed. Hyperthyroid cats with concurrent disease, including kidney disease, were excluded. UTI was defined as a positive aerobic bacterial culture of the urine. Findings on routine urinalysis, including specific gravity and the presence of white blood cells (more than 5/HPF) or bacteria, serum chemistries, and complete blood count were evaluated for an association with UTI. In addition, gender, effect of treatment of the primary disease, and clinical signs that could be caused by UTI were recorded.

**Results:** Of the 224 cats identified during the seven years studied, 90 had hyperthyroidism (42 were receiving methimazole at the time of study), 57 had diabetes mellitus, and 77 had chronic renal failure. Eleven of the 90 hyper-

thyroid cats had a UTI, while none had clinical signs of the infection. Only two cats with hyperthyroidism and UTI had pyuria, and eight had bacteriuria. Seven of the 57 cats with diabetes mellitus had UTI. Only one cat with diabetes had clinical signs of dysuria and stranguria. Two of the seven cats with UTI and diabetes had pyuria, and five had bacteriuria. Seventeen of 77 cats with chronic kidney disease had UTI, and four had clinical signs of infection. Eleven cats with kidney failure and UTI had pyuria while 14 had bacteriuria.

Glycosuria was associated with UTI in cats with diabetes and those with chronic kidney disease. Female cats that had hyperthyroidism or chronic kidney disease, but not those with diabetes mellitus, were predisposed to UTI. Eleven of all 224 cats studied had clinical signs consistent with UTI, and urine culture was positive in only six of the 11. *Escherichia coli* (46% of cases) and *Enterococcus faecalis* (27% of cases) were the most common isolates from urine.

**Conclusions:** UTI is a common complication of diabetes mellitus, chronic kidney disease, and hyperthyroidism and a urinalysis alone should not be used to exclude the presence of a urinary infection.

### ◆ CLINICAL IMPACT

The relatively high prevalence of UTI in cats with diabetes mellitus and chronic kidney disease was expected because of dilute urine, glycosuria, and altered function of the innate and adaptive immune systems, but that in hyperthyroid cats was not. The presence of UTI in cats with hyperthyroidism is not readily explainable. Because a control group of either healthy cats or cats with other diseases was not included, the prevalence of UTI in

**In any cat with diabetes mellitus, hyperthyroidism, or chronic kidney disease, a urine culture should be considered part of the routine data base**

the cat population is unknown. Therefore, the 12% prevalence of UTI in hyperthyroidism may not be much higher than in the general population, if evaluated in the same manner as this study.

Most cats with UTI in this study were asymptomatic and routine urinalysis did not always indicate infection. In any cat with diabetes mellitus, hyperthyroidism, or chronic kidney disease, a urine culture should be considered part of the routine data base. In cats without clinical signs, it is not known if treatment of the infection is necessary or not.



## Myelinated Nerve Pathology in Diabetes Mellitus

*Mizisin AP, Nelson RW, Sturges BK, et al. Comparable myelinated nerve pathology in feline and human diabetes mellitus. Acta Neuropathol 2007;113:431–442.*

### \* INTRODUCTION

**Background:** Peripheral neuropathy is a common complication of diabetes mellitus in cats, resulting in weakness and plantigrade stance, primarily of the hind limbs. The clinical signs are usually reversible with adequate control of the diabetes.

**Objectives:** The purpose of this study was to describe the clinical, electrophysiologic, and pathologic changes that occur in diabetic neuropathy of cats and to compare them with those of humans.

### ▲ SUMMARY

**Methods:** Twelve cats with diabetes mellitus underwent physical and neurologic examinations, clinical pathologic testing, electrophysiology including nerve conduction studies, and histopathology and electron microscopy of biopsies of the peroneal nerve (collected three months to three years after diagnosis of diabetes). Nerve samples were also collected from seven non-diabetic cats of similar age for comparison.

**Results:** Blood glucose, glycosylated hemoglobin, and serum fructosamine concentrations were elevated in the diabetic cats. All diabetic cats had signs of peripheral neuropathy that ranged from mild to severe and consisted of a plantigrade stance, irritability when touching and manipulating feet, mild generalized muscle atrophy, decreased postural reactions, and decreased tendon reflexes. Diabetic cats had motor nerve conduction velocity and action potential amplitudes that were less than 50% and 35% of normal, respectively. Nerves from nine of the 12 cats had histopathologic abnormalities visualized on light microscopy. Histopathologic abnormalities included splitting and ballooning of the myelin sheath, demyelination, and loss of

myelinated fibers with a significant reduction in axonal diameter compared with non-diabetic cats. Axonal degeneration was marked, resulting in a 50% decrease in myelinated fiber density. In addition to degeneration, axonal regeneration was present.

**Conclusions:** Both demyelination and axonal degeneration are present in nerves of cats with diabetes mellitus and clinical signs of peripheral neuropathy, similar to lesions noted in humans with the disease.

