

SMALL ANIMAL CLINICAL ENDOCRINOLOGY

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

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### Key Points

- Pulsatile secretion of ACTH in hypophysectomized dogs with pituitary-dependent hyperadrenocorticism signals the post-surgical risk of hyperadrenocorticism recurrence. *J Endocrinol* 2006;190:601-609.
- Radiation therapy is an effective primary treatment for cats with acromegaly or pituitary-dependent hyperadrenocorticism. *J Vet Intern Med* 2006;20:1151-1154.
- The accuracy of various selected methods of thyroxine measurement are acceptable and consistent. *Am J Vet Res* 2006;67:259-265.
- Epilepsy without medication can cause euthyroid sick syndrome serum concentrations of thyroid hormones. *J Vet Intern Med* 2006;20:516-522.
- Regular physical training of whippets for track racing does not have a significant effect on serum thyroid hormone concentrations. *Vet J* 2006;17:135-140.
- A family of Alaskan malamute-mixed breed dogs has been reported with calcitonin-positive thyroid carcinomas. *In J Oncol* 2006;29:1173-1182.
- Rottweiler dogs may be at higher than average risk for acute hypothyroid crisis. *J Vet Intern Med* 2006;20:32-37.
- Primary hypoparathyroidism is most common in terriers, mixed-breeds, German shepherd dogs, and Saint Bernard dogs. *Aust Vet J* 2006;84:285-290.
- The need for insulin therapy in diabetic cats may be reduced when cats are fed a low carbohydrate, low-fiber diet compared to a moderate carbohydrate, high fiber diet. *J Fel Med Surg* 2006;8:73-84.
- The topical application of an aldose reductase inhibitor may arrest or reverse the development of diabetic cataracts. *Am J Vet Res* 2006;67:1783-1787.
- Insulin-dependent diabetic cats may be best managed on once daily Glargine or twice daily Lente insulin injections while being fed a high-protein, low-carbohydrate diet. *J Vet Intern Med* 2006;20:234-238.
- Spontaneous lens capsule rupture can occur in association with diabetic cataract formation. *Vet Ophthalmol* 2006;9:328-334.
- Most diabetic cats have cataract formation, but the cataracts are small and linear requiring a close ophthalmic examination. *Vet Ophthalmol* 2006;9:341-349.

- Octreotide administration suppresses insulin secretion in dogs with insulinoma without adverse effects. *Res Vet Sci* 2006;80:25-32.
- A dog with hypoglycemia associated with a hepatocellular carcinoma developed diabetes mellitus following tumor resection. *J Vet Med Sci* 2006;68:765-767,
- Some dogs with pituitary-dependent hyperadrenocorticism may have normal suppression at eight hours after low-dose dexamethasone administration, but not after four hours which has been termed  $\Delta$ inverse@ results. *Vet Rec* 2006;159:489-491.
- Trilostane is more effective for the control of hyperadrenocorticism in dogs if administered twice per day than once per day. *Vet Rec* 2006;159:277-281.
- Retinoic acid may be an effective means of treating dogs with ACTH-secreting pituitary tumors. *Endocrinol* 2006;147:4438-4444.
- Trilostane inhibits 3  $\beta$ -hydroxysteroid dehydrogenase and 11  $\beta$ -hydroxylase activities in dogs with hyperadrenocorticism. *Dom Anim Endocrinol* 2006;31:63-75.
- Inhaled flunisolide in cats suppress the hypothalamic-pituitary-adrenocortical axis. *J Vet Intern Med* 2006;20:57-64.

## Hypothalamic-Neurohypophyseal Disorders

### **Plasma Hormone Concentrations After Hypophysectomy**

Hanson JM, Kooistra HS, Mol JA, et al. Plasma profiles of adrenocorticotrophic hormone, cortisol,  $\alpha$ -melanocyte-stimulating hormone, and growth hormone in dogs with pituitary-dependent hyperadrenocorticism before and after hypophysectomy. J Endocrinol 2006;190:601-609.

#### INTRODUCTION:

**Background:** The most common cause of spontaneous hyperadrenocorticism in dogs is pituitary-dependent, caused by a corticotrophic adenoma of the pars distalis or pars intermedia. Adenomas of the pars intermedia often produce excess plasma concentrations of  $\alpha$ -melanocyte stimulating hormone (MSH) in addition to adrenocorticotrophic hormone (ACTH). The secretion of other adenohipophyseal hormones may be suppressed by pituitary-dependent hyperadrenocorticism, such as growth hormone (GH). The disorder is typically controlled in dogs by drugs that impair the secretion of excessive adrenocortical hormones, but hypophysectomy has been a common form of treatment in the Netherlands.

**Objectives:** The objective of this study was to investigate the correlation between pituitary hormone plasma concentrations and the recurrence of hyperadrenocorticism after hypophysectomy.

#### SUMMARY:

**Methods:** Seventeen dogs with pituitary-dependent hyperadrenocorticism were evaluated before and after transphenoidal hypophysectomy. Six hour assessments (samples drawn every 10 minutes) were performed on plasma ACTH, cortisol,  $\alpha$ -MSH, and GH. Results were compared to those of eight healthy control dogs.

**Results:** Secretion of ACTH, cortisol,  $\alpha$ -MSH, and GH were pulsatile. Dogs with pituitary-dependent hyperadrenocorticism had significantly higher plasma cortisol concentrations and area under the curve (AUC) than did control dogs. Plasma ACTH and  $\alpha$ -MSH concentrations were not significantly different between dogs with pituitary-dependent hyperadrenocorticism and control dogs.

After hypophysectomy, dogs with pituitary-dependent hyperadrenocorticism had decreased plasma concentrations of cortisol, AUC for ACTH and cortisol, and pulse frequency of ACTH and cortisol. No significant changes occurred in basal plasma concentrations of ACTH,  $\alpha$ -MSH and AUC for  $\alpha$ -MSH, or GH, but  $\alpha$ -MSH pulses ceased after hypophysectomy. Recurrence of ACTH pulsatile secretion was predictive of recurrence of pituitary-dependent hyperadrenocorticism after hypophysectomy.

**Conclusions:** Hypophysectomy reduces the secretion of ACTH and, in turn, cortisol. ACTH, cortisol,  $\alpha$ -MSH, and GH are normally secreted in pulses. The post-surgical recurrence of ACTH pulsatile secretion is a marker for the recurrence of hyperadrenocorticism.

#### CLINICAL IMPACT:

Transphenoidal hypophysectomy in dogs is fraught with problems for the average dog

owner. It requires exceptional imaging of the pituitary fossa, a patient that can tolerate the anesthesia and stress of the surgical procedure, special surgical expertise, intensive post-surgical followup, and patient owners who are willing to pay the high expense and administer the life-long hormone replacements needed, among other problems. However, if hypophysectomy is selected as the means to manage pituitary-dependent hyperadrenocorticism in dogs, post-hypophysectomy recurrence of the pulsatile secretion of ACTH can signal the recurrence of the pituitary tumor and need for irradiation of the pituitary fossa.

**Note to the publisher- possible pull quote:** A post-hypophysectomy recurrence of the pulsatile secretion of ACTH can signal the recurrence of the pituitary tumor@

## **Pituitary Tumor Irradiation in Cats**

Mayer MN, Greco DS, LaRue SM. Outcomes of pituitary tumor irradiation in cats. J Vet Intern Med 2006;20:1151-1154.

### INTRODUCTION:

**Background:** Pituitary tumors are often functional and most often secrete either adrenocorticotrophic hormone (ACTH) or growth hormone, resulting in hyperadrenocorticism or acromegaly, respectively. These are life-threatening diseases in the cat, independent of the local effects of the pituitary tumor. In addition to the endocrinologic effects of pituitary tumors, they can enlarge sufficiently to result in neurological abnormalities which must be managed by either surgery or irradiation, or a combination of each.

**Objectives:** The purpose of this study is to describe the outcome and adverse effects of irradiation of pituitary tumors in cats.

### SUMMARY:

**Case Report:** This retrospective study evaluated medical records for eight cats that underwent irradiation of pituitary tumors with a linear accelerator. Cats received 4,500 to 5,400 cGy in 270 to 300 cGy fractions.

**Results:** Presenting complaints included hyperadrenocorticism and neurologic signs in four cats, acromegaly in three cats, and neurologic signs without endocrine dysfunction in one cat. Pituitary carcinoma was confirmed by pituitary biopsy in one case and was suspected in another cat based on computerized tomography findings and cytology of fluid from a pituitary cyst. Median survival was 523 days, with a range of 252 to 1,894 days. Six cats were alive at one year and three at two years after irradiation. Complications from tumors led to the deaths of three cats. Diabetes mellitus, poorly controlled and present in six cats, became more responsive to insulin after irradiation. Clinical signs improved in all cats after irradiation, although endocrine testing normalized in only one cat. Tumor size was decreased in two cats and unchanged in two cats on repeat imaging three to eight months after irradiation.

