SMALL ANIMAL CLINICAL ENDOCRINOLOGY

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A compendium of leading articles in the field of veterinary endocrinology selected for the veterinary practitioner.

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

David 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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- Low-dose (5 μg/kg) administration of cosyntropin produces equivalent adrenocortical stimulation in healthy dogs and dogs with hyperadrenocorticism. J Am Vet Med Assoc

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- Adrenocortical responsiveness to critical disease is enhanced primarily by the severity of the disease. Revue Med Vet 2006;157:213-218.

- Twice per day administration of trilostane requires a lower total daily dose than once per day administration to effectively and safely control pituitary-dependent hyperadrenocorticism. J Am Anim Hosp Assoc 2006;42:269-276.

- Vacuolar hepatopathy is not unique to hyperadrenocorticism. J Am Vet Med Assoc 2006;229:246-252.

- Aldosterone-to-renin and cortisol-to-ACTH ratios are specific for the diagnoses of primary hypoaldosteronism and primary hypocortisolism, respectively. J Vet Intern Med 2006;20:556-561.

- Alopecia, transient diabetes mellitus, and transient hypothyroidism may be complications of iatrogenic hyperadrenocorticism in cats. J Am Anim Hosp Assoc 2006;42:414-423.

- Budesonide suppresses adrenocortical function within four weeks of administration in dogs, but other adverse effects do not occur. Am J Vet Res 2006;67:1173-1178.

**Adenohypophyseal Disorder Therapies**

## Radiation Therapy for Pituitary Tumors in Cats

Brearley MJ, Polton GA, Littler RM, et al. Coarse fractionated radiation therapy for pituitary tumours in cats: a retrospective study of 12 cases. Vet Comp Oncol 2006:4:209-217.

INTRODUCTION:

**Background:** Primary pituitary tumors in cats are usually tumors of the adenohypophysis. Clinical signs of disease can be caused either by compression of surrounding tissue from the expanding intracranial mass or by excess tropic hormones from a functional tumor, or both. Functional tumors reported in cats secrete adrenocorticotropic hormone or growth hormone causing signs of hyperadrenocorticism or acromegaly, respectively. Both endocrinopathies produce insulin resistance that can lead to secondary diabetes mellitus.

Hypophysectomy is the preferred treatment in humans, but surgical expertise, cost, and post-surgical care has inhibited the common use of hypophysectomy for pituitary tumors in dogs and cats. External beam radiotherapy is the most common method of treating pituitary tumors in dogs. More information on the efficacy of external beam radiotherapy for pituitary tumors in cats is needed.

**Objectives:** The purpose of this report was to describe the efficacy of coarse fractionated radiation on pituitary tumors in cats.

SUMMARY:

**Methods:** Twelve cats with pituitary tumors confirmed by computerized tomography or magnetic resonance imaging were treated with external beam megavoltage radiation using a linear accelerator. Eight cats were castrated males, and four were spayed females. Ages ranged from 5 to 15 years with a mean of 9.8 years. Four of the cats had solely central nervous signs, and eight of the cats had acromegaly with insulin-resistant diabetes mellitus. One cat had both acromegaly and neurological signs. Neurological signs included amaurosis, ataxia or circling, and seizures. In addition to signs of diabetes, the cats with acromegaly had organomegaly, broad facial features, and nasal stertor. Eleven cats had macrotumors viewed on enhanced imaging. One cat with acromegaly had a mass that was within the upper limit of normal size, but the serum insulin-like growth factor concentration was consistent with acromegaly. Five once weekly treatments were given as 5 Gy followed by 8 Gy weekly treatments to a total radiation dose of 37 Gy.

**Results:** Three of the cats with neurological signs had complete remission after radiation therapy although two required corticosteriod therapy. The fourth cat with neurological signs died before treatments were completed.

After the eight cats with unstable diabetes mellitus had their pituitary macrotumor treated by radiation, five cats no longer required insulin administration, one required less insulin, and two became stable on insulin administration. Repeat imaging of the pituitary after completion of radiotherapy revealed reduction in size of the tumor in three cases. The median survival time was 72.6 weeks.

## Conclusions:

External beam coarse fractionated radiotherapy produces good long-term improvement of pituitary tumors in cats.

CLINICAL IMPACT:

Pituitary radiotherapy is the preferred current means of attempting to manage cats with pituitary macrotumors that are causing neurological problems. Results of this study demonstrate that radiotherapy can be an effective means of controlling pituitary macrotumor-associated neurological problems. However, only beneficial effects and survival times were well reported. No adverse effects of the radiotherapy were reported although nausea, otitis media, optic neuritis, and mucositis are among potential complications. One cat died during the radiotherapy. Radionecrosis of the tumor or surrounding brain tissue may have been the cause. None of the cats were necropsied.

Acromegalic cats with diabetes mellitus but without neurological signs of an expanding pituitary tumor can be attempted to be managed without pituitary radiation. No control group of acromegalic cats with diabetes treated only with insulin was included in this study. Despite variable improvement in control of diabetes occurred in the eight diabetic cats with acromegaly treated with radiotherapy, no evidence was provided that survival duration was longer in these cases with radiotherapy than without radiotherapy.

**Note to the publisher- possible pull quote:** Aradiotherapy is an effective means of controlling pituitary macrotumor-associated neurological problems@

## Mitotane Effects on Pituitary Corticotrophs

Taoda T, Hara Y, Takekoshi S, et al. Effect of mitotane on pituitary corticotrophs in clinically normal dogs. Am J Vet Res 2006;67:1385-1394.

INTRODUCTION:

**Background:** Mitotane has been used to treat pituitary-dependent hyperadrenocorticism in dogs for more than 30 years. It is cytotoxic to the adrenal cortex, particularly the zonas fasiculata and reticularis. The direct or indirect effects on pituitary corticotrophs in dogs has not been described although some dogs develop neurological problems soon after being administered mitotane. This could either be a direct adverse effect of mitotane or caused by rapid expansion of a pituitary tumor that had been partially suppressed by hypercortisolemia prior to mitotane administration.

**Objectives:** The goal of this investigation was to determine the effects of mitotane administration on the morphology and function of corticotrophs in normal dogs.

SUMMARY:

**Methods:** Twelve clinically healthy beagles were randomly assigned to either a control group or a mitotane-administration group. Mitotane treated dogs were administered mitotane for a month. Adrenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH) stimulation tests were performed. Magnetic resonance imaging (MRI) was done on the pituitary and brain of dogs treated with mitotane, before and after the administration of mitotane. Dogs were euthanized and necropsied and their pituitaries and adrenal glands examined histologically and the pituitaries by immunohistochemistry.

**Results:** Plasma ACTH concentrations after CRH stimulations were significantly higher in dogs treated with mitotane compared to the control dogs. MRI of the pituitary in mitotane treated dogs revealed significant enlargement compared with pretreatment size. Post-mortem examination revealed atrophy of the adrenal cortex and hypertrophy of corticotrophs. Weights of excised pituitaries were significantly increased in mitotane-treated dogs.

**Conclusions:** Mitotane-induced suppression of adrenocortical function results in hypertrophy and hyperfunction of corticotrophs.

CLINICAL IMPACT:

Nelson=s syndrome is the rapid enlargement of a corticotrophic adenoma after bilateral adrenalectomy for the treatment of hyperadrenocorticism. The effect of mitotane administration is a form of chemical adrenocortico-lectomy. It is logical to assume that mitotane administration could remove cortisol suppression of corticotrophic adenomas and allow for unimpeded growth of a corticotropic pituitary tumor. This occurs in some dogs with pituitary-depended hyperadrenocorticism. However, the morbidity risks and prognostic indicators are not known.

At least two related areas need to be investigated on the basis of the results of this study. One is to evaluate the effects on corticotrophs of hypocortisolemia induced

by adrenal steroid enzyme inhibitors such as trilostane. These too should cause hypertrophy of corticotrophs as did mitotane in this study. The other area that should be investigated is the effect on corticotrophs of dogs with pituitary-dependent hyperadrenocorticism when they are suppressed to eucortisolemia as opposed to the current practice of suppressing cortisol concentration with mitotane or trilostane to subnormal range for maintenance of hyperadrenocorticism. The risk of enhanced growth of corticotrophic adenomas may be greater with hypocortisolemia than with eucortisolemia in dogs with medically treated hyperadrenocorticism.

**Note to the publisher- possible pull quote:** AMitotane administration results in hypertrophy and hyperfunction of corticotrophs.@

**Thyroid Function Testing**

## Comparison of the Biological Activity of Human TSH to Bovine TSH

Boretti FS, Sieber-Ruchstuhl NS, Willi B, et al. Comparison of the biological activity of recombinant human thyroid-stimulating hormone with bovine thyroid-stimulating hormone and evaluation of recombinant human thyroid-stimulating hormone in healthy dogs of different breeds. Am J Vet Res 2006;67:1169-1172.