### ◆ CLINICAL IMPACT

This study indicated that severe neurologic injury is present in most cats with diabetic peripheral neuropathy. Although the clinical signs usually lessen in severity or resolve with adequate control of the diabetic state, it is likely that subclinical neuropathy persists. Thus, weakness can occur fairly abruptly in some cats with diabetic neuropathy if insulin therapy is inadequate.

**Both demyelination and axonal degeneration are present in nerves of cats with diabetes mellitus**



## Survival in Dogs with Insulinoma

Polton GA, White RN, Brearley MJ, et al. Improved survival in a retrospective cohort of 28 dogs with insulinoma. *J Sm Anim Pract* 2007;48:151–156.

### \* INTRODUCTION

**Background:** Insulinomas in dogs are pancreatic islet  $\beta$  cell tumors that are usually malignant and produce excessive insulin. Hyperinsulinemia causes hypoglycemia. The clinical signs of insulinoma are caused by hypoglycemia and the body's reaction to a rapid drop in blood glucose, i.e. epinephrine secretion. The preferred treatment is excision. In most cases, total excision is not possible, but debulking the primary tumor can extend quality and duration of life. Medical treatments are intended to suppress the occurrence of hypoglycemia by counteracting insulin effects with glucocorticoids and, in some cases, also suppressing insulin secretion with diazoxide.

**Objectives:** The purpose of this report was to determine the survival times for dogs with insulinoma and the effect of initial and post-surgical relapse medical treatment.

### ▲ SUMMARY

**Methods:** Twenty-eight dogs with insulinoma were studied retrospectively. All dogs had abnormal insulin:glucose ratios consistent with insulinoma. Twenty-five dogs had abdominal ultrasonograms and 18 dogs had thoracic radiographs. Nineteen of the 28 dogs with insulinomas received a partial pancreatectomy. Eight were treated medically. One dog was euthanized during exploratory laparotomy at the owner's request.

**Results:** Ultrasonography performed poorly in staging insulinomas. Only seven in 25 cases that were examined by ultrasound revealed possible pancreatic tumors. Five of the 21 dogs that had both abdominal ultrasonography and laparotomy had ultrasonographic determination of the final clinical

stage consistent with laparotomy findings. The median survival time for all dogs with insulinoma was 547 days, for dogs with partial pancreatectomy was 785 days, and for dogs treated with prednisolone was 1,316 days.

**Conclusions:** The longevity of dogs treated for insulinoma is improved with medical management, including dogs that have had relapse after partial pancreatectomy.

### ◆ CLINICAL IMPACT

The results of this study indicate that survival times (quantity of life) in dogs with insulinoma are improved with medical treatment using prednisolone. However, the dosage required and possibility of adverse effects affecting quality of life are not mentioned.

Abdominal ultrasonography did not detect the majority of pancreatic tumors or their metastasis to either the regional lymph nodes or the liver. Due to the typical small size of the primary tumor and insulinoma metastases, this finding is not surprising. Also not surprising was the failure to find pulmonary metastasis by thoracic radiography. Insulinomas do not typically metastasize to the lungs.

Dogs with hypoglycemia and an abnormally elevated fasting plasma insulin-to-glucose ratio should have thoracic radiography and abdominal ultrasonography performed prior to laparotomy to excise the primary tumor and accurately stage the neoplasm. The reasons for the exams are not to stage the disease with accuracy without a laparotomy but to properly evaluate an older patient for concurrent problems prior to the surgery. If surgery is not possible or a post-surgical relapse occurs confirmed by another elevated plasma insulin-to-glucose ratio, medical treat-

ment with prednisolone should be begun. A conventionally recommended oral dose of prednisone or prednisolone for insulinomas is 0.5 mg/kg/day.

**Survival times in dogs with insulinoma are improved with medical treatment using prednisolone**





## Paraneoplastic Hypoglycemia due to a Hepatocellular Carcinoma

Zini E, Glaus TM, Minuto F, et al. Paraneoplastic hypoglycemia due to an insulin-like growth factor type-II secreting hepatocellular carcinoma in a dog. *J Vet Intern Med* 2007;21:193–195.

### \* INTRODUCTION

**Background:** Symptomatic hypoglycemia has numerous causes in older dogs, including iatrogenic insulin overdose, hepatic failure, xylitol toxicity, insulinoma, and other paraneoplastic causes. Paraneoplastic hypoglycemia not caused by insulinoma is usually associated with hepatocellular carcinoma, splenic tumors, or leiomyosarcoma. The pathogenesis of the hypoglycemia caused by these non-insulin secreting tumors is largely unknown. Insulin-like growth factor-II (IGF-II) has insulin-like effects, and has been documented to be the cause of paraneoplastic hypoglycemia in some tumors in humans and in one dog with a gastric leiomyoma.

**Objectives:** This report describes a dog with severe hypoglycemia due to an IGF-II secreting hepatocellular carcinoma.

### ▲ SUMMARY

**Case Report:** An 8-year-old, female, mixed-breed dog was evaluated for anorexia, episodic shivering, and generalized seizures induced by mild exercise of one day duration. A cranial abdominal mass was found on examination. Marked hypoglycemia and mild to moderate elevations of alkaline phosphatase and alanine aminotransferase were found on serum chemistries.