Adverse effects from irradiation that were noted acutely occurred in two cats and consisted of epilation of the treated area in one and mild bilateral otitis externa in the other. Late ocular effects included cataracts in one cat diagnosed 13 months after treatment that worsened to the point of blindness that prompted the owner to euthanize the cat after 19.5 months. Impaired vision was noted in a second cat 42 months after irradiation, but no abnormalities explaining the blindness were apparent on ophthalmic examination. Two cats developed hearing loss (partial after one year in one cat and complete after 34 months in the other). The only cat that underwent necropsy examination, performed on day 252, had a carcinoma with necrosis adjacent to an area of tumor regrowth. Another cat developed progressive neurologic signs and died 523 days after irradiation.

**Conclusions:** Radiation therapy is an effective means of treatment of pituitary tumors in

some cats, resulting in improvement of clinical signs due to endocrinologic and neurologic effects.

CLINICAL IMPACT:

Acromegaly causes insulin resistant diabetes mellitus, progressive renal dysfunction and failure, cardiomyopathy, and painful arthropathy in cats. No effective medical treatment has been described, so pituitary irradiation as described in this report is the only effective non-surgical means of reducing growth hormone secretion and progression of the serious complications of the disease. Radiation therapy in cats has the disadvantages of multiple periods of anesthesia, delayed onset of beneficial effects, and radiation damage to nearby healthy tissues. Endocrinologic testing was not reported after irradiation nor was the survival of the specific cats with acromegaly. While other effective treatments for hyperadrenocorticism such as trilostane have been described in cats, neurologic signs are only effectively treated with irradiation or surgery.

**Note to the publisher- possible pull quote:** A Radiation therapy is an effective means of treatment of pituitary tumors in some cats@



## Thyroid Function Testing

### **Methods of Thyroxine Measurement**

Kemppainen RJ, Birchfield JR. Measurement of total thyroxine concentration in serum from dogs and cats by use of various methods. Am J Vet Res 2006;67:259-265.

#### INTRODUCTION:

**Background:** Measurement of serum total T<sub>4</sub> forms the basis for a diagnosis of both feline hyperthyroidism and canine hypothyroidism. Elevated serum T<sub>4</sub> is diagnostic of hyperthyroidism in a cat with appropriate clinical signs. However, many factors can lower a serum T<sub>4</sub> concentration, masking hyperthyroidism or making an accurate diagnosis of hypothyroidism more difficult. Numerous assay methods are available for serum T<sub>4</sub>, with practical in-house methods being introduced recently.

**Objectives:** This study was designed to compare different methods of measurement of T<sub>4</sub>, including evaluation of an in-house ELISA method.

#### SUMMARY:

**Methods:** Samples from clinical cases submitted to a veterinary endocrinology laboratory for measurement of T<sub>4</sub>, including 98 from dogs and 100 from cats were used. Assays used included a standard radioimmunoassay validated for use in dogs that was performed by the diagnostic laboratory personnel, an in-house ELISA Snap test that included reading in an analyzer performed by a veterinary student who had experience with the assay, and assays performed by an assay manufacturer including a radioimmunoassay and a chemiluminescent enzyme assay designed for use in humans. Assays were evaluated for precision, sensitivity, and overall agreement between methods.

**Results:** Precision and sensitivity were acceptable in all assays. The veterinary diagnostic laboratory provided measurements that were consistently slightly lower than results obtained using other assays. Overall agreement between the in-house ELISA assay and the other assays was good, although agreement was less consistent in some samples with a very elevated T<sub>4</sub> concentration.

Samples from 41 dogs that were submitted because of suspicion of hypothyroidism were classified as either normal or below the reference range provided with each assay or established by each laboratory. Serum T<sub>4</sub> concentration was low using the diagnostic lab assay, in house assay, company radioimmunoassay, and company chemiluminescent assay in 25, 14, 14, and 22 cases, respectively. When a standard low reference range (1.45 µg/dl) was used for all assays, 20, 20, 18, and 19 samples, respectively, were below this range. Sixteen dogs had low T<sub>4</sub> on all assays.

Similar comparison of samples from 64 cats submitted for evaluation of suspected hyperthyroidism, serum T<sub>4</sub> concentration was high using the diagnostic lab assay, in house assay, company radioimmunoassay, and company chemiluminescent assay in 29, 27, 30, and 30 cases, respectively. Twenty-five samples had elevated serum T<sub>4</sub> concentrations on all assays.

**Conclusions:** All assays, including the in-house method, agreed and were consistent. Variability in making clinical decisions was based more on the differences in normal ranges for the assays than accuracy of the measurements.

**CLINICAL IMPACT:**

The most important finding of this study is that the in-house assay, when using an analyzer for quantitative measurements, agrees with more standard assays in most cases. As with any assay, proper quality control, and consistent, precise assay performance is essential to have good results. Most veterinary diagnostic laboratories have rigorous protocols to maintain precision, while assays performed at veterinary practices may have less stringent quality control. It is rarely necessary to make a diagnosis of hypothyroidism or hyperthyroidism rapidly since these diseases rarely have life-threatening manifestations. In addition, there is inaccuracy inherent in making a diagnosis of hypothyroidism based solely on a serum total T<sub>4</sub> concentration. The attending veterinarian should consider submitting serum samples for total T<sub>4</sub> and additional measurements such as free T<sub>4</sub> and thyroid-stimulating hormone when evaluating thyroid function.

This study was funded in part by the IDEXX Corporation.

**Note to the publisher- possible pull quote:** There is inaccuracy inherent in making a diagnosis of hypothyroidism based solely on a serum total T<sub>4</sub> concentration@

## **Epilepsy Effects on Thyroid Function Tests**

Von Klopmann T, Boettcher IC, Rotermund A, et al. Euthyroid sick syndrome in dogs with idiopathic epilepsy before treatment with anticonvulsant drugs. J Vet Intern Med 2006;20:516-522.

### INTRODUCTION:

**Background:** The effects of illnesses, not involving the thyroid gland, that alter thyroid function tests has been called euthyroid sick syndrome or nonthyroidal illness. Numerous diseases have been documented to cause euthyroid sick syndrome in dogs. It is also well documented that anticonvulsants, particularly phenobarbital, have an important effect on thyroid function that results in a reduction in serum T<sub>4</sub> and free T<sub>4</sub> concentrations. However, less is known about the effect of recent seizures and idiopathic epilepsy in dogs not receiving anticonvulsant drugs.

**Objectives:** The objective of this study was to determine if idiopathic epilepsy results in alteration of thyroid function tests prior to administration of anticonvulsants.

### SUMMARY:

**Methods:** Serum total T<sub>4</sub> and canine thyroid-stimulating hormone (cTSH) concentrations were measured in 113 dogs with seizures. Dogs were divided into groups consisting of those with confirmed (evaluation including normal CT or MRI of the brain) or presumed (no imaging) idiopathic epilepsy without anticonvulsant treatment, those with confirmed or presumed idiopathic epilepsy and currently receiving phenobarbital, and those with secondary epilepsy where a specific cause of seizures was found. The type and duration of the most frequent seizure as well as the time span between that seizure and blood sampling was evaluated. The time between the first seizure and blood sampling and the frequency and type of seizure that occurred was also evaluated for any association with thyroid hormone concentrations.

Dogs were classified according to T<sub>4</sub> and cTSH concentrations as euthyroid if both were in the reference range, euthyroid sick if the T<sub>4</sub> was below the reference range but cTSH was normal, and hypothyroid if T<sub>4</sub> was below and cTSH above the reference range. Some dogs underwent a thyrotropin-releasing hormone (TRH) stimulation test with post-TRH stimulated serum cTSH and T<sub>4</sub> measured.

**Results:** Idiopathic epilepsy was diagnosed in 94 dogs. Forty-two had a confirmed diagnosis and were not receiving anticonvulsants, 18 had a presumptive diagnosis and were not receiving anticonvulsants, while 24 and 10 dogs treated with anticonvulsants were diagnosed with confirmed and presumptive idiopathic epilepsy, respectively. Numerous acquired diseases were diagnosed in the remaining 19 dogs, including hypothyroidism in three. The majority of the dogs studied had generalized seizures.