INTRODUCTION:

**Background:** Serum thyroid hormone concentrations are susceptible to many non-thyroidal influences. Maximal stimulation of thyroid hormone secretion by the administration of thyroid-stimulating hormone (TSH) prior to measuring thyroid hormone sample collection eliminates non-thyroidal influences on fluctuating thyroid hormone concentrations. Although mammalian TSH molecules have species specificity for immunoreactivity, they have cross-species biological effects. The relative biological activity of recombinant human (rh)TSH compared to bovine (b)TSH is not known nor is comparative responses to rhTSH when administered intramuscularly (IM) compared to intravenously (IV) or among various breeds of dogs.

**Objectives:**.The objectives of this study were to compare the biological effects of rhTSH and bTSH in dogs and the response to intramuscular administration of rhTSH to that of IV administration, and to evaluate the effects of rhTSH in various large dog breeds.

SUMMARY:

**Methods:** Eighteen clinically normal beagles were randomly assigned to a group that received 75 μg of rhTSH either IM or IV or 1 unit of bTSH, IM. The three groups were treated in a crossover design. Twenty clinically normal large breed (more than 20 kg) dogs were administered 75 μg of rhTSH, IV. Serum total $T_4$ concentrations were determined before and six hours after TSH administration in all dogs. In addition, serum $T_4$ concentrations were determined at two and four hours after rhTSH, IM in beagles.

**Results:** All dogs had a significant increase in serum $T_4$ concentration after TSH administration without significant differences relating to administration route, type of TSH, or breed of dog.

**Conclusions:** With the dosages used in this study, there is equivalent bioactivity between rhTSH and bTSH in dogs and responses do not significantly differ among breeds of dogs. Euthyroid dogs have serum $T_4$ concentrations of at least 2.5 μg/dl and an increase of at least 1.5 times the pre-stimulation $T_4$ concentration.

CLINICAL IMPACT:

TSH stimulation is the gold standard for diagnosis of hypothyroidism in dogs. Sterile bovine TSH is no longer available as a pharmaceutical preparation, and rhTSH is very expensive. Fortunately, TSH stimulation is only needed for clinical purposes to diagnose equivocal early cases of hypothyroidism. Since TSH is water soluble and not protein bound, IV administration results in the loss of some activity compared with IM administration before receptors can be stimulated. Based on the results of this study,

the poorer response to IV administration of rhTSH compared to IM, rhTSH is not significant.

**Note to the publisher- possible pull quote:** Athere is equivalent bioactivity between rhTSH and bTSH in dogs and responses do not significantly differ among breeds of dogs@

## Effects of Storage on the Effects of Recombinant Human TSH

De Roover K, Duchateau L, Carmichael N, et al. Effect of storage of reconstituted recombinant human thyroid-stimulating hormone (rhTSH) on thyroid-stimulating hormone (TSH) response testing in euthyroid dogs. J Vet Intern Med 2006;20:812-817.

INTRODUCTION:

**Background:** While a diagnosis of hypothyroidism can be made accurately in many cases using a single measurement of serum $T_4$ , free $T_4$ by equilibrium dialysis, and endogenous canine thyroid stimulating hormone (cTSH), many factors can alter results of these tests with subsequent inaccurate diagnostic conclusions. The functional reserve of the thyroid gland has historically been evaluated by measurement of the serum $T_4$ concentration before and after administration of bovine TSH, and has been considered the Agold standard@ method of assessing thyroid function. Bovine TSH is no longer available, but recombinant human TSH (rhTSH) can be readily purchased and is effective in stimulating release of $T_4$ from thyroid glands of normal dogs.

**Objectives:** The purpose of this study was to evaluate the bioactivity of rhTSH following storage under differing conditions.

SUMMARY:

**Methods:** Recombinant human TSH was reconstituted and administered (91.5 μg intravenously) at the time of reconstitution, or after storage for 4 weeks at $4^o$ C or at $-20^o$ C for 8 weeks to 12 healthy dogs. All dogs received each preparation of rhTSH in a random order with a four week period between tests. Serum $T_4$ and free $T_4$ (f $T_4$) concentrations were measured before and four and six hours after intravenous administration of rhTSH.

**Results:** Serum $T_4$ and f $T_4$ concentrations increased significantly after administration of TSH and there was no difference between serum $T_4$ concentrations when the 4 and 6 hour times were compared. There were no differences in the TSH stimulated serum $T_4$ or free $T_4$ concentrations after administration of rhTSH when the different storage methods were compared. No adverse reactions were noted after TSH administration. Serum TSH concentration remained normal and unchanged for 15 months after completion of the study.

**Conclusions:** Human recombinant TSH can be stored reconstituted refrigerated for four weeks or frozen for at least eight weeks without affecting its bioactivity in dogs.

CLINICAL IMPACT:

The TSH stimulation test is a more accurate method for the diagnosis of canine hypothyroidism than measurement of basal hormone concentrations. The primary limiting factor for use of rhTSH in clinical practice will be its cost of approximately $1200 US for a Akit@ containing two 1,100 μg vials. This study did not establish its use in dogs suspected of being hypothyroid, or those with nonthyroidal illness. The optimal dose and expected response in euthyroid and hypothyroid dogs as well as dogs with nonthyroidal illness have yet to be established. Use of the TSH stimulation test should

be restricted to cases where the results of standard testing is equivocal.

**Note to the publisher- possible pull quote:** Athere was no difference between serum $T_4$ concentrations when the 4 and 6 hour times were compared@

**Hyperthyroidism and Thyroid Neoplasia**

## Ionized and Total Serum Magnesium in Hyperthyroid Cats

Gilroy CV, Horney BS, Burton SA, et al. Evaluation of ionized and total serum magnesium concentrations in hyperthyroid cats. Can J Vet Res 2006;70:137-142.

INTRODUCTION:

**Background:** Magnesium is an essential cofactor for many cellular functions that utilize ATP. Magnesium deficiency may contribute to cardiac arrhythmias, weakness, hypokalemia, and hypocalcemia, although overt clinical manifestations appear to be uncommon in small animals. Magnesium circulates, as does calcium, in three different forms, including protein-bound, chelated to anions, and ionized. The most common causes of hypomagnesemia are depletion because of gastrointestinal or renal disease, or lack of intake. Hyperthyroidism can cause hypomagnesemia, but this has not been confirmed in cats.

**Objectives:** The purpose of this study was to evaluate serum total and ionized magnesium concentrations in cats with hyperthyroidism.

SUMMARY:

**Methods:** Total and ionized magnesium concentrations, total $T_4$, and limited biochemistries were measured in serum samples from 15 hyperthyroid cats. Although all hyperthyroid cats had elevated serum $T_4$ concentrations, three had not been treated, seven were receiving methimazole at the time of testing, one had previously been treated with methimazole, and treatment status was unknown for four cats. Similar measurements were made in sera from 40 healthy cats. All samples were obtained anaerobically. Serum from hyperthyroid samples mailed to the laboratory was removed from serum separator tubes and stored with minimal exposure to air at $4^{o}$ C until analyzed. Samples from healthy cats were analyzed immediately after harvesting serum.

**Results:** The mean serum total and ionized calcium concentrations in hyperthyroid cats were not significantly different from those of healthy cats, and the ranges between the groups were very similar. Hyperthyroid cats had a significantly lower mean ratio of ionized to total magnesium concentration and mean total protein concentration than control cats. The decrease in the ionized to total magnesium concentration was due primarily to hyperthyroid cats with a serum $T_4$ concentration above the median (101 nmol/L) for the hyperthyroid group. A negative correlation between ionized magnesium and log-transformed serum $T_4$ concentrations was found in hyperthyroid cats.

**Conclusions:** Serum total protein and ionized to total magnesium ratio were decreased in hyperthyroid cats.

CLINICAL IMPACT:

This study failed to demonstrate any important alterations in serum magnesium in hyperthyroid cats. Because the ranges of serum ionized and total magnesium were

very similar between the groups, it seems very unlikely that hyperthyroidism alone alters serum magnesium. While cats with the highest serum $T_4$ concentrations were more likely to have a low ionized to total magnesium concentration, albumin (the primary binding serum `protein) was not measured in the cats, so it is not clear how alterations in protein binding might have affected these results. Differences in sample handling in the hyperthyroid group where samples were mailed to the laboratory compared with the testing in normal cats that was performed very shortly after sample collection might have influenced the results. In addition, differences in ages of the healthy cats compared with the hyperthyroid cats could have affected the results, but the ages of the healthy cats were not given.

**Note to the publisher- possible pull quote:** Ait seems very unlikely that hyperthyroidism alone alters serum magnesium@

**Multiple Endocrine Neoplasia, Type I, in Cats**

Roccabianca P, Rondena M, Paltrinieri S, et al. Multiple endocrine neoplasia type-I-like syndrome in two cats. Vet Pathol 2006;43:345-352.