A 15 cm diameter, focal hepatic mass was identified on abdominal ultrasound, and numerous hypoechoic foci were present in the liver unaffected by the mass. Serum bile acids were normal and the insulin concentration was below the reference range, ruling out hepatic failure and insulinoma, respectively. Hepatocellular carcinoma was diagnosed by liver biopsy. Serum IGF-II concentration was markedly higher in the hypoglycemic dog compared with that of normal dogs.

Immunohistochemical staining of the liver biopsy of both the affected dog and a normal dog was positive for IGF-II. The dog was treated with prednisone and frequent feedings, but was euthanized 10 days later because of recurrent seizures.

**Conclusions:** The hepatocellular carcinoma caused hypoglycemia in this dog because of excessive secretion of IGF-II.

### ◆ CLINICAL IMPACT

Most non-insulin secreting tumors that cause paraneoplastic hypoglycemia are quite large and readily detectable on physical examination or with diagnostic imaging. It seems likely that excessive IGF-II is responsible for many cases of paraneoplastic hypoglycemia rather than excessive use of glucose, ectopic insulin production, hepatic failure, or other causes that have been postulated. Surgical excision of the tumor or the primary tumor mass is often effective in resolving the hypoglycemia, at least temporarily.

**Serum IGF-II was markedly higher in the hypoglycemic dog compared with that of normal dogs**



## Alopecia with High Urinary Corticoid:Creatinine Ratios and Resistance to Glucocorticoid Feedback

*Cerundolo R, Lloyd DH, Vaessen MMAR, et al. Alopecia in Pomeranians and miniature poodles in association with high urinary corticoid:creatinine ratios and resistance to glucocorticoid feedback. Vet Rec 2007;160:393–397.*

### \* INTRODUCTION

**Background:** An idiopathic bilateral alopecia is relatively common in Pomeranians and miniature poodles. Many, possibly all, may have the same cause. The condition was referred to initially as “pseudo-Cushing’s” syndrome since thyroid and gonadal hormone concentrations were normal and other signs of hyperadrenocorticism, such as a pendulous abdomen and polyuria and polydipsia, did not occur. Later, an adult-onset growth hormone deficiency (“growth hormone responsive alopecia”) was proposed, but not substantiated. More recently, a bilateral hyperadrenocorticism caused by a congenital tardive steroidogenesis enzyme deficiency has been suspected, but proof was scant.

None of these proposed causes have been proven as a unifying source of bilateral alopecia in Pomeranians and miniature poodles with normal thyroid and gonadal hormone concentrations. A new theory that such cases are the result of mild and fluctuating hyperadrenocorticism has now been suggested.

**Objectives:** The aim of this investigation was to determine if alopecia in Pomeranians and miniature poodles non-associated with hypothyroidism or gonadal hormones is caused by mild and fluctuating hyperadrenocorticism.

### ▲ SUMMARY

**Methods:** Twenty-two Pomeranians and 12 miniature poodles with idiopathic bilateral alopecia were investigated. All alopecic dogs were otherwise healthy and, unlike dogs with classic hyperadrenocorticism, had normal serum alkaline phosphatase activity. Eighteen clinically normal Pomeranians and three clinically normal miniature poodles were used as controls. Basal urinary corticoid:creatinine

ratios (UCCRs) were measured on 10 consecutive mornings. An oral low-dose (0.01 mg/kg) dexamethasone suppression test was done using changes produced every two hours for 10 hours in UCCRs as a response assessment. A high dose (0.1 mg/kg, every eight hours for 24 hours) dexamethasone suppression test was also performed

**Most dogs with idiopathic alopecia called “alopecia X” respond favorably to suppression of adrenocortical activity with mitotane or trilostane**

**Results:** The basal UCCRs in dogs with alopecia varied widely and overlapped with healthy Pomeranians, although the mean basal UCCRs were significantly higher in alopecic dogs than non-alopecic dogs. Mean low-dose dexamethasone suppression UCCRs were significantly higher in 12 alopecic Pomeranians and eight alopecic miniature poodles compared to control dogs. Seven alopecic Pomeranians and five alopecic miniature poodles had significantly suppressed UCCRs after high-dose dexamethasone administration.

**Conclusions:** Idiopathic alopecia in Pomeranians and miniature poodles can be associated with increased cortisol production, resistance to glucocorticoid feedback on the hypothalamus and pituitary, and suppression by high dose dexamethasone administration despite the lack of classical hyperadrenocorticism physical and laboratory serum biochemistry findings.

### ◆ CLINICAL IMPACT

Most dogs with idiopathic alopecia called “pseudo-Cushings”, “growth hormone responsive alopecia”, congenital tardive “adrenocortical hyperplasia”, or “alopecia X” respond favorably to suppression of adrenocortical activity with mitotane or trilostane. Although a good screening exam for possible hyperadrenocorticism, the urine test used in

this study (corticoids) is not specific for urinary cortisol. Other adrenocortical steroids may have been in excess in the urine. This might explain the lack of physical and laboratory serum biochemistry findings typical of classical hyperadrenocorticism while responding to drugs that suppress adrenocortical activity.