Plasma cholesterol concentration was elevated in one euthyroid dog that had a normal serum T<sub>4</sub> and cTSH concentration. When dogs with idiopathic epilepsy not treated with anticonvulsants that had a seizure within 24 hours of blood sampling were compared with those that had not had a seizure for more than 24 hours, there was no

difference in  $T_4$  or cTSH concentrations. Dogs with idiopathic epilepsy treated with anticonvulsants and those with secondary epilepsy had a lower  $T_4$  concentration than those not receiving the drugs. Results of TRH stimulation testing were considered normal in all 27 cases in which it was performed.

Euthyroid sick syndrome was diagnosed in 50% of the dogs, including 38% of those with idiopathic epilepsy that were not receiving anticonvulsants, 68% that were receiving anticonvulsants, and 58% of dogs with secondary epilepsy. While there was no association between low serum  $T_4$  and a seizure within 24 hours of testing, a higher seizure frequency was correlated with a lower serum  $T_4$  concentration.

**Conclusions:** Idiopathic epilepsy commonly causes euthyroid sick syndrome and that phenobarbital treatment may only partly explain the low serum  $T_4$  concentrations frequently found in dogs treated with this drug.

**CLINICAL IMPACT:**

The results of this study show that careful selection and interpretation of thyroid function tests is necessary when evaluating thyroid function in dogs with seizures. Although not evaluated in this study, measurement of serum free  $T_4$  by equilibrium dialysis would be recommended in these cases as it is less often affected by nonthyroidal illness.

Although hypothyroidism has been reported as a possible cause of seizures in dogs, this has not been well documented. It is possible that the euthyroid sick syndrome found in seizure disorders in this study could have resulted in a false diagnosis of hypothyroidism in some cases.

**Note to the publisher- possible pull quote:** Aa higher seizure frequency was correlated with a lower serum  $T_4$  concentration@

## **Physical Training Effects on Thyroid Hormone Concentrations and Thyroglobulin Antibodies**

Van Geffen C, Bavegems V, Duchateau L, et al. Serum thyroid hormone concentrations and thyroglobulin autoantibodies in trained and non-trained healthy whippets. *Vet J* 2006;17:135-140.

### INTRODUCTION:

**Background:** Many factors other than hypothyroidism can be responsible for low serum thyroid hormone concentrations, including non-thyroidal illnesses; drugs; age, sex, and body size; reproductive state, and prolonged endurance exercise. Breed difference in normal reference range can also be a reason for spuriously low serum thyroid hormone concentrations.

Greyhounds and Scottish deerhounds have lower normal reference ranges for total and free T<sub>4</sub> than the average range combined for other breeds. Whippets are sight hounds distantly related to greyhounds and may have lower normal serum thyroid hormone ranges as do greyhounds.

Endurance racing in sled dogs lowers serum thyroid hormone concentrations in healthy sled dogs. It is unknown if track racing of sight hounds decreases serum thyroid hormone concentrations in healthy dogs.

**Objectives:** The reasons for this study were to determine if there are significant differences in thyroid hormone concentrations between trained and non-trained whippets and if the whippet breed of dogs has a significance difference in thyroid hormone concentrations than generic reference ranges for dogs.

### SUMMARY:

**Methods:** Fifty-one healthy adult whippets of both genders were studied. Intact females in diestrous or pregnant were excluded. The dogs were assigned to either a racing group (30 dogs) that received intensive training for racing or a companion/show group (21 dogs) that did not receive intensive training for racing. Twenty-five healthy adult dogs of other breeds (not including greyhounds or Scottish deerhounds) that did not receive training for racing were used as a control group. Serum was assayed in all dogs for total T<sub>4</sub>, free T<sub>4</sub>, canine thyroid-stimulating hormone (cTSH), and thyroglobulin autoantibodies (TgAA).

**Results:** Whippets had significantly lower serum total T<sub>4</sub> concentrations than control dogs. There was no significant difference between serum total T<sub>4</sub> concentrations in racing whippets and companion/show whippets. There were no significant differences between whippets and control dogs nor between racing whippets and companion/show whippets in the serum concentrations of free T<sub>4</sub> and cTSH or the prevalence of TgAA.

**Conclusions:** Healthy whippets have a lower reference range for serum total T<sub>4</sub> than most other dog breeds, and regular training for the short term physical exertion of track racing does not have a significant effect on serum thyroid hormone concentrations.

### CLINICAL IMPACT:

The whippet breed can be added to the list of sight hounds that have a lower reference

range of normal serum total  $T_4$  concentrations than the generic range for dogs. Since  $T_4$  concentrations in whippets do not differ from control dogs, an alternation in the affinity of  $T_4$  binding plasma proteins may be the reason, but the specific cause is unknown.

**Note to the publisher- possible pull quote:** Aphysical exertion of track racing does not have a significant effect on serum thyroid hormone concentrations@

## Thyroid Neoplasia

### **Familial Medullary Thyroid Neoplasia**

Lee J, Larsson C, Lui W, et al. A dog pedigree with familial medullary thyroid cancer. In J Oncol 2006;29:1173-1182.

#### INTRODUCTION:

**Background:** Multiple Endocrine Neoplasia (MEN) are two groups of familial syndromes in which neoplasia occurs in groups of endocrine glands but not necessarily at the same time. The cell types in the neoplasias are believed to have a common embryologic precursor in the neuroectoderm. The most common component of MEN 2a and MEN 2b is medullary thyroid carcinoma which is a tumor of the parafollicular, calcitonin-secreting cells of the thyroid. The majority of MEN 2a and 2b also have either pheochromocytoma or parathyroid adenomas or hyperplasia. Humans with MEN 2 usually have mutations in the *RET* (rearranged during transfection) proto-oncogene which encodes a tyrosinase kinase receptor for an unknown growth factor.

Serum calcitonin concentration is a marker for medullary thyroid carcinoma and is used to screen family members for possible MEN. Calcitonin is normally secreted under the stimulus of hypercalcemia. Its physiologic purpose is to lower rising or elevated serum calcium concentration by inhibiting osteoclastic activity and renal calcium reabsorption.

**Objectives:** The reason for this case report was to describe dogs with familial thyroid carcinoma.

#### SUMMARY:

**Case Report :** Four dogs of mixed breeding, partly Alaskan malamutes, 8- to 9-years-old, were presented with similar clinical signs that primarily included chronic dermatitis. The first dog examined was diagnosed with hypothyroidism, subsequently died, and was not necropsied. Three other dogs that were daughters of the first dog each had ventral cervical mass in addition to anemia, hypothyroidism, antithyroglobulin antibodies, partial alopecia, and chronic dermatitis. One of the daughters had hypercalcemia (magnitude unreported). A fourth member of the litter, a male, was unaffected.

The three female littermates were euthanized and necropsied. Histopathologic examination and immunohistochemistry revealed portions of all three dogs= tumors to be calcitonin-positive and two to also be thyroglobulin-positive. None were parathyroid hormone-positive. Based on the histopathology and immunohistochemical findings the tumors were presumed to be medullary or mixed follicular-medullary thyroid carcinomas. One dog had elevated serum calcium concentration and multinodular adrenocortical hyperplasia.

The dog *Ret* gene was identified and screened for mutations. No mutations were detected.

**Conclusions:** This is report of a dog family with four members with medullary thyroid carcinoma with a dominant inheritance of autosomal or X-linked type.

CLINICAL IMPACT:

The authors of this report concluded that four dogs in this report had familial medullary thyroid carcinoma, but the evidence is scant. The diagnosis of medullary thyroid carcinoma in the three sibling dogs of this report was based primarily on various portions (percentage not stated) of the tumors containing calcitonin. Serum calcitonin concentrations and provocative testing with pentagastrin or calcium gluconate were not done. The father of these dogs was included in the family described to have medullary thyroid carcinoma, but no necropsy was performed on the father dog. None of the siblings with a thyroid tumor had either concurrent pheochromocytoma or parathyroid adenoma or hyperplasia, which is typical of most cases of MEN 2. Purebred dogs are at greater risk to demonstrated familial problems such as MEN, but the dogs of this report were mixed breed. In humans with MEN 2, no association with hypothyroidism has been reported, but diarrhea is a frequent presenting sign. All the dogs of this report had hypothyroidism, and none had diarrhea. The secretion of calcitonin in medullary thyroid carcinoma is autonomous, and its action is normally to lower serum calcium concentration. Yet, one of the dogs of this report had hypercalcemia of unknown origin. None of the dogs had mutations in the *Ret* gene as do nearly all humans with MEN 2.

**Note to the publisher- possible pull quote:** ΔNone of the dogs had mutations in the *Ret* gene as do nearly all humans with MEN 2@



## Hypothyroidism

### **Intravenous Levothyroxine**

Pullen WH, Hess RS. Hypothyroid dogs treated with intravenous levothyroxine. J Vet Intern Med 2006;20:32-37.