INTRODUCTION:

**Background:** Multiple Endocrine Neoplasia (MEN) is a group of multiglandular syndromes believed to be caused by an inherited mutation and loss of function of a tumor suppressor gene, the *menin* gene. Tumors begin to develop at the same time in endocrine organs with the same embryologic precursor in the neuroectoderm. The three best defined types in humans are MEN types I, IIa, and IIb. Major components of MEN, type I, are tumors of the parathyroids, pituitary, and pancreatic islets. The most common tumors involved are chromophobe adenoma, gastrinoma, and multiglandular parathyroid adenomas or hyperplasia.

**Objectives:** The purpose of this study was to describe the findings of MEN-1-like syndrome in two cats and to compare the *menin* gene in cats to that in humans.

SUMMARY:

**Case Reports:** A 12- and a 13-year-old, castrated male, domestic short haired cat were each presented with symmetrical alopecia, polyuria, and polydipsia. Routine laboratory findings were consistent with diabetes mellitus. Dermal atrophy was diagnosed from skin biopsy. Treatment with insulin revealed insulin-resistance. Pituitary-dependent hyperadrenocorticism was investigated as a possible cause of insulin resistance with dermal atrophy and was confirmed by results of a dexamethasone suppression test in one cat and adrenocorticotropic hormone (ACTH) stimulation test in the other cat and abdominal ultrasonography in both. In addition to bilateral adrenal enlargement, one cat also had a pancreatic mass imaged on abdominal ultrasound. The owners requested euthanasia and authorized necropsy of both cats.

Necropsies revealed pancreatic beta cell carcinomas, pituitary corticotroph adenomas, thyroid medullary carcinomas, and parathyroid hyperplasia in both cats. Hepatocellular carcinoma was also present in one of the cats. An attempt to detect feline *menin* gene mutation was unsuccessful.

**Conclusions:** This is the first detailed report of MEN-1-like syndrome in cats.

CLINICAL IMPACT:

A probable case of MEN-1 in a cat was reported in 2005 (J Am Vet Med Assoc 2005;227:101-104) which involved an aldosteronoma, insulinoma, and parathyroid adenoma. The cats of this report had pancreatic beta cell carcinomas, pituitary corticotroph adenomas, thyroid medullary carcinomas, and parathyroid hyperplasia. In humans, most common tumors involved are chromophobe adenoma, gastrinoma, and multiglandular parathyroid adenomas or hyperplasia. The authors described the findings Aconsistent with an MEN-1-like syndrome subtype in humans that has seldom been described.@ No attempt was made in the previous report to detect the gene mutation associated with MEN-1, and the attempt in the present report was

unsuccessful.

The cats of this report were apparently unrelated, and no familial history of either cat was provided. They were elderly and presented with diabetes mellitus and dermal signs suggestive of hyperadrenocorticism which was later confirmed. All other findings were subclinical and detected at necropsy with the exception of detecting a pancreatic mass on abdominal ultrasonography.

Whether these two cats with hyperadrenocorticism and secondary diabetes mellitus with subclinical neoplasia truly represent MEN-1 or they were two older cats that had hyperadrenocorticism, secondary diabetes mellitus, and coincidental subclinical neoplastic changes in pancreas, thyroid, and parathyroids is not clear. Evidence of a mutated gene, familial history, or a combination of endocrine neoplasia that parallels typical MEN-1 in humans and dogs would have provided better evidence of MEN-1 in these cats.

Clinicians should be mindful of possible MEN whenever multiple endocrine neoplasia is detected. However, the typical combination of MEN-1 in cats may not appear as the combination of endocrinopathies and neoplasias in the cats of this report.

**Note to the publisher- possible pull quote:** ANecropsies revealed pancreatic beta cell carcinomas, pituitary corticotroph adenomas, thyroid medullary carcinomas, and parathyroid hyperplasia in both cats.@

**Radioiodine Therapy of Non-resectable Thyroid Tumors**

Turrel JM, McEntee MC, Burke BP, et al. Sodium iodide I 131 treatment of dogs with nonresectable thyroid tumors: 39 cases (1990-2003). J Am Vet Med Assoc 2006;229:542-548.

INTRODUCTION:

**Background:** Thyroid tumors in dogs are usually malignant. Surgical excision is most effective in small tumors and those that are not locally invasive. However, many thyroid carcinomas invade surrounding tissue and are highly vascular, making complete surgical excision difficult. While most thyroid carcinomas in dogs are nonfunctional, they still retain the ability to concentrate iodine and thus are likely to be susceptible to the effects of $^{131}$I administration.

**Objectives:** The objective of this study was to retrospectively evaluate the efficacy of radioiodine treatment in dogs with nonresectable thyroid carcinomas.

SUMMARY:

**Methods:** Medical records of dogs with a thyroid carcinoma that was not surgically resectable and did not receive chemotherapy or external beam irradiation were reviewed. Dogs that had undergone surgical debulking of the tumor were included. Results of thyroid pertechnetate Tc-99m scintigraphy, thoracic radiographs, serum $T_4$, complete blood cell counts, and serum biochemistries performed in each case were reviewed. Dogs with high serum $T_4$ concentration were administered radioiodine shortly after scintigraphy, while dogs with a low or normal $T_4$ concentrations were discharged with instructions to return after being fed a low iodine diet for three weeks so that scintigraphy could be repeated and radioiodine treatment administered. The dosage of $^{131}$I was determined empirically based on tumor size, scintigraphic appearance, and serum $T_4$ concentration. Surgery was performed after radioiodine administration if deemed appropriate.

**Results:** A solitary cervical mass was present in 25 dogs, a mass at the base of the tongue in five, and the mediastinum in two. Metastatic disease was present in the remaining seven dogs. The serum $T_4$ was elevated in 21 dogs, while two dogs were hypothyroid. The mean $^{131}$I dose was 4.2 mCi/kg. Four dogs were treated twice, and one was treated three times. The serum $T_4$ concentration was below the reference range in 29 of 30 dogs in which it was measured at the time of discharge one to two weeks after radioiodine administration. Surgery performed three to six weeks after $^{131}$I treatment resulted in complete resection in eight of 12 dogs. Median survival time was significantly longer for the 32 dogs with local or regional disease (839 days) compared to dogs with metastasis at the time of the procedure (366 days). No other factors evaluated, including surgery, were correlated with survival. Three dogs died of radiation-induced bone marrow suppression 4-18 weeks after $^{131}$I treatment.

**Conclusions:** Radioiodine administration is an effective treatment for thyroid tumors in most dogs whose tumors accumulate sodium pertechnetate.

CLINICAL IMPACT:

The large dose of $^{131}$I required to treat dogs with thyroid carcinoma limits the availability of this treatment because many facilities that treat feline hyperthyroidism are licensed for much smaller quantities of radioactive material. It is not clear how the investigators arrived at the dose of $^{131}$I used in this study. Because 3 dogs developed myelotoxicity that received 0.20 to 0.22 Gbq/kg, a lower dose (0.19 Gbq/kg or less) of radioiodine should be tried. Another study had similar efficacy using dosages that were less than half those of the current study.

Thyroid tumors that cause hyperthyroidism are more susceptible to radioiodine therapy. A surprisingly high proportion of cases in this report from a referral center had hyperthyroidism (54%), perhaps a reflection of selective referrals for radioiodine therapy. Most previous reports of thyroid tumors in dogs have found less than 20% to be hyperthyroid. So, overall results might be less effective in a larger group of dogs that do not have hypersecretion of thyroid hormones.

**Note to the publisher- possible pull quote:** Aa lower dose (0.19 Gbq/kg or less) of radioiodine should be tried@

**Hypothyroidism and Thyroiditis**

## Hypothyroidism and Central Vestibular Disease

Higgins MA, Rossmeisl JH, Panciera DL. Hypothyroid-associated central vestibular disease in 10 dogs: 1999-2005. J Vet Intern Med 2006;20:1363-1369.

INTRODUCTION:
**Background:** Neurological manifestations of primary hypothyroidism are uncommon. When present, the signs usually relate to the peripheral nervous system and include facial nerve paralysis, polyneuropathy, peripheral vestibular disease, and laryngeal paralysis. Hypothyroidism has been associated with central vestibular disease, but the clinical significance of the concurrent appearance of hypothyroidism and central vestibular disease in the dog has not been established.
**Objectives:** The reason for this report was to describe the clinical findings, diagnostic test results, treatment, and outcome of 10 dogs with primary hypothyroidism which also had central vestibular disease.