## Hypokalemic Respiratory Failure from Hyperaldosteronism

Haldane S, Graves TK, Bateman S, et al. Profound hypokalemia causing respiratory failure in a cat with hyperaldosteronism. *J Vet Emerg Crit Care* 2007;17:202–207.

### \* INTRODUCTION

**Background:** Hyperaldosteronism is typically caused by an adrenal tumor that secretes high levels of aldosterone. Excessive aldosterone causes renal excretion of potassium and hydrogen ions resulting in hypokalemia consistently and metabolic alkalosis in some cases. In addition, hypertension is a common consequence of the disease. Weakness secondary to hypokalemia is one of the most common clinical signs of hyperaldosteronism.

**Objectives:** This report describes a cat with primary hyperaldosteronism and severe hypokalemia that contributed to marked hypoventilation.

### ▲ SUMMARY

**Case Report:** A 15-year-old, spayed female cat was evaluated for severe hind limb weakness, depression, and anorexia of one day duration. Significant findings on physical examination included a grade III/VI heart murmur, dry mucous membranes, weak pulses, and severe weakness of the hind limbs. Indirect systolic blood pressure was 160 mm Hg. Mild anemia with a mild regenerative response was found on complete blood count. Mild elevations of serum urea nitrogen, creatinine, and bilirubin were present. Hyperglycemia (268 mg/dl), glycosuria, isosthenuria, mild hypophosphatemia, and a moderate elevation of cholesterol were also noted.

Serum potassium was 2.7 mEq/L (reference range 3.8–5.4 mEq/L). Lactated Ringer's solution with 24 mEq/L KCl added was administered at 6 ml/kg/h in addition to ranitidine for eight hours. Increased respiratory effort was noted and progressed to respiratory distress, cyanosis, bradycardia and severe hypothermia. Marked hypokalemia (potassium less than 2.0 mEq/L), severe

hypercapnia (pCO<sub>2</sub> of 115 mm Hg), and severe mixed metabolic and respiratory acidosis were present.

The cat was anesthetized and positive pressure ventilation was instituted along with measures to resolve the hypothermia. An infusion of potassium at 0.7 mEq/kg/h was initiated as was further intravenous fluid therapy with 0.9% saline. Ventilation maintained oxygen saturation as measured by pulse oximetry at 99% for the first hour, when it decreased to 90%. After muffled lung sounds were detected, thoracocentesis yielded free air consistent with pneumothorax. The cat was soon euthanized.

Necropsy revealed an unilateral adrenal adenoma with atrophy of the contralateral adrenal cortex, pneumothorax, atelectasis, a 4 mm mass in one lung lobe, chronic interstitial nephritis and glomerulonephritis, and concentric myocardial hypertrophy. The lung mass was diagnosed as a carcinoma. Serum aldosterone concentration was markedly elevated.

**Conclusions:** Respiratory failure occurred in this cat with primary hyperaldosteronism because of weakness secondary to severe hypokalemia.

### ◆ CLINICAL IMPACT

An antemortem diagnosis was not established in this case as its condition deteriorated rapidly during hospitalization. Based on clinical findings and clinicopathologic tests, the cat may have had diabetes mellitus, hyperadrenocorticism, and renal failure either in addition to, or instead of, hyperaldosteronism. The hind limb weakness may have resulted from diabetic peripheral neuropathy rather than hypokalemia as proposed by the authors. While the plasma aldosterone concentration

was substantially elevated and an unilateral adrenocortical adenoma was found, atrophy of the contralateral adrenal cortex should not have occurred without excessive glucocorticoid from an endogenous or exogenous source. The hypokalemia was likely worsened by the intravenous fluid administration despite supplemental potassium. It is unclear if the hypoventilation resulted from respiratory muscle weakness or a pre-existing pneumothorax.

**Marked hypokalemia, severe hypercapnia, and severe mixed metabolic and respiratory acidosis were present**



## Histological Evaluation of Adrenal Glands Treated with Trilostane for Hyperadrenocorticism

Reusch CE, Sieber-Ruckstuhl N, Wenger M, et al. Histological evaluation of the adrenal glands of seven dogs with hyperadrenocorticism treated with trilostane. *Vet Rec* 2007;160:219–224.

### \* INTRODUCTION

**Background:** Trilostane inhibits production of corticosteroids by inhibiting 3-beta-hydroxysteroid dehydrogenase and other enzymes in the adrenal cortex. However, when used for treatment of pituitary dependent hyperadrenocorticism, some dogs develop acute hypoadrenocorticism that can be permanent. Adrenal gland necrosis has been documented in a few cases.

**Objectives:** The purpose of this study was to examine histologically the adrenal glands of dogs with hyperadrenocorticism that had been treated with trilostane.