#### INTRODUCTION:

**Background:** The most dangerous form of primary hypothyroidism in adults is traditionally referred to as myxedema coma. The terminology is misleading because most dogs with severe hypothyroidism are presented prior to coma. The clinical signs include physical weakness, bradycardia, hypoventilation, hypotension, and nonpitting edema of the face and neck. A cardinal sign is hypothermia without an apparent other cause than possible hypothyroidism. Stupor and coma are usually triggered by infection or hypotensive factors. Death will ensue quickly if hypothyroidism is not treated aggressively. This may require intravenous (IV) levothyroxine administration.

**Objectives:** The aim of this retrospective study was to determine the clinical and laboratory findings, response to treatment, and outcome of dogs treated with IV levothyroxine.

#### SUMMARY:

**Methods:** The medical records of seven dogs treated with IV levothyroxine were evaluated. Historical data assessed included patient history, signalment, clinical signs, physical examination findings, neurological examination findings, laboratory findings, and radiographic findings.

**Results:** Rottweilers were three of the seven dogs. Five dogs each had excessive body weight and mental dullness. Four had nonpitting edema. Laboratory abnormalities noted were anemia in four dogs and hypercholesterolemia in five dogs. Concurrent disease, usually infection, was observed in five dogs.

The dosage range used for IV levothyroxine was 1 to 9 µg/kg. Improvement in mentation or ambulation occurred in six of seven dogs within 30 hours of levothyroxine IV administration. Six of the seven dogs responded to the therapy and were discharged from the hospital.

**Conclusions:** Clinical findings in dogs with hypothyroid crisis are nonspecific. Rottweilers may be at increased risk for hypothyroid crisis. Infection can be associated with hypothyroid crisis. A favorable response should occur within 30 hours of administering IV levothyroxine, and the prognosis for most treated dogs is good.

#### CLINICAL IMPACT:

Although all the dogs of this report may have been in crisis and hypothyroid, most did not demonstrate classical myxedema coma. The value in treating dogs in hypothyroid crisis without classical myxedema coma may be demonstrated by this report. However, if presented with classical myxedema coma, the prognosis for survival is unlikely to approach that reported in these seven dogs.

Myxedema coma is characterized by depressed respiratory rate, heart rate, hypothermia, and dilutional hyponatremia. In this report, only one dog each had

hypothermia or bradycardia, while four had tachypnea. The single abnormality in serum sodium concentration noted was a dog with hypernatremia.

The seven dogs of this report were gathered from 10 years of clinical cases and 806 cases diagnosed with hypothyroidism. It is impractical for an average small animal practice to maintain IV levothyroxine in their pharmacy. Yet, it is essential for maximizing the chance of survival from myxedema coma. Most practitioners will need to seek IV levothyroxine from a local major hospital in order to administer it in a timely manner.

Low doses of IV levothyroxine were used in the dogs of this report. Three received one IV injection of 9  $\mu\text{g}/\text{kg}$ , or less. The remaining four dogs received 9  $\mu\text{g}/\text{kg}$ , or less, for five to 13 doses with at least eight hours separating each dose. The appropriate dosage is not established in dogs but there is a large pool of unbound plasma proteins that first must be saturated with a loading dose that is much greater than the usual oral maintenance dose (20  $\mu\text{g}/\text{kg}$ , once or twice per day in dogs). For example, the loading dosage for IV levothyroxine in humans is 400  $\mu\text{g}$ , but the average oral maintenance dose is 200  $\mu\text{g}/\text{day}$ . This suggests that the appropriate dose of IV levothyroxine for myxedema coma or stupor in dogs could be 40  $\mu\text{g}/\text{kg}$ .

**Note to the publisher- possible pull quote:** AInfection can be associated with hypothyroid crisis@

## Hypoparathyroidism

### Primary Hypoparathyroidism

Russell NJ, Bond KA, Robertson ID, et al. Primary hypoparathyroidism in dogs: a retrospective study of 17 cases. Aust Vet J 2006;84:285-290.

#### INTRODUCTION:

**Background:** Primary (spontaneous, non-surgical) hypoparathyroidism is an uncommon, potentially life-threatening disease characterized by hypocalcemia and resultant clinical signs. It is thought to result most often from immune-mediated destruction of the parathyroid glands. Diagnosis is made by excluding other causes of hypocalcemia and finding low to normal serum parathyroid hormone (PTH) concentrations in the presence of hypocalcemia.

**Objectives:** The purpose of this study was to describe the clinical findings and treatment of dogs with primary hypoparathyroidism.

#### SUMMARY:

**Methods:** Medical records of dogs from a 15 year period were reviewed for a diagnosis of primary hypoparathyroidism. The diagnosis of primary hypoparathyroidism was made by finding persistent hypocalcemia with resultant clinical signs, and inappropriately low serum PTH concentration in the presence of hypocalcemia or exclusion of other causes of severe hypocalcemia including periparturient hypocalcemia, ethylene glycol toxicosis, intestinal malabsorption, rhabdomyolysis, tumor lysis syndrome, pancreatitis, and administration of phosphate containing enemas.

**Results:** Of the 17 cases identified, three were Saint Bernard dogs, three were mixed-breed, and two each were Chihuahua, German shepherd dogs, or Jack Russell terrier, while the remainder were single cases within a breed. The median age was 5.4 years with a range of 1 to 11. All dogs were fed a balanced commercial diet. Clinical signs were present a median of 13 days prior to presentation, but were present for 173 days in one dog. Clinical signs present in over 50% of cases included seizures, muscle tremors or fasciculations, stiff gait or tetany, and behavior changes such as lethargy, anxiety, or aggression. Hyperventilation, vomiting, hyperthermia, inappetence, facial pruritus, abdominal pain, ataxia, and weakness were also noted. Cataracts were found in two cases. Electrocardiograms were recorded in four dogs, and prolongation of the ST-segment was noted in each case.

The median serum calcium concentration was 5.2 mg/dl. The serum phosphorus concentration was elevated in five dogs and normal in the others. Serum PTH concentration was below the reference range in eight of 10 cases in which it was measured and was at the lower limit of the reference range in another dog. The PTH concentration in the remaining dog was normal, but inappropriate when concurrent with hypocalcemia. Fractional urinary excretion of calcium was increased in one dog and in the upper 50% of the reference range in the other four dogs evaluated.

Initial treatment in consisted of parenteral calcium gluconate in 10 of the 16 treated, while anticonvulsant treatment was administered in five cases. All 16 dogs were administered oral vitamin D and calcium, but no details of the long-term response to treatment was given. Tissue necrosis developed in one dog due to subcutaneous administration of calcium gluconate. Multiple surgeries were required, but the dog survived. Twelve dogs were alive at a median follow-up of 13 months. One dog was euthanized because of acute renal failure that was thought to have been a complication of treatment and another due to aural hematoma apparently secondary to facial pruritus.

No other deaths were associated with treatment or complications of primary hypoparathyroidism. Parathyroid glands from two dogs that were euthanized were considered normal on histopathology.

**Conclusions:** The prognosis for long-term survival is good in dogs with primary hypoparathyroidism treated with oral vitamin D and calcium.

CLINICAL IMPACT:

The clinical findings and response to treatment of this report are similar to previous descriptions of primary hypoparathyroidism. Because of the wide availability of reference laboratories that measure serum PTH and ionized calcium, a diagnosis is easily confirmed in dogs with unexplained hypocalcemia. Tissue mineralization following subcutaneous administration of calcium gluconate results in severe tissue necrosis and even death in some cases. Calcium gluconate should be administered intravenously because even when the 10% solution is diluted prior to subcutaneous administration, necrosis at the injection site can result.

**Note to the publisher- possible pull quote:** A Calcium gluconate should be administered intravenously because even when diluted prior to subcutaneous administration, necrosis at the injection site can result.@

## Diabetes Mellitus

### **Dietary Management of Feline Diabetes Mellitus**

Bennett N, Greco DS, Peterson ME, et al. Comparison of a low carbohydrate-low fiber diet and a moderate carbohydrate-high fiber diet in the management of feline diabetes mellitus. *J Fel Med Surg* 2006;8:73-84.

#### INTRODUCTION:

**Background:** Cats appear to most often have a form of diabetes mellitus that is similar to type 2 diabetes in humans. This form of diabetes results from a combination of insulin resistance and impaired insulin secretion, but the beta-islet cells of the pancreas retain their ability to secrete insulin. While transient diabetes mellitus has been known to occur in cats for many years, it has recently been found that feeding a low carbohydrate, high protein diet can promote resolution of the diabetic state when combined with insulin administration.