SUMMARY:
**Methods:** Case records of 10 dogs with primary hypothyroidism and central vestibular disease were examined to determine consistency of clinical findings, diagnostic results, treatment response, and outcome.
**Results:** All dogs were referred for evaluation of progressive neurologic disease. Six were male, and four were females. The median age at presentation was seven years. Neurological examinations indicated lesions in the myelencephalic region and the vestibulocerebellum in five dogs each. Multifocal lesions were diagnosed in two dogs. Typical signs of hypothyroidism were evident in three of the 10 dogs. Laboratory findings consistent with hypothyroidism included hypercholesterolemia in seven dogs and abnormally low serum total and free $T_4$ concentrations. Serum canine thyroid-stimulating hormone concentrations were abnormally elevated in nine of 10 dogs. Indirect blood pressure was normal in five dogs in which it was measured. Eight dogs had intracranial imaging performed. Three had abnormalities suggestive of infarctions. Cerebrospinal fluid analysis revealed elevated albumin concentration in five of six examined dogs. Four dogs were examined by brainstem auditory-evoked potential. Three of the four had abnormal results (prolonged wave V latencies) although their intracranial imaging studies were normal. Within four weeks of initiating thyroxine replacement treatment, vestibular signs resolved in nine dogs.
**Conclusions:** Central vestibular dysfunction in dogs can be a sequelae of hypothyroidism that is reversible with treatment.

CLINICAL IMPACT:
Hypothyroidism is the most commonly diagnosed endocrinopathy in the dog. Some abnormalities are causally associated with it such as alopecia. Other diseases can be coincidentally associated with it. Whether central vestibular dysfunction is causally or

coincidentally associated with hypothyroidism is not fully established by this group of 10 dogs with hypothyroidism and central vestibular dysfunction. However, the similarities of clinical findings and rapid response in resolution of the vestibular signs to treatment for hypothyroidism is good circumstantial evidence.

If a causal relationship exists between hypothyroidism and cerebral infarcts, it is probably due to thromboembolism originating on atherosclerotic plaques. Most of the seven dogs with hypercholesterolemia had serum concentrations that were extremely high. The median was 791 mg/dl with a range of 504 to 1,833 mg/dl. The two dogs with abnormally high serum triglyceride also had marked elevations of 588 and 1609 mg/dl.

Only 10 dogs met the inclusion criteria for this retrospective case study, but 113 dogs with hypothyroidism and vestibular dysfunction were seen by the authors= institution in six years. A prospective study is therefore feasible for the future involving a placebo treatment. A prospective study that involved a placebo group could potentially demonstrate that thyroxine therapy was associated with rapid improvement in central vestibular dysfunction while a placebo is not. Or, it might demonstrate that improvement was spontaneous and not the result of thyroid hormone replacement.

**Note to the publisher- possible pull quote:** AWithin four weeks of initiating thyroxine replacement treatment, vestibular signs resolved in nine dogs.@

**Vaccinations and Thyroiditis**

Scott-Moncrieff JC, Glickman NW, Glickman LT, et al. Lack of association between repeated vaccination and thyroiditis in laboratory beagles. J Vet Intern Med 2006;20:818-821.

INTRODUCTION:
**Background:** Autoimmune thyroiditis is the cause of hypothyroidism in at least 50% of cases. It appears to be an inherited disease in some purebred dogs. Vaccination has been suggested to be responsible for triggering some autoimmune diseases in dogs including hypothyroidism, but proof is lacking.
**Objectives:** The objective of this study was to evaluate the effects of vaccination on the development of autoimmune thyroid disease in dogs.

SUMMARY:
**Methods:** Twenty healthy female beagle dogs were divided into groups of five and received rabies vaccine, a multivalent vaccine, both rabies and multivalent vaccines, or saline in control dogs. The multivalent vaccine or saline was administered at 8, 10, 12, 16, 20, 26, and 52 weeks of age, then every six months. Rabies vaccine was administered at 16 and 52 weeks of age, then annually. Blood samples for measurement of serum total $T_4$ and thyroid stimulating hormone (TSH) concentrations and antithyroglobulin antibodies were collected immediately before and two weeks after each vaccine was administered. Dogs were euthanized at 5.5 years of age, and the thyroid glands were examined for the presence of lymphocytic thyroiditis.
**Results:** Only results of tests performed at 5.5 years were included in this study as other results had been reported previously. There was no difference between groups in serum $T_4$, TSH, or antithyroglobulin antibody levels or thyroid gland weight. Lymphocytic thyroiditis was found in eight of the 20 dogs, including three in the control group, two in the multivalent group, two in the group receiving both vaccines, and one dog receiving rabies vaccine. The serum $T_4$ concentration was significantly lower and the antithyroglobulin antibody level significantly higher in dogs with thyroiditis compared to those without histopathologic abnormalities in the thyroid glands. Two dogs had abnormal thyroid function tests: one with an elevated serum TSH concentration and one with a low serum $T_4$ concentration. No dog showed clinical evidence of hypothyroidism.

**Conclusions:** Vaccination is not associated with the development of autoimmune thyroid disease.

CLINICAL IMPACT:
In an earlier study using the same dogs and research protocol, the investigators reported development of thyroglobulin autoantibodies after vaccination. However, it is likely that vaccination resulted in production of acute phase reactants and other proteins that caused nonspecific interference on the antithyroglobulin antibody assay, resulting in a false positive result. This is supported by the lack of evidence for vaccines causing

autoimmune thyroid disease as found on histopathology of thyroid glands. The high prevalence (60%) of autoimmune thyroid disease in the unvaccinated group was a reflection of the breed predisposition. Vaccination of dogs at risk for the disease being prevented should never be withheld on the basis of possibly inducing hypothyroidism.

**Note to the publisher- possible pull quote:** AVaccination of dogs at risk for the disease being prevented should never be withheld on the basis of possibly inducing hypothyroidism.@

**Thyroid Peroxidase Autoantibodies and Hypothyroidism**

Skopek E, Patzl M, Nachreiner RF. Detection of autoantibodies against thyroid peroxidase in serum samples of hypothyroid dogs. Am J Vet Res 2006;67:809-814.

INTRODUCTION:

**Background:** Approximately 50% of hypothyroid dogs have autoimmune thyroiditis that is associated with autoantibodies to thyroglobulin, $T_4$, $T_3$, or a combination of these. While thyroglobulin autoantibodies are found in many humans with autoimmune thyroiditis, over 90% have autoantibodies directed against thyroid peroxidase. Thyroid peroxidase is the enzyme that is responsible for thyroid hormone synthesis on the thyroglobulin molecule. The autoimmune destruction results primarily from cell-mediated immunity, but anti-thyroid peroxidase antibodies may be involved in the autoimmune process in some cases.

**Objectives:** The purpose of this study was to establish an assay for thyroid peroxidase autoantibodies and to determine the prevalence of these antibodies in dogs with autoimmune thyroid disease.

SUMMARY:

**Methods:** Thyroid peroxidase was extracted from canine thyroid glands and used in an assay to detect antibodies against the enzyme. Serum samples from 195 dogs with autoantibodies to thyroglobulin, $T_4$, and/or $T_3$ and samples from 24 healthy dogs without thyroid autoimmunity were screened for antibodies against thyroid peroxidase using an immunoblot assay.

**Results:** Thyroid peroxidase was successfully extracted from canine thyroid glands. Antibodies to human thyroid peroxidase did not react with the canine molecule. Sera from 33 (17%) of the 195 dogs with autoimmune thyroid disease reacted with thyroid peroxidase. Golden retrievers accounted for 52% of the positive samples but made up only 18% of the population tested. Findings on thyroid function tests of the 33 positive samples included 20 with elevated thyroid stimulating hormone (TSH) and decreased free $T_4$, two with elevated TSH and normal free $T_4$, three with normal TSH and decreased free $T_4$, and eight with normal TSH and free $T_4$ concentrations.

**Conclusions:** An immunoblot assay was successfully developed that detected thyroid peroxidase autoantibodies in a small fraction of dogs with autoimmune thyroid disease.

CLINICAL IMPACT:

The finding that autoantibodies to thyroid peroxidase are uncommon compared with those to thyroglobulin in dogs with thyroid disease is consistent with older studies. The test is difficult to perform because isolation of canine thyroid peroxidase is complex and impractical for diagnostic use. The high prevalence of thyroid peroxidase autoantibodies in golden retrievers with evidence of autoimmune thyroid disease may indicate a unique pathogenesis of thyroiditis in this breed.

**Note to the publisher- possible pull quote:** Aautoantibodies to thyroid peroxidase are

uncommon compared with those to thyroglobulin in dogs with thyroid disease @

## Hypervitaminosis D

### Clodronate Treatment of Hypervitaminosis D

Ulutas B, Voyvoda H, Pasa S, et al. Clodronate treatment of vitamin D-induced hypercalcemia in dogs. J Vet Emerg Crit Care 2006;16:141-145.

INTRODUCTION:

**Background:** Vitamin D toxicosis frequently causes hyperphosphatemia as well as severe hypercalcemia, making soft tissue mineralization and renal failure likely. When treatment with intravenous saline and furosemide fail to lower plasma calcium, as often is the case, other agents such as calcitonin or bisphosphonates are used. Bisphosphonates decrease plasma calcium by inhibiting osteoclast activity.
**Objectives:** The purpose of this study was to evaluate the efficacy of clodronate, a bisphosphonate, administration for treatment of vitamin D toxicosis in dogs.