### ▲ SUMMARY

**Methods:** Adrenal glands were removed at necropsy from six dogs with pituitary dependent hyperadrenocorticism (PDH) and one with an adrenocortical tumor that were treated with trilostane at a dosage ranging from 2.7 to 17.3 mg/kg for 10 weeks to 25 months. Glands were examined with routine histopathology and were evaluated for evidence of apoptosis.

**Results:** All dogs had a moderate to good response to treatment based on clinical signs and adrenocorticotrophic hormone (ACTH) response tests. One dog died of septic peritonitis while the cause of death was not apparent in the other dogs. Adrenal glands were moderately to greatly enlarged and had irregular surfaces in the six dogs with PDH. One of these dogs had a unilateral pheochromocytoma as well. The dog with an adrenal tumor diagnosed antemortem was found to have a 6 cm diameter adrenocortical adenoma. Diffuse or nodular adrenocortical hyperplasia, primarily of the zona fasciculata, was present in adrenal glands from all dogs, including the

dog with the adrenal tumor. Variable degrees of necrosis were present in adrenals of five dogs. Evidence of apoptosis was found in the necrotic areas of adrenals from three dogs, in the adrenal cortex of one dog without necrosis, and in the cortical adenoma. Adrenocortical hemorrhage of variable severity was present in three dogs. The necrosis and hemorrhage in the adrenal glands was severe in some cases and considered to possibly be sufficient to cause hypoadrenocorticism.

**Conclusions:** Adrenocortical hyperplasia occurs in dogs treated with trilostane and necrosis and hemorrhage can also occur and be severe.

### ◆ CLINICAL IMPACT

The adrenocortical hyperplasia found in all dogs after trilostane treatment for at least 10 weeks is likely the result of elevations of ACTH induced by the lack of negative feedback caused by the inhibition of cortisol production. Ultrasound examination of adrenal glands from dogs with PDH while on trilostane treatment have shown growth and irregularity over time. The findings of adrenal necrosis and hemorrhage are consistent with reports of hypoadrenocorticism during trilostane treatment that persists long after withdrawal of the drug and cause mineralocorticoid deficiency as well as a cortisol deficiency. It is important to recognize that, despite its mechanism of action as an inhibitor of cortisol synthesis, trilostane has the potential to cause acute and severe adrenocortical necrosis that can result in life-threatening hypoadrenocorticism. Unfortunately, information regarding the serum cortisol response to ACTH and serum electrolytes was not provided in this report.

**Trilostane has the potential to cause acute and severe adrenocortical necrosis that can result in life-threatening hypoadrenocorticism**



## Relative Adrenal Insufficiency with Sepsis

Burkitt JM, Haskins SC, Nelson RW, et al. Relative adrenal insufficiency in dogs with sepsis. *J Vet Intern Med* 2007;21:226–231.

### \* INTRODUCTION

**Background:** Relative adrenal insufficiency may occur during periods of sepsis. Relative adrenal insufficiency has been characterized as having a normal to elevated basal serum cortisol concentration and a blunted response to adrenocorticotropic hormone (ACTH) stimulation. Humans with relative adrenal insufficiency and sepsis are reported to have lower mortality rates if treated with low doses of hydrocortisone.

**Objectives:** The goal of this study was to determine if relative adrenal insufficiency occurs in dogs with sepsis and if dogs with relative adrenal insufficiency have higher mortality risk.

### ▲ SUMMARY

**Methods:** Thirty-three dogs with septic diseases and without recent prior treatments that could affect the hypothalamic-pituitary-adrenal axis were included in the study. Basal serum cortisol and endogenous ACTH concentrations were determined, as well as systemic blood pressure. Cosyntropin (synthetic ACTH) was administered and serum cortisol concentration one hour later was measured. Changes in serum cortisol concentration ( $\Delta$  cortisol) in response to cosyntropin were evaluated.

**Results:** Dogs with lower  $\Delta$  cortisol values more frequently had hypotension. If the  $\Delta$  cortisol value was 3.0  $\mu\text{g}/\text{dl}$ , or less, the risk of mortality was 4.1 times greater than dogs with a  $\Delta$  cortisol value of more than 3.0  $\mu\text{g}/\text{dl}$ .

**Conclusions:** Septic dogs with post-ACTH stimulated cortisol that does not rise from baseline by more than 3.0  $\mu\text{g}/\text{dl}$  are at higher risk for hypotension and death.

### ◆ CLINICAL IMPACT

It is well established that glucocorticoids sensitize the cardiovascular system to catecholamines. Deficiency of glucocorticoids causes hypotension. The ill dogs of this report (sepsis was not confirmed in all) were considered to have a “relative” deficiency of glucocorticoids based on subnormal rise in serum cortisol after ACTH stimulation, regardless of the baseline concentration of cortisol. Insufficient response to ACTH stimulation with normal or high baseline cortisol concentration should not directly produce cortisol deficiency-induced hypotension.