**Objectives:** The objective of this study was to compare the effects of a low carbohydrate, low fiber food with a moderate carbohydrate, high fiber food on control and resolution of diabetes mellitus in cats.

#### SUMMARY:

**Methods:** Sixty three cats with diabetes mellitus were randomly assigned to receive either a low carbohydrate, low fiber diet (Science Diet Feline Growth canned; 31 cats) or a moderate carbohydrate, high fiber diet (Hills w/d canned; 32 cats) for four months in addition to insulin administration. Control of the diabetes was determined every four weeks for 16 weeks by assessing clinical signs, physical examination, urine glucose, serum fructosamine, and single blood glucose concentrations at the time of each evaluation. Adjustments in insulin dosage were made based on findings of these tests every four weeks. Insulin treatment was discontinued when clinical signs had resolved and the cats were receiving 1 unit of insulin per dose. A **Δresponder@** was defined as a cat with a stable body weight, normal water and food intake, normal activity, and a serum fructosamine concentration less than 400 μmol/L without insulin administration. A responder was **Δwell-regulated@** if the above findings occurred while the cat was still receiving insulin.

**Results:** Nineteen cats had been diabetic for more than one year, 24 were diabetic 1 to 12 months, and 19 were diabetic for 45 days or less prior to entry in the study. Cats were fed a wide variety of diets prior to study. Insulin had been administered to 52 cats prior to entry in the study while 11 had not been treated prior to entry into the study. Fifty-three cats were administered PZI insulin with the remainder receiving NPH, Lente, or Ultralente insulin. Thirty-one cats were responders in which insulin was discontinued. Insulin treatment was successfully discontinued in 68% of cats on the low carbohydrate diet and in 41% on the moderate carbohydrate diet, a difference that was statistically significant. Cats fed the low carbohydrate diet had a 1.5 times greater chance of being well-regulated than those on the moderate carbohydrate diet regardless of whether

insulin was discontinued or not. There was no difference in the likelihood of being a responder based on duration of the diabetes mellitus prior to entry in the study. However, no cat that had been diabetic for over 36 months had insulin discontinued.

**Conclusions:** A low carbohydrate diet plays a significantly beneficial role in the response to treatment and need for long-term insulin administration of cats with diabetes mellitus.

**CLINICAL IMPACT:**

The cats in this study had a very high rate of rate of remission of their diabetes mellitus, regardless of diet fed. Perhaps this occurred because the cats were monitored more closely and more effort went into assuring adequacy of treatment than if they were not entered into a standardized study. This study confirms that diabetic cats fed a low carbohydrate diet are more likely to have resolution of their clinical signs and hyperglycemia, allowing insulin therapy to be discontinued. Feeding diabetic cats a low carbohydrate diet combined with carefully regulated insulin treatment should allow resolution of the diabetic state to be a goal of treatment rather than just control of clinical signs with continued insulin administration.

**Note to the publisher- possible pull quote:** Adiabetic cats fed a low carbohydrate diet are more likely to have resolution of their clinical signs and hyperglycemia@

## Topical Aldose Reductase Inhibitor Effects on Cataract Formation

Kador PF, Betts D, Wyman M, et al. Effects of topical administration of an aldose reductase inhibitor on cataract formation in dogs fed a diet high in galactose. *Am J Vet Res* 2006;67:1783-1787.

### INTRODUCTION:

**Background:** Dogs with uncontrolled diabetes mellitus will develop cataracts. The lenticular change is irreversible and severely impairs vision. Diabetic cataracts may be surgically removed, but the procedure requires special expertise and is expensive. Many diabetic patients are also poor anesthetic or surgical candidates. A practical means of medically preventing, arresting, or reversing the development of cataracts would be preferable to surgical extraction.

The formation of diabetic cataracts involves formation of sorbitol or galactitol by the action of aldose reductase on glucose and galactose, respectively. Some sorbitol is oxidized to fructose by sorbitol dehydrogenase. Sorbitol, fructose, or galactitol becomes entrapped in the lens, osmotically drawing in water, and separating the lenticular fibers. Myo-inositol concentration in the lens is decreased as sorbitol or galactitol concentration increases.

**Objectives:** The purpose of this study was to determine the efficacy of a topical aldose reductase inhibitor in impairing the development of cataracts in dogs fed a diet high in galactose.

### SUMMARY:

**Methods:** Ten, 6-month-old, beagles were fed a diet containing 30% galactose. After 16 weeks, six dogs were treated with a topical aldose reductase inhibitor (kinostat) while the remaining four dogs were treated with a topical placebo. The development of cataracts was monitored by slit-lamp biomicroscopy and funduscopy. After 10 weeks of treatment, all dogs were euthanized. Lens from each dog were evaluated for opacity and concentrations of myo-inositol, galactitol, and kinostat. Red blood cells (RBCs) were monitored for galactose and galactitol concentrations at weeks 0, 12, and 25.

**Results:** All dogs developed bilateral cortical cataracts within 16 weeks of being fed the galactose containing diet. Kinostat treatment arrested further development of the cataracts. Placebo-treated dogs had cataracts that continued to develop during the 10 week treatment period and eventually matured. At the end of the 26th week on the galactose containing diet, the kinostat treated dogs had significantly less optically dense cataracts than placebo-treated dogs. Myo-inositol concentration in the lens was significantly greater in kinostat-treated dogs. Week 26 RBC galactitol concentrations were significantly lower in the kinostat-treated dogs than those in control dogs.

**Conclusions:** The topical application of an aldose reductase inhibitor may arrest or reverse the development of cataracts caused by a diet high in galactose and possibly also in diabetic dogs.

### CLINICAL IMPACT:

Topical kinostat appears to be a safe and effective means of arresting or reversing

galactose induced cataracts. Aldose reductase inhibitors have the potential of inhibiting other enzymes, particularly in the liver. Liver enzyme activity was not significantly changed by the topical administration of kinostat, but galactitol concentrations in RBCs became significantly lower in kinostat-treated dogs indicating subclinical systemic effects of the topical administration.

Galactose-induced cataract development is very similar, but not identical to diabetic cataracts. Aldose reductase inhibitors have been effective in preventing diabetic cataracts in rats, but clinical trials of topical kinostat are now needed on dogs with diabetic cataracts.

The principal authors disclosed financial interests in a company which produces kinostat, but the claims of this study do not seem overstated.

**Note to the publisher- possible pull quote:** AThe topical application of an aldose reductase inhibitor may arrest the development of cataracts caused by a diet high in galactose@



## **Glargine and Lente Insulins in Diabetic Cats**

Weaver KE, Rozanski EA, Mahony OM, et al. Use of Glargine and Lente insulins in cats with diabetes mellitus. *J Vet Intern Med* 2006;20:234-238.

### INTRODUCTION:

**Background:** Glargine is a synthetic insulin analog that differs from human insulin in three amino acids. The structural change causes decreased solubility of Glargine at a neutral pH, resulting in gradual resorption from subcutaneous tissue. Its administration to humans results in a steady release from the injection site and stable, peakless plasma insulin concentrations. Glargine management of insulin-dependent feline diabetes mellitus may have advantages over other insulin therapy.

**Objectives:** This study was designed to compare the efficacy of once daily Glargine administration with twice daily Lente insulin administration on glycemic control in cats with diabetes mellitus.

### SUMMARY:

**Methods:** Seventeen cats with diabetes mellitus were studied. Eight were newly diagnosed diabetics and nine were poorly controlled with insulin treatment but not thought to be insulin resistant. Cats were assigned to receive human recombinant Lente insulin at 0.5 U/kg, every 12 hours or Glargine insulin at 0.5 U/kg, every 24 hours. All cats were fed a commercial high protein, low carbohydrate diet manufactured for management of diabetes mellitus. Control of diabetes mellitus was assessed after 1, 2, 4, 8, and 12 weeks of treatment by history, physical examination, a 16 hour blood glucose curve, and serum fructosamine concentration.

**Results:** Thirteen cats finished the study, seven treated with Lente insulin and six with Glargine. All cats had improvement in their clinical signs during treatment. There was no significant difference between the two treatment groups in the change from pretreatment level in peak glucose concentration, mean insulin concentration during the glucose curve, serum fructosamine concentration, insulin dosage, or body weight. Four cats (three receiving Lente, one Glargine) had complete remission of diabetes mellitus during the study.

**Conclusions:** Either once daily Glargine or twice daily human recombinant Lente insulin combined with feeding of a high protein, low carbohydrate diet are effective treatments for diabetes mellitus in cats.