SUMMARY:

**Methods:** A toxic dose of vitamin $D_3$ was administered to 14 healthy dogs. Twenty-four hours later they were divided into two groups of seven dogs and treated with either a single intravenous dose of clodronate (4 mg/kg) in 150 ml of 0.9% saline, or with 150 ml of 0.9% saline alone. Serum calcium, phosphorus, urea nitrogen, creatinine, albumin, total protein, and alkaline phosphatase activity and urine specific gravity were measured before and 1, 4, 7 and 12 days after vitamin D administration.
**Results:** Dogs in both groups developed vomiting, lethargy, anorexia, weakness, and polyuria beginning 48 hours after vitamin D administration, but the signs were more severe in the control group. Serum calcium and phosphorus increased similarly in both groups of dogs on day 1, but both decreased on day 4 in the clodronate group and were significantly lower in the that the control for the remainder of the study. Serum alkaline phosphatase activity, urea nitrogen, and creatinine were also significantly lower in the clodronate treated group beginning on day 4.
**Conclusions:** Intravenous clodronate can be efficacious in the treatment of hypercalcemia and hyperphosphatemia in dogs intoxicated with vitamin D if administered within 24 hours of the ingestion of excessive vitamin D.

CLINICAL IMPACT:

Bisphosphonates are useful for treating vitamin D toxicosis in dogs provided the drug is administered sufficiently early in the course of disease. Once calcium and phosphorus is deposited in soft tissue such as the renal tubules, the damage is irreversible. A single administration of clondronate has a relatively rapid onset of action and a prolonged duration. The optimal dose of clodronate for treatment of hypercalcemia in dogs has not been determined. Although the dose used in this study was effective at reducing

hypercalcemia, it may be less effective with a higher vitamin D dosage. Intravenous saline and furosemide should always be used to their full effect before resorting to adjunct treatments such as clodronate to lower serum calcium concentration.

**Note to the publisher- possible pull quote:** AIntravenous clodronate can be efficacious in the treatment of dogs intoxicated with vitamin D@

**Diabetes Mellitus and Hyperglycemia**

## Urinary Tract Infections in Diabetic Cats

Bailiff NL, Nelson RW, Feldman EC, et al. Frequency and risk factors for urinary tract infection in cats with diabetes mellitus. J Vet Intern Med 2006;20:850-855.

INTRODUCTION:

**Background:** Diabetes mellitus is associated with a increased incidence of bacterial cystitis in diabetic dogs. Neutrophil bactericidal function is impaired, cellular immunity is impaired, and urine antibacterial properties are diluted. The incidence of bacterial cystitis in diabetic cats has not been evaluated.

**Objectives:** The purposes of this study were to determine the incidence and characteristics of bacterial cystitis in diabetic cats and its risk factors.

SUMMARY:

**Methods:** A review was performed of the medical records of 141 diabetic cats that had antepubic cystocentesis to collect urine for bacterial culture. Only data from initial urine cultures were collected. None of the cats had urethral obstruction or received antibiotics, undergone surgery on the urinary tract, nor been catheterized in the urethra within two weeks of the urine collection.

**Results:** Bacteria were recovered from the urine in 18 (13%) of the 141 cases. The most common bacteria (67%) found was *Escherichia coli* which was susceptible to trimethoprim-sulfamethoxazole in every case and to amoxicillin/clavulanic acid, chloramphenicol, enrofloxacin, and cephalexin in all cases but one each. Female cats were at a significantly higher risk. Clinical signs of lower urinary tract infection and findings on urinary sediment were usually predictive of positive bacterial cultures. All cats with bacterial cystitis examined (16 cats) had either pyuria or bacteriuria, or both. Owners of 56% of diabetic cats with bacterial cystitis had not noticed signs of lower urinary tract infection.

**Conclusions:** Diabetic cats are at increased risk of urinary tract bacterial infection and should be routinely examined by urinary sediment examination or urinary bacterial culture.

CLINICAL IMPACT:

If hyperglycemia from diabetes mellitus is high enough to cause glucosuria and polyuria, signs of lower urinary tract infection will be overshadowed by polyuria. Polyuria will also dilute the urine and reduce the chance of finding bacteriuria or pyuria.

This study found positive bacterial cultures in 11% of newly diagnosed diabetic cats. Urine bacterial cultures and antibiotic sensitivity testing should be a part of the core initial examination of all diabetics regardless of species, case history, or urine sediment findings. Lower urinary tract infections are usually due to ascending bacteria. Due to their relatively short and wide urethra, females will have positive cultures more often than males.

**Note to the publisher- possible pull quote:** A@

**Prognosis for Dogs with Diabetic Ketoacidosis**

Hume DZ, Drobatz KJ, Hess RS. Outcome of dogs with diabetic ketoacidosis: 127 dogs 1993-2003). J Vet Intern Med 2006;20:547-555.

INTRODUCTION:
**Background:** Diabetic ketoacidosis is a serious complication of diabetes mellitus. Insulin resistance, concurrent illness, anorexia, and dehydration are key factors in development of ketoacidosis. The prognosis is guarded, but little information exists regarding outcome of dogs with this disorder.
**Objectives:** The objective of this study was to describe clinical findings and to determine factors that are associated with the outcome of dogs with diabetic ketoacidosis.

SUMMARY:
**Methods:** Diabetic ketoacidosis, defined by the presence of diabetes mellitus, ketonuria, and acidosis based on a venous blood gas was diagnosed in 127 dogs. Medical records were reviewed retrospectively and clinical, clinicopathologic, treatment, and outcome were recorded. The relationship between these data and length of hospitalization, time to initiation of intermediate-acting insulin treatment, and survival were evaluated.
**Results:** Diabetes mellitus had been diagnosed prior to presentation for ketoacidosis in 35% of the cases, while 65% were diagnosed at the time of presentation. Moderate to severe dehydration was present in 91% of cases at presentation, 51% had cranial organomegaly, 36% had abdominal pain, and 30% had cardiac murmurs. Neutrophilia with was the most common abnormality on complete blood count (64%), and a left shift was present in over half of these dogs. Anemia was present in 52%. Hypokalemia was found at presentation or during hospitalization in 92%, hypophosphatemia in 55%, and hypomagnesemia in 60% of cases. Ionized calcium was low in 60% of cases as well. The median pH was 7.3 and base deficit was -14.5. Urinary tract infection was confirmed by culture in 20%, but pyuria was found in only 7% of dogs. A concurrent illness was found in 69% of dogs, with pancreatitis being the most common (41%). Urinary tract infection, hyperadrenocorticism, and bacterial pneumonia were also relatively common. Most dogs received intravenous fluids that usually were supplemented with potassium and less frequently phosphorus or magnesium. Sodium bicarbonate was administered to 34% of dogs. Insulin was administered as a constant rate intravenous infusion in 92% of cases. The median length of hospitalization was 6 days, and the median time to administration of intermediate acting insulin was 79 hours. Serum phosphorus and magnesium concentrations, venous blood pH, and base deficit were correlated with length of hospitalization. Seventy percent of dogs survived and were discharged. Dogs that did not survive had lower ionized calcium, hematocrit, or pH, or higher base deficit than survivors. The only parameter significantly associated with survival on multivariate analysis was a decrease in survival as the base deficit increased.

**Conclusions:** Electrolyte abnormalities, particularly hypokalemia, hypophosphatemia, and hypocalcemia are common in dogs with diabetic ketoacidosis and, along with acidosis, may be associated with mortality.

CLINICAL IMPACT:

It is important to fully assess dogs with diabetic ketoacidosis, because concurrent illness, most commonly acute pancreatitis, glucocorticoid excess, and urinary tract infection, are present in most dogs and must be managed successfully for recovery to occur. Because length of hospitalization and survival were associated with changes in serum electrolytes and acid-base status, diabetic dogs with ketoacidosis should be carefully monitored and treated for electrolyte disturbances that may develop during hospitalization and treatment.

A surprisingly large percentage of dogs in this study were administered sodium bicarbonate. Because ketone body formation accounts for most of the high anion gap acidosis typical in ketoacidosis, insulin, and intravenous fluid administration results in metabolism of ketone bodies, which act as bicarbonate precursors. General recommendations for bicarbonate administration in diabetic ketoacidosis are a pH less than7.1 or hyperchloremic metabolic acidosis. It is possible that bicarbonate administration could result in a more rapid decrease in serum potassium, phosphorus, and ionized calcium concentrations and subsequent detrimental effects.