Poor response to ACTH stimulation may be a marker for illness severity, hypotension, and a poor prognosis in dogs with systemic inflammatory responses. However, this study does not establish that it is sepsis that causes poor responses to ACTH or that poor response to ACTH is the direct cause of hypotension and poor outcomes. Rather than being called a relative deficiency of glucocorticoids, the phrase “diminished margin of adrenocortical reserve” might be more descriptive of a low  $\Delta$  cortisol value. The findings of this study do not justify or discount the possible advantages of administering glucocorticoids to dogs with a low  $\Delta$  cortisol value.

**Rather than being called a relative deficiency of glucocorticoids, the phrase “diminished margin of adrenocortical reserve” might be more descriptive of a low  $\Delta$  cortisol value**





## Classic Hypoadrenocorticism Compared with Glucocorticoid-Deficient Hypoadrenocorticism

Thompson AL, Scott-Moncrieff JC, Anderson JD. Comparison of classic hypoadrenocorticism with glucocorticoid-deficient hypoadrenocorticism in dogs: 46 cases (1985–2005). *J Am Vet Med Assoc* 2007;230:1190–1194.

### \* INTRODUCTION

**Background:** Classic hypoadrenocorticism was first described by Thomas Addison. Primary hypoadrenocorticism (Addison's disease) is characterized by signs of a destructive process of all zones of both adrenal cortices which are clinical and laboratory findings of mineralocorticoid and glucocorticoid deficiency.

Secondary hypoadrenocorticism is caused by a lack of adrenocorticotrophic hormone (ACTH). ACTH is required for the normal rate of production of glucocorticoids, but it is not a primary stimulus for mineralocorticoid production. Hypotension or hyperkalemia are stimuli for mineralocorticoid production. Some cases of primary hypoadrenocorticism have glucocorticoid deficiency with near-normal mineralocorticoid production.

**Objectives:** The purpose of this study was to compare the patient history, clinical findings, and outcome of dogs having mineralocorticoid and glucocorticoid deficiencies with dogs having solely glucocorticoid deficiency.

### ▲ SUMMARY

**Methods:** The medical records of 46 dogs with hypoadrenocorticism based on ACTH stimulated cortisol concentrations were investigated. Data searched included signalment, patient history, laboratory findings, treatment, and outcome. Dogs were categorized as being mineralocorticoid deficient based on the finding of hyponatremia, hyperkalemia, or both. Dogs were excluded if they had been treated with mitotane or had more than one dose of corticosteroids in the preceding month.

**Results:** Of the 46 dogs with hypoadrenocorticism, 11 were categorized as having solely

glucocorticoid deficiency. The remaining 35 dogs were determined to have classic primary hypoadrenocorticism. Compared to dogs with classic hypoadrenocorticism, dogs with solely glucocorticoid deficiency were older and more frequently had anemia, hypoalbuminemia, and hypocholesterolemia.

**Conclusions:** Solely glucocorticoid deficient hypoadrenocorticism is more common in referral hospital patients than previously recognized. Dogs under stress with the absence of a stress leukogram and chronic signs of gastrointestinal disease should be evaluated by an ACTH-stimulation test prior to more invasive exams to determine a cause of the signs.

**Dogs under stress with the absence of a stress leukogram should be evaluated by an ACTH-stimulation test**

### ◆ CLINICAL IMPACT

The findings of this retrospective study reiterate the inappropriate lack of a stress leukogram being an indication of possible hypoadrenocorticism. Although dogs with chronic signs of gastrointestinal disease were particularly mentioned, a patient under obvious physiologic stress of any kind without a stress leukogram should be evaluated for hypoadrenocorticism.

The authors were impressed by the number of glucocorticoid deficient dogs in their study. Only one dog among 10 with follow-up information was believed to have secondary hypoadrenocorticism and one progressed to also having mineralocorticoid deficiency. The causes for glucocorticoid deficiency in the remaining eight were not identified. The most common cause of glucocorticoid deficiency in dogs is iatrogenic, caused by oral, injectable, or topical glucocorticoid administration. Among the authors' exclusion criteria was the administration of more than one dose of glu-

corticoids in the four weeks prior to diagnosis. However, it is not clear if topical medications with glucocorticoids were considered. Three dogs were still alive one to three years after diagnosis and on continued prednisone administration for a glucocorticoid deficiency. There was no mention of attempted tapered withdrawal.

Dogs with glucocorticoid deficiency should be carefully examined for signs of intracranial disease. If no neurological signs of disease exist, a thorough review of the history of administered medications, including topicals in the last three months is warranted. If iatrogenic secondary hypoadrenocorticism is diagnosed, replacement glucocorticoids should be administered and a controlled tapered withdrawal should be later attempted. Dogs without signs of intracranial disease or evidence of possible iatrogenic hypoadrenocorticism should be repeatedly examined for the possibility that ensuing primary hypoadrenocorticism will eventually lead to mineralocorticoid deficiency.