### CLINICAL IMPACT:

This study failed to provide an adequate comparison of the two treatments because of the difference in frequency of administration. Glargine insulin is most effective when administered twice daily as was Lente insulin in this study. Also, there was no assessment of adequacy of control of the diabetic state. It only compared changes from pretreatment values in the two treatment groups. In addition, the feeding of a high protein, low carbohydrate diet that may have greatly influenced control of the diabetes in many of the cats. Therefore based on the structure of this study, it is not possible to

determine if Glargine is more or less effective than Lente insulin when used for treatment of diabetes mellitus in cats. Human recombinant Lente insulin is no longer manufactured.

**Note to the publisher- possible pull quote:** A Glargine insulin is most effective when administered twice daily as the Lente insulin was in this study@

## **Cataracts and Spontaneous Lens Capsule Rupture**

Wilkie DA, Gernesky-Metzler AJ, Colitz MH, et al. Canine cataracts, diabetes mellitus and spontaneous lens capsule rupture: a retrospective study of 18 dogs. *Vet Ophthalmol* 2006;9:328-334.

### INTRODUCTION:

**Background:** Bilateral cataracts are perhaps the most common long-term complication of diabetes mellitus in dogs. Within the first year of diagnosis of diabetes, at least three-fourths of diabetic dogs will have cataracts. Once initiated, cataract formation progresses rapidly. Diabetic cataracts are osmotically induced. Water is drawn into the lens by entrapped sorbitol. This expands the volume of the lens against the constraint of the lens capsule. Rapid enlargement can result in lens capsule rupture which, in turn, can cause lens-induced uveitis and secondary glaucoma. The incidence of lens capsule rupture and prognosis for cataract surgery in dogs with diabetic lens capsule rupture are not known.

**Objectives:** The goal of this study was to describe the clinical findings and surgical outcome in dogs with diabetic cataracts that had preoperative spontaneous lens capsule rupture.

### SUMMARY:

**Methods:** The medical records of 20 diabetic dogs (40 eyes) were evaluated retrospectively. Presurgical ophthalmologic examinations were performed including routine diagnostic examination, ocular ultrasound, and electroretinography.

**Results:** At presentation, all dogs had diabetes mellitus for at least 30 days and all eyes had cataract formation that had been present for at least 14 days. Among the 40 eyes, 28 had spontaneous rupture of the lens capsule diagnosed prior to surgery. Two additional eyes had lens capsule rupture discovered intraoperatively. The rupture site was equatorial in 29 of the 30 eyes. One had the rupture in the posterior capsule. Eyes with lens rupture had associated problems, including aqueous flare, anterior uveitis, keratic precipitates, increased intraocular pressure, retinal detachment, posterior synechia, and prolapse of the lens nucleus into the anterior chamber.

Surgery was performed on 38 eyes. Phacoemulsification was done on 28 eyes, 20 of which had intraocular lens implanted. In eyes that had concurrent retinal detachment or secondary glaucoma, intrascleral prosthesis was placed in eight eyes and enucleation performed for two eyes. Nineteen of the 20 dogs had follow-up examinations at least one month after surgery (mean 12.9 months). All eyes that had cataract surgery had sight perception at the time of the last post-surgical examination.

**Conclusions:** Diabetic lens in dogs undergo rapid intumescence and spontaneous lens capsule rupture often occurs. Early cataract surgery improves prognosis for a good outcome.

### CLINICAL IMPACT:

Spontaneous lens rupture is more common in diabetic dogs with cataracts than previously thought. It also can trigger multiple complications, particularly phacoclastic

uveitis and secondary glaucoma. In this six year survey, 9% of all dogs with diabetes mellitus presented to a referral hospital for cataract surgery had spontaneous lens capsule rupture. Twenty percent of the eyes with lens rupture had glaucoma secondary to the inflammation caused by exposed intralenticular protein. Some capsular ruptures were not directly visualized. They were instead indicated by posterior synechia and intralenticular pigment.

Diabetic cataracts can become clinically severe within a week of onset. The rate at which they form varies with the degree of glycemic control and the intralenticular aldose reductase activity. Early surgical intervention for diabetic cataracts that are developing rapidly is logical, but may not be possible in many situations due to the rapidity of formation and subtleness of early lens rupture. Fortunately, even in cases in which cataract surgery is not performed as early as possible, all eyes that had cataract surgery with or without intraocular lens placement became sighted.

**Note to the publisher- possible pull quote:** A Diabetic lens in dogs undergo rapid intumescence and spontaneous lens capsule rupture often occurs@

## **Feline Cataracts**

Williams DL, Heath MF. Prevalence of feline cataract: results of a cross-sectional study of 2000 normal animals, 50 cats with diabetes and one hundred cats following dehydrational crises. *Vet Ophthalmol* 2006;9:341-349.

### INTRODUCTION:

**Background:** The prevalence of cataracts in cats is less than in dogs. No large epidemiological study on the incidence of cataracts in cats has been conducted. Among the most common visually impairing cataracts of dogs are diabetic cataracts. The typical diabetic cat is over eight years of age at diagnosis and have not been reported to develop the same type of diabetic cataracts that are common in diabetic dogs.

**Objectives:** The purpose of this study was to determine the presence of cataracts in normal and diabetic cats and in cats with a history of dehydration crisis.

### SUMMARY:

**Methods:** Ophthalmoscopic examinations were performed by a single ophthalmologist on 2000 normal cats, 50 cats with diabetes mellitus, and 100 cats with a history of dehydration crisis from chronic renal failure (85 cats), chronic vomiting (17 cats), or chronic diarrhea (8 cats). The age at which 50% (C50) of the cats at risk for each disorder showed cataracts was determined.

**Results:** The C50 for normal cats was 12.7  $\nabla$  3.4 years. The median age for cataracts in normal cats was 8.3 years. All cats older than 17.5 years had lens opacity. The C50 for diabetic cats was significantly earlier (5.6  $\nabla$  1.9 years) than normal cats. Cats that had a history of repeated episodes of dehydration in the last year had a C50 of 9.9  $\nabla$  2.5 which was not significantly different than normal cats.

**Conclusions:** The incidence of aging cataracts in cats has been determined in this study. Cats with diabetes mellitus and cats with repeated episodes of dehydration have earlier onsets of cataracts than normal cats.

### CLINICAL IMPACT:

Cataracts can be categorized as clinically significant (vision impairing) and clinically insignificant (no noticeable effect on vision). In this survey of cats only the presence of cataracts was assessed. Most of the cataracts reported were clinically insignificant small linear opacities in the posterior cortex. None were described as vision impaired in a manner similar to dogs with diabetic cataracts.

Only two of the 50 diabetic cats were free of cataracts, but nearly half of those affected had opacities similar to the aged normal cats. The remainder were posterior cortical opacities or posterior polar subcapsular plaques. These are not sugar induced, rapidly developing mature cataracts typical of diabetic dogs. Lenticular aldose reductase activity, which is centrally involved in canine cataract development, is generally gone in cats by the age of four years, long before most cats develop insulin-dependent diabetes mellitus. The clinical impact of cataracts in diabetic cats is insignificant as compared to

diabetic cataracts in dogs.

**Note to the publisher- possible pull quote:** Most of the cataracts were clinically insignificant small linear opacities in the posterior cortex.@

## Hypoglycemia

### **Octreotide Effects on Hormone Secretion by Insulinomas**

Robben JH, van den Brom WE, Mol JA, et al. Effect of octreotide on plasma concentrations of glucose, insulin, glucagon, growth hormone, and cortisol in healthy dogs and dogs with insulinoma. Res Vet Sci 2006;80:25-32.

#### INTRODUCTION:

**Background:** Most insulinomas in dogs are malignant and have metastasized by the time of diagnosis. However, the quality of life can be improved and duration of survival extended by excision of the primary tumor. Relapse after surgery can sometimes be managed by frequent small meals and the administration of glucocorticoids to antagonize the effects of insulin or diazoxide to inhibit insulin secretion. However, better options for medical treatment of dogs with inoperable insulinomas or dogs with post-surgical relapse of hypoglycemia are needed.

**Objectives:** The goal of this study was to report the acute effects of a single subcutaneous dose of octreotide to healthy dogs and dogs with insulinoma.

#### SUMMARY:

**Methods:** Seven healthy, fasting dogs and 12 dogs with insulinoma were administered 50 µg of octreotide subcutaneously. Plasma concentrations of glucose, insulin, glucagon, growth hormone (GH), adrenocorticotrophic hormone (ACTH), and cortisol were monitored at -30, -15, 0, 15, 30, 60, 120, and every 30 minutes for 240 minutes after octreotide administration.