Potassium concentration was determined in this study to not be associated with mortality. However, it should be noted that the dogs in this study were carefully monitored in a large referral center during treatment. Ketoacidosis and polyuria of diabetes depletes total body potassium, most of which is a masked loss because 95% of the body=s potassium is intracellular. Intensive insulin therapy drives extracellular potassium into cells exacerbating cell membrane hyperpolarization from hypokalemia. This can be life-threatening. Serum potassium concentration should be closely monitored and hypokalemia treated with potassium supplementation, as needed, particularly during initial treatment of diabetic ketoacidosis.

**Note to the publisher- possible pull quote:** Adiabetic dogs with ketoacidosis should be carefully monitored and treated for electrolyte disturbances that may develop during hospitalization and treatment.@

**Tests of Adrenocortical Function**

## Adrenocortical Stimulation Testing with Intramuscular, Low Dose ACTH

Behrend EN, Kemppainen RJ, Bruyette DS, et al. Intramuscular administration of a low dose of ACTH for ACTH stimulation testing in dogs. J Am Vet Med Assoc 2006;229:528-530.

INTRODUCTION:

**Background:** Cosyntropin is a synthetic adrenocorticotropic hormone (ACTH) preparation, and is the only ACTH that is commercially available in the USA. Because the drug is costly, use of smaller doses than the traditional 250 μg per dog have been evaluated. Administration of 5 μg/kg intravenously has been shown to cause an increase in serum cortisol concentration similar to that when higher doses are used. In addition, reconstituted cosyntropin can be stored frozen for six months without degradation, so it is practical to use multiple doses from a single 250 μg vial.

**Objectives:** The purpose of this study was to determine if the route of administration of cosyntropin influenced results of the ACTH response test in healthy dogs and those with hyperadrenocorticism.

SUMMARY:

**Methods:** Nine healthy dogs and nine dogs with hyperadrenocorticism underwent ACTH response testing twice a minimum of six days apart. In each dog, cosyntropin was administered at 5 μg/kg intramuscularly on one occasion and intravenously on another. In healthy dogs, blood samples for measurement of serum cortisol concentration were obtained before and at 30, 60, 90, and 120 minutes after cosyntropin administration, while only basal and 60 minute samples were collected in dogs with hyperadrenocorticism.

**Results:** In healthy dogs, serum cortisol concentrations increased over basal concentrations at all time points after administration of cosyntropin. Regardless of the route of administration, the peak mean cortisol concentration occurred at 60 minutes after cosyntropin, and the peak concentration in all individual dogs occurred at either 60 or 90 minutes. The most consistent increase in serum cortisol concentration was found at 60 minutes post-cosyntropin with both intramuscular and intravenous administration. In dogs with hyperadrenocorticism, there was no difference in cortisol concentrations when the two routes of administration were compared.

**Conclusions:** The ACTH response test can be performed using cosyntropin at a dose of 5 μg/kg either intravenously or intramuscularly.

CLINICAL IMPACT:

Low dose, intramuscular cosyntropin admininistration is a convenient and cost-effective method for performing and ACTH response test for hyperadrenocorticism. In dogs with suspected hypoadrenocorticism or other causes for hypotension, intravenous administration might be a better choice as poor peripheral perfusion from hypotension could impair absorption of ACTH from an intramuscular site.

**Note to the publisher- possible pull quote:** ALow dose, intramuscular cosyntropin admininistration is a convenient and cost-effective method for performing and ACTH response test for hyperadrenocorticism. @

## Adrenocortical Responsiveness in Critically Ill Dogs

Goy-Thollot I, Decosne-Junot C, Berny P, et al. Adrenal responsiveness in critically ill dogs: prospective study. Revue Med Vet 2006;157:213-218.

INTRODUCTION:

**Background:** During critical non-adrenal illnesses, the hypothalamic-pituitary-adrenal axis adjusts to provide more glucocorticoids to assist the stress response. However, studies in critically ill humans suggest that in some cases corticotropin-releasing hormone-mediated adrenocorticotropic hormone (ACTH) response is blunted by cytokines and tumor necrosis factor-alpha leading to relative adrenal insufficiency.

It has not been established if relative adrenal insufficiency occurs in all critically ill dogs or if it does, whether they would benefit from glucocorticoid supplementation during their critical non-adrenal illness.

**Objectives:** The purpose of this study was to evaluate adrenocortical response to ACTH in critically ill dogs and to determine if corticosteroid supplementation would be generally beneficial to dogs in an intensive care unit.

SUMMARY:

**Methods:** The adrenal response was assessed in 34 critically ill dogs with various illnesses and in 32 healthy dogs. Within 24 hours from admission, all dogs were administered ACTH (0.25 mg) intravenously after collecting plasma for determination of basal cortisol and aldosterone concentrations. Cortisol and aldosterone concentrations 45 minutes after ACTH stimulation were also determined. Delta cortisol and aldosterone values were calculated (differences between ACTH-stimulated concentrations and basal concentrations). Systolic blood pressure and serum sodium and potassium concentrations were determined.

**Results:** Twenty-five critically ill dogs were survivors, and nine did not survive. Critically ill dogs had significantly higher basal cortisol concentrations than control dogs, but no significant difference occurred between survivors and non-survivors. ACTH-stimulated cortisol and aldosterone, delta-cortisol, and basal aldosterone concentrations were significantly higher in non-survivors than in survivors. Systolic arterial blood pressure, sodium-to-potassium ratio, and sodium and potassium concentrations were not different between critically ill dogs and control dogs.

**Conclusions:** Adrenocortical responsiveness is activated and may be enhanced by the severity of disease in critically ill dogs.

CLINICAL IMPACT:

During critical illness a variety of stress-induced mediators of ACTH secretion are released. Enhanced ACTH secretion stimulates higher secretion of cortisol and aldosterone. Although hypotension and hyperkalemia are also stimuli for increased aldosterone secretion, increased ACTH secretion alone is sufficient to elevate circulating aldosterone concentrations.

Adrenocortical response to stress is beneficial, at least to point. However, the

highest responses in this study were in the non-survivors of critical illnesses. Without evidence or strong suspicion of hypoadrenocortical responsiveness in patients with critical illness, it is imprudent to administer glucocorticoids or mineralocorticoids to assist the recovery. A point of negative returns of high circulating concentrations of adrenocorticoids, such as expanded intravascular volume with weakened cardiac function, immunosuppression, or other adverse effects of corticosteroids, probably exists since the highest plasma corticosteroid concentrations in this study were correlated with failure to survive.

**Note to the publisher- possible pull quote:** Athe highest plasma corticosteroid concentrations in this study were correlated with failure to survive@

**Hyperadrenocorticism**

## Twice Daily Administration of Trilostane

Alenza DP, Arenas C, Lopez ML, et al. Long-term efficacy of trilostane administered twice daily in dogs with pituitary-dependent hyperadrenocorticism. J Am Anim Hosp Assoc 2006;42:269-276.

INTRODUCTION:

**Background:** Trilostane, an inhibitor of 3-β-hydroxysteroid dehydrogenase and 11-β-hydroxylase, has been found to be an effective treatment for canine hyperadrenocorticism. Multiple studies have evaluated once daily administration of the drug and have found it to be effective in controlling clinical signs of hyperadrenocorticism. However, cortisol secretion is suppressed for only about 12 hours after trilostane administration.

**Objectives:** The purpose of this study was to evaluate the efficacy and safety of twice daily administration of trilostane in dogs with pituitary-dependent hyperadrenocorticism (PDH).

SUMMARY:

**Methods:** Forty-four dogs with PDH were administered trilostane orally at an initial dose of 15 mg, twice per day, for dogs weighing less than 5 kg; 30 mg, twice per day, for dogs 5-20 kg; 60 mg in the morning and 30 mg in the evening for dogs 20-40 kg; and 60 mg, twice per day, for dogs more than 40 kg. Dogs were evaluated prior to treatment and seven days and one, three, and six months after initiating treatment, and then every six months. A recording of the medical history, physical examination, hemogram, serum biochemistries, and an adrenocorticotropic hormone (ACTH) stimulation test were performed at each recheck.

At the initial recheck, the ACTH response test was performed 4-6 hours after the last trilostane treatment. No change in trilostane dosage was made if there was clinical improvement and the post-ACTH plasma cortisol concentration was 1-5 μg/dl. If clinical signs of hyperadrenocorticism persisted and the post-ACTH cortisol was more than 5 μg/dl, the trilostane dosage was increased by 25-50%. If signs of hypoadrenocorticism, such as vomiting, anorexia, weakness, or diarrhea, and the post-ACTH cortisol was less than 1 μg/dl, trilostane was discontinued for two days and subsequently administered at a dosage reduction of 25-50%. If signs of hypoadrenocorticism persisted, trilostane was discontinued for three or more days, and another ACTH stimulation test was performed to determine if trilostane could be continued or if glucocorticoid and mineralocorticoid treatment should be instituted.