## Urinary Catecholamine and Metanephrine to Creatinine Ratios

*Kook PH, Boretti FS, Hersberger M, et al. Urinary catecholamine and metanephrine to creatinine ratios in healthy dogs at home and in a hospital environment and in 2 dogs with pheochromocytoma. J Vet Intern Med 2007;21:388–393.*

### \* INTRODUCTION

**Background:** Pheochromocytoma is a neoplasm of the adrenal medulla that has the potential to secrete catecholamines. While many dogs with pheochromocytoma are asymptomatic, clinical signs can occur related to local invasion of the tumor into the surrounding vasculature or release of catecholamines resulting in hypertension, arrhythmias, and clinical signs such as collapse, episodic weakness, and other vague abnormalities. Often, pheochromocytoma is suspected only when an unexplained adrenal mass is found on abdominal ultrasound. Measurement of urine catecholamines and other products of the adrenal medulla in a 24 hour urine sample is commonly used for diagnosis of pheochromocytoma in humans.

**Objectives:** This study was designed to evaluate the effect of hospitalization and diagnostic procedures on urine catecholamine and metanephrine concentrations in dogs.

### ▲ SUMMARY

**Methods:** Fourteen healthy dogs, including nine dogs naive to the hospital environment and five familiar with the hospital, were studied. Voided urine samples were collected in the morning seven days before and one and seven days after presenting to the hospital, and immediately after examination, blood sampling, and ultrasonography. Epinephrine, norepinephrine, dopamine, metanephrine, and normetanephrine were measured in urine samples using high pressure liquid chromatography. Urine creatinine was also measured in each sample and a urine catecholamine:creatinine ratio was calculated. In addition to the normal dogs, two dogs with pheochromocytoma had catecholamines measured in urine collected either during hos-

pitalization or seven days after discharge from the hospital.

**Results:** In dogs unaccustomed to the hospital, epinephrine:creatinine ratios were significantly higher at the time of the hospital visit compared with that seven days after hospitalization. The same dogs had a significantly higher urine norepinephrine:creatinine ratio on initial hospitalization compared with that one and seven days afterwards. Normetanephrine and metanephrine:creatinine ratios were not different between samples collected before, during, or one day after hospitalization in naive dogs. However, metanephrine and normetanephrine:creatinine ratios were lowest seven days after hospitalization, a difference significant when compared with those before, during, and one day after hospitalization. In dogs familiar with the hospital environment, there was no difference in any measurement among the different times. At multiple time points, the group of dogs unaccustomed to the hospital had higher ratios of epinephrine, norepinephrine, dopamine, metanephrine, and normetanephrine:creatinine than those familiar with the hospital. However, the concentrations of all hormones were similar in the two groups seven days after hospitalization. One dog with pheochromocytoma had high norepinephrine and normetanephrine:creatinine ratios while the other dogs with pheochromocytoma had only an increased normetanephrine:creatinine ratio, although the actual values were not provided.

**Conclusions:** Urine catecholamine and metanephrine concentrations increase with the stress of hospitalization, but the effect resolves within one week after discharge.

### ◆ CLINICAL IMPACT

As expected, stress of hospitalization elevated urine catecholamine and, to a lesser degree metanephrine concentrations. Metanephrines are largely derived from consistent metabolism of the catecholamines, epinephrine and norepinephrine, in chromaffin cells. Because of this, metanephrine concentrations are less variable than those of epinephrine and norepinephrine which are subject to abrupt changes in secretion. Because stress has a major influence on these hormones, it will be important to determine their urine concentrations in dogs with illnesses other than pheochromocytoma as well as those in dogs with pheochromocytoma. This assay is not commercially available and further research is necessary for appropriate interpretation of results.

**Stress of hospitalization elevated urine catecholamine and, to a lesser degree metanephrine concentrations**



## Methylprednisolone Acetate Effects on Serum Biochemical Parameters in Cats

*Sharkey LC, Ployngam T, Tobias AH, et al. Effects of a single injection of methylprednisolone acetate on serum biochemical parameters in 11 cats. Vet Clin Path 2007;36:184–187.*

### \* INTRODUCTION

**Background:** Systemic administration of glucocorticoids to dogs for more than two weeks consistently induces increased activity of an isoenzyme of alkaline phosphatase. Elevated serum alkaline phosphatase activity, with an appropriate medical history, can be a marker of iatrogenic hyperadrenocorticism, its severity, and indicator of recovery.

Cats do not have a glucocorticoid-induced isoenzyme of alkaline phosphatase. Reported serum biochemistry abnormalities associated with iatrogenic hyperadrenocorticism in cats have been few. The primary reported laboratory change associated with hyperadrenocorticism in cats has been hyperglycemia caused by insulin antagonism. Conventional wisdom has assumed that cats are relatively resistant to the adverse effects of glucocorticoid administration.

**Objectives:** The aim of this study was to describe clinical serum biochemical changes induced in cats by methylprednisolone acetate administration.

### ▲ SUMMARY

**Methods:** Eleven cats with skin diseases that were treated with a single intramuscular dose of 5 mg/kg of methylprednisolone acetate were examined for changes in serum biochemistry parameters at baseline, 3–6 days, and 16–24 days after treatment.