**Results:** Plasma insulin and glucagon concentrations declined significantly after octreotide administration in healthy dogs. Basal plasma GH and ACTH concentrations were not changed significantly. Plasma glucose concentration was slightly decreased.

Plasma glucagon, GH, ACTH, and cortisol concentration were not significantly different between fasting healthy dogs and dogs with insulinomas. In dogs with insulinomas, basal plasma insulin concentrations were significantly higher and glucose concentrations significantly lower than in fasting healthy dogs. Plasma insulin concentration decreased significantly in response to octreotide administration. Plasma glucose concentration increased. Plasma concentrations of glucagon, GH, ACTH, and cortisol did not change.

No adverse effects of octreotide administration were observed in healthy dogs or dogs with insulinoma.

**Conclusions:** Subcutaneous administration of octreotide can suppress plasma insulin concentration in dogs with insulinoma without suppressing insulin antagonistic hormones or causing other adverse effects.

#### CLINICAL IMPACT:

The effects seen in this study were observed within the initial four hours of one parenteral administration of octreotide. Octreotide has a short duration of effect and

potential effects on multiple hormones. To effectively manage insulinoma, a long-duration octreotide preparation would be necessary. Octreotide acetate is a long duration preparation for intramuscular use, and an octreotide analog, lanreotide, for intramuscular or subcutaneous administration has anti-insulin effects. Whether these preparations would be safe and effective in dogs with insulinomas is not known.

**Note to the publisher- possible pull quote:** ΔOctreotide has a short duration of effect and potential effects on multiple hormones.@



## Hepatocellular Carcinoma with Hypoglycemia

Sakai M, Asano K, Nakata M, et al. Diabetes mellitus after resection of hepatocellular carcinoma with hypoglycemia in a dog. *J Vet Med Sci* 2006;68:765-767.

### INTRODUCTION:

**Background:** Hypoglycemia can be caused by non-insulinoma tumors in the retroperitoneum, thorax, or abdomen. Intra-abdominal tumors that may cause hypoglycemia include hepatocellular carcinoma, hepatoma, leiomyoma, leiomyosarcoma, melanoma, and hemangiosarcoma. Hepatocellular carcinomas are also the most common primary liver tumor in dogs. Removal of a hepatocellular carcinoma associated with hypoglycemia should correct the hypoglycemia.

**Objectives:** The intent of this case report was to describe a dog with hypoglycemia associated with hepatocellular carcinoma that developed diabetes mellitus after the liver tumor resection.

### SUMMARY:

**Case Report:** A 10-year-old, male, beagle was referred for treatment of hypoglycemic seizure and a large intra-abdominal tumor. Physical examination revealed cachexia and a palpable mass in the cranial aspect of the abdomen. There were no neurological deficits. Laboratory findings included a normal hemogram, hypoglycemia (34.6 mg/dl), hypoalbuminemia, and low urea nitrogen. All routine serum liver enzyme activities were abnormally high. Fasting and postprandial serum bile acid concentrations were high. Serum insulin and insulin-like growth factor I concentrations were low.

Abdominal radiographs confirmed the intraabdominal mass. Thoracic radiographs did not reveal any evidence of metastasis. The liver mass was evident by ultrasonography and hypoechoic. Computerized tomography images revealed a liver mass, but it was not enhanced by contrast medium. Laparoscopy confirmed the presence of a liver mass in the quadrate lobe. A needle biopsy findings were consistent with hepatocellular carcinoma.

The hepatocellular carcinoma was excised. Immediately after surgery the blood glucose concentration was high (203.8 mg/dl) and the serum insulin rose but to a low level (5.2  $\mu$ U/ml). Dietary therapy was tried for a week to attain euglycemia to no avail. Insulin-dependent diabetes mellitus was diagnosed and insulin therapy was begun. The dog responded beneficially to insulin therapy and lived two years after the hepatocellular carcinoma excision.

**Conclusions:** Blood glucose and serum fructosamine concentrations should be monitored periodically in dogs after the resection of large abdominal tumors that have caused hypoglycemia.

### CLINICAL IMPACT:

Large non-islet cell tumors in the abdomen have been previously been associated with hypoglycemia. There may be more than one cause, but the most common is believed to be tumor production of insulin-like growth factors, especially IGF-2. The tumor may produce excessive IGF-2 or impair IGF-2 binding to serum proteins. Other contributing factors may be rapid glucose utilization by the tumor or deficiency of insulin antagonists.

A consistent finding is suppressed serum insulin concentration concurrent with hypoglycemia.

The unique aspect of this case report is that after rectifying hypoglycemia and secondary suppressed insulin secretion by excising the hepatocellular carcinoma, insulin-dependent diabetes mellitus occurred. Removal of a non-islet cell tumor associated with hypoglycemia should not be the cause of diabetes. However, if a dog coincidentally had undiagnosed or subclinical insulin insufficiency and developed a non-islet cell tumor causing hypoglycemia, the insulin insufficiency could be masked until the tumor is removed. This unusual sequence of events may be the reason for the lack of previous reports of diabetes mellitus after hypoglycemia-causing, non-islet tumors have been excised.

**Note to the publisher- possible pull quote:** Removal of a non-islet cell tumor associated with hypoglycemia should not be the cause of diabetes.@

## Tests of Adrenal Function

### **Inverse Low-Dose Dexamethasone Test Results**

Mueller C, Sieber-Ruckstuhl N, Wenger M, et al. Low-dose dexamethasone test with Ainverse@ results: a possible new pattern of cortisol response. Vet Rec 2006;159:489-491.

#### INTRODUCTION:

**Background:** The low-dose dexamethasone suppression test (LDDST) is a sensitive test for diagnosis of hyperadrenocorticism, but false negatives do occur. It is considered positive for a diagnosis of hyperadrenocorticism when the serum cortisol concentration in the eight hour post-dexamethasone sample is elevated. Suppression of serum cortisol below normal or to less than 50% of the baseline concentration in the four hour sample is consistent with pituitary-dependent hyperadrenocorticism (PDH).

**Objectives:** The purpose of the study was to describe the cortisol response during the LDDST in dogs with PDH but normal cortisol concentration on the 8-hour post-dexamethasone.

#### SUMMARY:

**Methods:** Medical records of 80 dogs with a diagnosis of hyperadrenocorticism in which a LDDST was performed were examined. All cases where the eight hour sample on the LDDST was normal (less than 27.6 nmol/L; 1 µg/dl) were included in the study. A diagnosis of hyperadrenocorticism was based on appropriate clinical findings including an adrenocorticotrophic hormone (ACTH) response test or urine cortisol:creatinine ratio consistent with hyperadrenocorticism, adequate response to treatment with trilostane or mitotane, and/or histopathology of adrenal glands. Differentiation of PDH from adrenal tumor was made by abdominal ultrasound or computerized tomography of the pituitary gland. A LDDST result was considered inverse when the eight hour cortisol concentration was normal but the four hour level was elevated.

**Results:** Of 80 dogs with a diagnosis of hyperadrenocorticism, 10 had normal suppression of serum cortisol concentration on the eight hour sample during the LDDST. Five dogs had both four and eight hour serum cortisol concentrations in the normal range, three of which had PDH, and two had a unilateral adrenal adenoma. Of four dogs evaluated with an ACTH response test, two with PDH had an abnormal response while one with PDH and another with an adrenal tumor had normal results. Urine cortisol:creatinine ratio was elevated in all four dogs in which it was evaluated. The remaining five dogs all had PDH and fulfilled the criteria for an inverse response to the LDDST. The ACTH response test was abnormal in three of the dogs, and the urine cortisol:creatinine ratio was abnormal in two of the three dogs tested.

**Conclusions:** Some dogs with hyperadrenocorticism have normal suppression of cortisol at eight hours but not at four hours on the LDDST.

#### CLINICAL IMPACT:

Previous studies have shown that the LDDST is diagnostic of hyperadrenocorticism in

85-99% of dogs with hyperadrenocorticism, but the inverse result where the four hour sample is elevated but the eight hour sample is normally suppressed has not been previously reported. It is important to note that not all dogs with an inverse result have hyperadrenocorticism, but rather this result should cause the veterinarian to consider further testing.

Only dogs with PDH were examined in this study. It is possible that disease stressed dogs without PDH might have inverse LDDST results. A more frequent problem with the LDDST is its lack of specificity (false positive results due to the presence of nonadrenal illness).