At subsequent rechecks, the ACTH stimulation test was performed 8-12 hours after the last trilostane treatment. The target post-ACTH cortisol concentration was 1-9 μg/dl. Clinical signs of hyperadrenocorticism combined with a post-ACTH cortisol concentration more than 9 μg/dl resulted in a dosage increase while signs consistent with hypoadrenocorticism combined with a post-ACTH cortisol less than 1 μg/dl

prompted a dose reduction.
**Results:** Initially, the mean daily trilostane dose was 6.2 mg/kg. The dosage was unchanged in 10 dogs, increased in 19 dogs, decreased in five dogs, and both increased and decreased in 10 dogs. Improvement in clinical signs was noted on the first recheck in 86% of dogs. Eight dogs with persistent clinical signs of hyperadrenocorticism and post-ACTH cortisol concentrations more than 10 μg/dl had their trilostane dosage increased, while five dogs with gastrointestinal signs had their dosage reduced. At one month of treatment, polyuria and polydipsia had resolved in all dogs, although polyphagia and post-ACTH cortisol concentrations more than 9 μg/dl necessitated a dosage increase in 10 dogs. The trilostane dosage was decreased in two dogs with mild gastrointestinal signs and post-ACTH cortisol concentrations less than 1.2 μg/dl. After three months of treatment, 10 dogs had clinical signs and elevated cortisol, so the trilostane dosage was increased, while 1 dog with gastrointestinal signs had its trilostane dosage decreased. At six months, clinical signs and cortisol concentrations resulted in an increase in trilostane dosage in five dogs and a reduction in three. After this time, several dogs continued to require an increase or decrease in the trilostane dosage. Over time, the mean dosage of trilostane increased up to 8.3 mg/kg daily, but the range in individual dogs was quite wide (2.1-18.1 mg/kg). Clinical signs resulting from low plasma cortisol concentration were noted in 11 dogs on one or more occasions and were associated with a post-ACTH cortisol less than 2 μg/dl in all cases and hyperkalemia and/or hyponatremia in about 50% of these cases. Trilostane treatment was discontinued indefinitely in five dogs because of hypoadrenocorticism. Only one of these five dogs required long-term glucocorticoid and mineralocorticoid administration.
**Conclusions:** Twice daily administration of trilostane is a safe and effective treatment for pituitary-dependent hyperadrenocorticism.

CLINICAL IMPACT:
This study found that plasma cortisol concentration was suppressed to the level desired during treatment of hyperadrenocorticism for 8-12 hours after trilostane administration during twice daily treatment. Based on this, twice daily administration of trilostane is a more effective method of consistently controlling hypercortisolemia in dogs with PDH than once daily treatment. While once daily treatment is effective at improving clinical signs of hyperadrenocorticism, more consistent reduction of cortisol concentrations throughout the day should result in more complete resolution of the clinical signs. This may be particularly important in dogs with complications of hyperadrenocorticism such as diabetes mellitus. Although a direct comparison with once daily treatment was not made, the daily total of divided doses of trilostane found effective in the present study was less than the recommended once daily dose for control of PDH.

**Note to the publisher- possible pull quote:** A the daily total of divided doses of trilostane found effective in the present study was less than the recommended once daily dose for control of PDH.@

**Vacuolar Hepatopathy and Hyperadrenocorticism**

Sepesy LM, Center SA, Randolph JF, et al. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). J Am Vet Med Assoc 2006;229:246-252.

INTRODUCTION:
**Background:** Vacuolar hepatopathy is a term that is applied to hepatocytes that accumulate substances such as glycogen or triglycerides packaged in vacuoles. Vacuolar hepatopathy is most commonly thought to be caused by endogenous or exogenous glucocorticoid excess. However, the presence of vacuolar hepatopathy can be found in dogs without a history of glucocorticoid excess.
**Objectives:** The purpose of this study was to determine what disorders, in addition to known glucocorticoid excess, are associated with vacuolar hepatopathy in dogs.

SUMMARY:
**Methods:** A retrospective analysis of medical records from dogs with a histologic diagnosis of hepatocellular vacuolation was performed. Histopathologic findings of all cases was reviewed and only those with vacuolation of more than 25% of hepatocytes were included. The hepatocellular vacuolation was graded as moderate or severe, and the predominant acinar zonal distribution was recorded. Cases were grouped according to the primary diagnosis, including neoplasia, diabetes mellitus, and acquired hepatobiliary, adrenal, neurologic, immune-mediated, gastrointestinal, renal, infectious, portosystemic vascular, cardiac, and miscellaneous disorders.
**Results:** Of 336 cases included in the study, 165 had liver tissue collected at necropsy and 171 had samples collected as biopsies. Neoplasia was the most common diagnosis in dogs with vacuolar hepatopathy (94 dogs), while acquired hepatobiliary disease (43 dogs), adrenal gland dysfunction (40 dogs), neurologic disease (38 dogs), and immune-mediated diseases (34 dogs) were also frequently found. Exposure to excessive glucocorticoids, either exogenous administration of endogenous production, was noted in 55% of cases. Dogs with glucocorticoid exposure were more likely to have severe vacuolar hepatopathy than those without. Zonal distribution of vacuolar change was not related to known glucocorticoid exposure. Elevated serum alkaline phosphatase activity was found in 67% of dogs with vacuolar hepatopathy. Alkaline phosphatase activity was elevated in 124 dogs with glucocorticoid exposure and 102 dogs without exposure, a difference that was not significant. Nine dogs with vacuolar hepatopathy had compromised hepatic function, parenchymal stromal collapse, and regenerative nodules.
**Conclusions:** Vacuolar hepatopathy frequently occurs in dogs without obvious glucocorticoid excess.

CLINICAL IMPACT:
Vacuolar hepatopathy is a consistent finding in dogs with spontaneous or iatrogenic hyperadrenocorticism. This study showed that it commonly occurs in dogs with a variety of systemic illnesses and frequently with a concurrent increase in serum alkaline

phosphatase activity. This may be the result of excess cortisol secretion that is commonly found in dogs with nonadrenal illness, although it seems likely that vacuolar hepatopathy has a multifactorial pathogenesis. Glucocorticoid excess causes glycogen accumulation in hepatocytes, while other disorders can cause lipid accumulation. Special stains are necessary to differentiate the contents of the hepatocyte which was apparently not performed in this study. Another interesting finding was that 1/3 of dogs exposed to glucocorticoid excess apparently had normal alkaline phosphatase activity despite having moderate or severe vacuolar hepatopathy. Glucocorticoid administration consistently results in increased alkaline phosphatase activity in dogs, so the reasons for the lack of increase in some dogs of this study are not clear.

**Note to the publisher- possible pull quote:** AVacuolar hepatopathy commonly occurs in dogs with a variety of systemic illnesses and frequently with a concurrent increase in serum alkaline phosphatase activity. @

**Hypoadrenocorticism**

## Aldosterone-to-Renin and Cortisol-to-ACTH Ratios

Javadi S, Galac S, Boer P, et al. Aldosterone-to-renin and cortisol-to-adrenocorticotropic hormone ratios in healthy dogs and dogs with primary hypoadrenocorticism. J Vet Intern Med 2006;20:556-561.

INTRODUCTION:

**Background:** Primary hypoadrenocorticism usually results in deficient secretion of glucocorticoids ( particularly cortisol) and mineralocorticoids (especially aldosterone). Conventional diagnostic evaluations are assessments of basal and post-adrenocorticotrophic hormone (ACTH)-stimulated plasma cortisol concentrations. However, a selective deficiency of either cortisol or aldosterone occurs occasionally. As primary hypoadrenocorticism develops, plasma cortisol concentration declines with concurrent rise in plasma ACTH. Plasma cortisol-ACTH ratio (CAR) may be more sensitive than either hormone concentration alone in identifying early primary hypoadrenocorticism. In a similar manner, while plasma aldosterone declines in primary hypoadrenocorticism, renin activity increases. The ratio of aldosterone-to-renin (ARR) may be more sensitive than either hormone concentration alone in identifying early primary hypoadrenocorticism.

**Objectives:** The goal of this study was to investigate the usefulness of the CAR and the ARR in diagnosing hypoadrenocorticism in dogs.

SUMMARY:

**Methods:** Reference ranges of plasma cortisol, ACTH, and aldosterone concentrations; renin activity; and CAR and ARR were determined in 60 clinically healthy dogs. The same parameters, plus post-ACTH stimulated cortisol concentrations were measured in 22 dogs with spontaneous primary hypoadrenocorticism.

**Results:** Plasma cortisol and ACTH concentrations were significantly different between healthy dogs and dogs with hypoadrenocorticism. Plasma cortisol concentrations were lower and ACTH concentrations were higher in dogs with hypoadrenocorticism compared to healthy dogs. However, the dog groups= ranges overlapped. CAR ranges did not.

Plasma aldosterone concentration and renin activity were significantly different between healthy dogs and dogs with hypoadrenocorticism. Plasma aldosterone concentrations were lower and renin activities were higher in dogs with hypoadrenocorticism compared to healthy dogs. However, the dog groups= ranges overlapped. AAR ranges did not.