**Results:** No adverse effects from methylprednisolone acetate were noted. Median serum albumin and bicarbonate concentrations, as well as amylase activity, were increased following the administration of methylprednisolone acetate at both post-treatment sampling periods. At 3–6 days after methylprednisolone acetate administration, serum aspartate

aminotransferase activity and magnesium concentrations were increased, and at 16–24 days following treatment, serum alkaline phosphatase activity and total calcium concentration were increased. Median serum creatinine concentration decreased at both post-treatment sampling periods. Changes among individual cats varied significantly.

**Conclusions:** A single intramuscular dose of methylprednisolone acetate to cats results in significant increases in serum albumin, bicarbonate, calcium, and creatinine concentrations and in amylase, aspartate aminotransferase, and alkaline phosphatase activities, but changes vary considerably among individual cats.

**The serum biochemical changes produced in cats by a single intramuscular injection of methylprednisolone acetate lasted at least three weeks**

### ◆ CLINICAL IMPACT

The serum biochemical changes produced in cats by a single intramuscular injection of methylprednisolone acetate were statistically significant and lasted at least three weeks. Still, the changes were relatively minor and have little clinical significance. The anti-insulin, gluconeogenic, and adrenocortical suppressive effects of long-term effect glucocorticoid administration are more significant in iatrogenic hyperadrenocorticism of longer duration and in producing clinical signs. The effect of methylprednisolone acetate in this short-term, one dose study on serum glucose was apparently insignificant.

## **Rx** Estrogen Receptor Antagonist and Hair Regrowth in Dogs with Alopecia X

Frank LA. Oestrogen receptor antagonist and hair regrowth in dogs with hair cycle arrest (alopecia X). *Vet Dermatol* 2007;18:63–66.

### \* INTRODUCTION

**Background:** A form of bilateral alopecia occurs in Pomeranian dogs that is not caused by hypothyroidism, hyperadrenocorticism, nor functional gonadal neoplasia. It has been referred to as growth hormone responsive alopecia and alopecia X, among other names.

Excessive estrogen inhibits the hair growth cycle in dogs. Estrogen can be formed at the skin by aromatization of androgens. Estrogen effects can also be modified by estrogen receptor sensitivity. If excessive estrogen effects are the cause of alopecia X, an estrogen receptor antagonist may have therapeutic value.

**Objectives:** The purpose of this study was to assess whether an estrogen receptor antagonist, fulvestrant, can cause regrowth in hair in dogs with alopecia X.

### ▲ SUMMARY

**Methods:** Eleven Pomeranian dogs with alopecia X were studied. There were eight males, four castrated and four sexually intact. Two were sexually intact females and one was spayed. All had neither hypothyroidism nor hyperadrenocorticism. Six dogs were randomly assigned to be treated intramuscularly (IM) with 10 mg of fulvestrant/kg or saline. Owners were blinded to the type of treatment. Dogs were monitored with complete blood count, chemistry panel, and urinalysis performed prior to the first treatment, and after the first and second treatment. They were also evaluated for hair growth, the percentage of body affected, and quality of new hair growth. Re-evaluations of physical findings were conducted at the same times as the collection of blood samples, plus additional rechecks by telephone and e-mail to owners.

Three control treatment dogs were treated with fulvestrant after the original study.

Three months after the first treatment, one dog originally treated with fulvestrant and one control treatment dog were treated twice with 20 mg/kg, subcutaneously, a month apart.

**Results:** None of the nine dogs that received 10 mg/kg of fulvestrant/kg, IM regrew any hair. One of the dogs, an intact female, that was twice administered 20 mg/kg, subcutaneously regrew a significant amount of hair a month after the first injection. There were no significant changes in laboratory findings, and no adverse effects noted.

**Conclusions:** Fulvestrant, administered at 10mg/kg, IM, is not effective treatment for alopecia X.

### ◆ CLINICAL IMPACT

Alopecia X may not be one disorder since the underlying cause or causes have not been identified. Some cases respond to gonadectomy, some to trilostane, mitotane, or melatonin. Fulvestrant when administered at a higher than original dose and given subcutaneously rather than IM appeared to be associated with the regrowth of hair in an intact female, but it may not have been the cause of hair regrowth. Since no withdrawal to reproduce hair loss was attempted, whether the association of the regrowth of hair and higher dose of fulvestrant administered subcutaneously was a cause and effect association or just coincidental is unknown. The dose chosen was extrapolated from a human dose. The basis for the frequency of administration was not stated. The dose and/or frequency of administration may have been too low to be effective in most dogs.

If fulvestrant was effective in this single case because of blocking estrogen receptors, a more economical potentially successful option exists by being spayed. Before cases with alopecia X are treated with any expensive drug

or drug with potential serious adverse effects, gonadectomy should be considered.

**Alopecia X may not be one disorder**

# Thyro-Tabs<sup>®</sup>

(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<sup>®</sup> 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 older and middle-aged 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 the 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 and 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 an adequate 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 9 concentrations: 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg and 1.0 mg in 28 tablet strip packs, 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.



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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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