Spayed healthy dogs had plasma aldosterone concentrations and AARs that were significantly lower than sexually intact healthy female dogs.

**Conclusions:** Plasma cortisol, ACTH, and aldosterone concentrations and renin activity, plus CAR and ARR calculations, are collectively diagnostic of primary hypoadrenocorticism in dogs.

CLINICAL IMPACT:

One impetus for this study was the irregular availability and cost of ACTH preparations for ACTH stimulation testing to diagnose hypoadrenocorticism. Although CAR and ARR calculations are a good substitute for ACTH stimulation testing, measurements of plasma cortisol, aldosterone, ACTH, and renin activity are also expensive and some require special handling. ACTH-stimulated plasma cortisol concentration is still preferable when ACTH for injection is available.

Another reason for this study was to assess means to screen for singular mineralocorticoid deficiency. This is a rare endocrinopathy and when present, is associated with electrolyte imbalances (hyponatremia and hyperkalemia). It is more practical to screen for electrolyte imbalances and pursue a definitive diagnosis with aldosterone and renin activity assays, when more appropriate.

**Note to the publisher- possible pull quote:** AACTH-stimulated plasma cortisol concentration is still preferable when ACTH for injection is available.@

**Glucocorticoid Therapy**

## Iatrogenic Hyperadrenocorticism in Cats

Lien YH, Huang HP, Chang PH. Iatrogenic hyperadrenocorticism in 12 cats. J Am Anim Hosp Assoc 2006;42:414-423.

INTRODUCTION:
**Background:** Few cases of iatrogenic hyperadrenocorticism have been reported in the cat. Those that have been reported have had alopecia, thin and fragile skin, polyuria, polydipsia, and secondary diabetes mellitus. Post-adrenocorticotropic hormone (ACTH)-stimulated serum cortisol concentration is suppressed in cats with iatrogenic hyperadrenocorticism.
**Objectives:** The purpose of this study was to retrospectively evaluate cats with iatrogenic hyperadrenocorticism.

SUMMARY:
**Methods:** Twelve cats with a history of chronic corticosteroid administration for at least one month and progressive skin lesions consistent with iatrogenic hyperadrenocorticism were retrospectively studied. A minimum followup of 18 months was required to be included in the study. Initial examinations included a hemogram, serum biochemistry panel, baseline serum $T_4$, baseline serum cortisol, and post-ACTH serum cortisol concentration. Ten cats were evaluated by thyroid hormone stimulating hormone stimulation.
**Results:** Common clinical signs observed were lethargy, polydipsia, polyuria, and thigh muscle atrophy. Alopecia was the most obvious skin abnormality and occurred most often on the head, ears, and trunk. Skin tears occurred in two cats. Abnormal laboratory findings were leukocytosis, increased alanine aminotransferase activity, and hyperglycemia. Serum cortisol concentrations were subnormal in all cases. Eleven of the 12 cats had low serum $T_4$ concentrations. Four cats had secondary diabetes mellitus, and four were suspected of having hypothyroidism and administered levothyroxine for six weeks. Mean recovery time after discontinuing corticosteroid administration was 4.9 months.
**Conclusions:** Iatrogenic hyperadrenocorticism in cats causes transient hypothyroidism.

CLINICAL IMPACT:
Cat are believed to be more resistant to the adverse effects of corticosteroid administration than dogs. This may be true to some extent because cats have been reported to have fewer corticosteroid receptors than dogs. The assumption that cats are resistant to iatrogenic hyperadrenocorticism may be overstated because older cats= hair coat and typical lethargic behavior when not hunting or playing can mask muscle weakness and pendulous abdomen. Cats also do not have an isoenzyme of alkaline phosphatase with activity that is greatly enhanced by corticosteroids, a marker of hyperadrenocorticism in dogs. However, previous reports of the effects of exogenous corticosteroids on differential white blood cell counts and mobilization of hepatic

glycogen appear in cats are comparable to that in dogs and humans.

Because cats with iatrogenic hyperadrenocorticism had low serum $T_4$ concentrations and after eight weeks from corticosteroid withdrawal there was cutaneous hyperpigmented skin similar to hypothyroidism in dogs, it was assumed that iatrogenic hyperadrenoocorticism causes transient hypothyroidism in cats. This was presumptuous, and transient treatment for hypothyroidism during recovery from iatrogenic hypoadrenocorticism as done in this study is not recommended. All cats with iatrogenic hyperadrenocorticism (direct effect of exogenous corticosteroids on peripheral target cells such as the skin) also have iatrogenic hypoadrenocorticism (adrenocortical atrophy from suppression of endogenous ACTH). Excessive corticosteroids suppress thyroid activity, but withdrawal of the excessive corticosteroids is sufficient treatment for the thyroid to regain normal activity. Exogenous thyroid supplementation can impair the speed of recovery of normal thyroid activity from corticosteroid suppression.

Endogenous ACTH secretion is enhanced during recovery of iatrogenic hypoadrenocorticism. ACTH contains $\alpha$-melanocyte stimulating hormone (MSH) as the first 13 amino acids within its structure. As ACTH is cleaved, MSH is released. Prolonged exposure to ACTH and MSH stimulates hyperpigmentation particularly at sites of inflammation, exposure to UV light, or trauma. Hyperpigmentation of the skin during recovery from iatrogenic hyperadrenocorticism is therefore not a reason to administer thyroid hormone supplements.

The cats in this report were abruptly withdrawn from corticosteroid administration. Although each of the cats survived, gradual withdrawal of exogenous corticosteroids is highly recommended since the ability to survive unforeseen stress in the early stages of adrenocortical recovery is certainly impaired.

**Note to the publisher- possible pull quote:** Agradual withdrawal of exogenous corticosteroids is highly recommended since the ability to survive unforeseen stress in the early stages of adrenocortical recovery is certainly impaired.@

## Oral Administration of Budesonide and Adrenocortical Suppression

Stroup ST, Behrend EN, Kemppainen RJ, et al. Effects of oral administration of controlled-ileal-release budesonide and assessment of pituitary-adrenocortical axis suppression in clinically normal dogs. Am J Vet Res 2006;67:1173-1178.

INTRODUCTION:

**Background:** Budesonide is a glucocorticoid developed for oral administration to humans. It is metabolized primarily on first pass through the liver which confines most of its activity to the intestinal mucosa while minimizing its systemic adverse corticosteroid effects. Budesonide has been used in dogs with inflammatory bowel disease with anecdotal evidence of success. The potential for adverse effects in dogs has not been well investigated.

**Objectives:** The aim of this study was to evaluate the effects of controlled-ileal-release (CIR) budesonide on the hypothalamic-pituitary-adrenal (HPA) axis in dogs with a normal gastrointestinal mucosal barrier.

SUMMARY:

**Methods:** Ten healthy dogs were randomly assigned to with a group of five to be treated with budesonide orally or a group of five to receive a placebo for 28 days. Dogs weighing less than 18 kg administered CIR received 2 mg budesonide. CIR-treated dogs weighing more than 18 kg received 3 mg budesonide.

Plasma cortisol concentrations before and after adrenocorticotropic hormone (ACTH) stimulation, endogenous ACTH concentration, and body weight were measured on days 0,7, 14, 21, 28, and 35. Serum biochemical analyses, hemogram, and urinalysis were performed on days 0, 28, and 35. On days 7, 14, and 21 serum alkaline phosphatase and alanine aminotransferase activities, glucose concentration, and urine specific gravity were determined.

**Results:** Basal and post-ACTH stimulated plasma cortisol concentrations and endogenous ACTH concentrations were significantly suppressed by CIR budesonide treatment. No other measured parameters were significantly affected.

**Conclusions:** A four week course of treatment with CIR budesonide suppresses the HPA axis in dogs with a normal gastrointestinal mucosal barrier.

CLINICAL IMPACT:

CIR budesonide is not sufficiently suppressed by first pass hepatic metabolism to prevent suppression of the HPA axis in healthy dogs. Therefore, treatment in dogs with an altered gastrointestinal barrier or hepatic dysfunction will cause more severe adrenoocortical suppression and delay in HPA axis recovery after discontinuing CIR budesonide. Depending on the dosage of budesonide and alteration of the gastrointestinal barrier, treatment of dogs for longer than a month could additionally cause signs of iatrogenic hyperadrenocorticism.

Budesonide treatment may be as effective as prednisone or prednisolone for inflammatory bowel disease in dogs with fewer adverse effects, but it is not devoid of adverse effects. The efficacy and safety of budesonide compared to prednisolone for the treatment of inflammatory bowel disease in dogs needs to be investigated and the

high cost of budesonide needs to be factored into the final decision that budesonide is a better choice in treating inflammatory bowel disease in dogs.

**Note to the publisher- possible pull quote:** ABudesonide treatment is not devoid of adverse effects.@

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