**Note to the publisher- possible pull quote:** A more frequent problem with the LDDST is its lack of specificity@

## Hyperadrenocorticism

### **Once Daily Trilostane Administration**

Bell R, Neiger R, McGrotty Y et al. Study of the effects of once daily doses of trilostane on cortisol concentrations and responsiveness to adrenocorticotrophic hormone in hyperadrenocorticoid dogs. *Vet Rec* 2006;159:277-281.

#### INTRODUCTION:

**Background:** Trilostane is a synthetic steroid that competes with  $3\beta$ -hydroxysteroid dehydrogenase, and as a result, decreases the synthesis of cortisol, aldosterone, and androstenedione. It has been used to manage pituitary-dependent or adrenal-dependent hyperadrenocorticism. Results with once daily trilostane administration to dogs have been inconsistent. The duration of effects of trilostane may be less than 24 hours in some dogs.

**Objectives:** The purposes of this study were to determine the effects of once daily administration of trilostane to dogs with hyperadrenocorticism on basal serum or plasma cortisol concentrations and on cortisol concentrations four and 24 hours after ACTH stimulation.

#### SUMMARY:

**Methods:** Study 1: Nine dogs with pituitary-dependent hyperadrenocorticism were administered trilostane. Dosages ranged from 2.5 to 20 mg/kg (mean 6.3 mg/kg), once daily, for 10 days. Basal cortisol concentrations were measured every four hours for 24 hours prior to and after 10 days of trilostane administration.

Study 2: Another group of 10 dogs with pituitary-dependent hyperadrenocorticism were evaluated by ACTH stimulation testing. After administering trilostane at 2.0 to 8.2 mg/kg, once daily for at least three weeks, ACTH stimulation tests were performed at four and 24 hours after their last trilostane administration. Each dog was assigned to either a controlled or poorly controlled group based on physical examination and subjective evaluation of the patient history. Four dogs were considered controlled; six were considered poorly controlled.

**Results:** In Study 1, eight of the nine dogs responded to trilostane with decreased cortisol concentrations below the normal reference range between two and 13 hours. Cortisol concentrations rebounded to normal or above normal reference range before or by 13 hours after trilostane administration. The remaining dog responded to trilostane by decreased cortisol concentration but not below normal reference range.

In Study 2, there were no significant differences in trilostane dosage administered or between controlled and poorly controlled dogs= post-ACTH cortisol concentrations prior to trilostane administration. However, there was significantly greater responses to ACTH stimulation in poorly controlled dogs compared to controlled dogs. In both groups, there was significant increases in ACTH stimulation results at 24 hours after trilostane administration compared to those at four hours after trilostane administration.

**Conclusions:** The duration of trilostane biological effects is less than 24 hours and once per day administration adversely affects its clinical efficacy.

CLINICAL IMPACT:

Trilostane must be administered at least twice per day in most dogs to control pituitary-dependent hyperadrenocorticism. At the dosage used in this study, trilostane depressed serum cortisol concentration rapidly to lower than normal reference range although it did not adequately maintain the depressed cortisol concentrations. A higher single dose per day might prolong trilostane's effects but more rapid and lower depression of cortisol concentration in the first four or so hours could cause depression, anorexia, or cardiovascular collapse. Twice, or more often, per day administration of trilostane is required for reasonably safe and effective results, but this is considerably more expensive and time-consuming for affected dog owners than mitotane treatment.

**Note to the publisher- possible pull quote:** Trilostane must be administered at least twice per day in most dogs to control pituitary-dependent hyperadrenocorticism.®

## Retinoic Acid Therapy for Cushing=s Disease

Castillo V, Giacomini D, Paez-Pereda M, et al. Retinoic acid as a novel medical therapy for Cushing=s disease in dogs. *Endocrinol* 2006;147:4438-4444.

### INTRODUCTION:

**Background:** Treatment of pituitary-dependent hyperadrenocorticism in dogs has primarily been directed at reducing cortisol secretion by the adrenal glands. Surgical hypophysectomy, while potentially curative, is not widely available. Medical treatment of excessive adrenocorticotrophic hormone (ACTH) secretion with selegiline is generally successful. Retinoic acid inhibits tumor growth and invasion, and inhibits ACTH secretion. Therefore, it may be useful in treatment of hyperadrenocorticism due to pituitary neoplasia.

**Objectives:** The main objective of this study was to evaluate the efficacy of retinoic acid in the treatment of pituitary-dependent hyperadrenocorticism in the dog.

### SUMMARY:

**Methods:** Forty-two dogs with pituitary-dependent hyperadrenocorticism, diagnosed as having at least four clinical signs consistent with the disease, a urine cortisol:creatinine ratio (UCCR) more than 70 nmol/L, detectable plasma ACTH concentration, and evidence of a pituitary mass on magnetic resonance imaging (MRI) were evaluated. Dogs were randomly assigned to receive treatment with 9-cis retinoic acid at 2 mg/kg/day (22 dogs) or ketoconazole at 20 mg/kg/day (20 dogs) for 180 days. Clinical signs, specifically measurement of daily water intake, urination, food intake, dermatologic signs, abdominal distension, and body weight were monitored during treatment. Prior to and on days 120 and 180 of treatment, UCCR was measured. Plasma ACTH and alpha-melanocyte stimulating hormone (MSH) were measured before and monthly during treatment. The pituitary MRI was repeated after 180 days of treatment.

**Results:** Dogs receiving retinoic acid had significantly more improvement in water intake, polyuria, dermatologic signs, food intake, and abdominal distension than those treated with ketoconazole. The plasma ACTH and MSH concentrations were significantly decreased from 90B180 days of treatment in dogs receiving retinoic acid but was not affected by ketoconazole treatment. However, the ACTH levels were still elevated above the typical reference range in most dogs. The UCCR was decreased from pretreatment levels in both treatment groups but was significantly more decreased in the retinoic acid group at 180 days compared with dogs receiving ketoconazole.

The size of the pituitary tumor decreased significantly in the retinoic acid treatment group, with clear reduction in the tumor in all but one case. Dogs treated with ketoconazole showed no change in tumor size during treatment. Dogs treated with retinoic acid had significantly longer survival than those receiving ketoconazole, with two and 10 dogs dying from complications of hyperadrenocorticism in the retinoic acid and ketoconazole groups, respectively, during the 180 days of treatment. None of the dogs treated with retinoic acid showed recurrence of clinical signs of hyperadrenocorticism up to 12 months after cessation of retinoic acid administration. Adverse effects of retinoic

acid administration were not noted in any dog, although one developed hyperkeratosis of the footpads.

**Conclusions:** Retinoic acid administration is an effective treatment for pituitary tumors causing hyperadrenocorticism in dogs.

CLINICAL IMPACT:

This novel approach to treatment of pituitary tumor appears promising based on results of this study. However, the retinoic acid administered orally in this study is expensive and not readily available. Most of the benefits of this treatment were compared to a poor medical treatment for hyperadrenocorticism. The comparison of retinoic acid with ketoconazole effects may have unknowingly been biased since ketoconazole is not a particularly effective drug for controlling hyperadrenocorticism. Mitotane or trilostane would have been more effective than ketoconazole.

The reasons for the inconsistencies in findings of this study compared with previous ones is unclear. The single investigator evaluating clinical response was not blinded to treatment groups, and dosage adjustments for either treatment were not mentioned.

Response of corticotrophic adenomas to 9-cis retinoic acid is thought to be due to its interaction with both the retinoic acid receptor and retinoic X receptor, resulting in decreased ACTH production and reduced proliferation of adenomatous tissue. Other forms of retinoic acid have not been shown to have similar effects.

**Note to the publisher- possible pull quote:** ΔDogs treated with retinoic acid had significantly longer survival than those receiving ketoconazole@



## Adrenal Hormones and ACTH Responses to Trilostane Therapy

Sieber-Ruckstuhl NS, Boretti FS, Wenger M, et al. Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Dom Anim Endocrinol* 2006;31:63-75.

### INTRODUCTION:

**Background:** Trilostane is an antagonist of 3- $\beta$ -hydroxysteroid dehydrogenase in the adrenal cortex. As such, it is expected to reduce secretion of cortisol, sex steroids, and aldosterone. However, based on a small number of patients, trilostane administration to dogs with hyperadrenocorticism has not necessarily reduced 17-hydroxyprogesterone concentrations and may have variable effects on aldosterone secretion. With the recognition of atypical hyperadrenocorticism where non-cortisol steroid hormones such as 17-hydroxyprogesterone are elevated despite normal tests of cortisol secretion, it is important to understand the action of trilostane on adrenal steroid secretion.

**Objectives:** The objective of this study was to determine the effect of trilostane administration to dogs with pituitary-dependent hyperadrenocorticism on hormones in the adrenal steroidogenesis pathway that would be affected by inhibition of the 3- $\beta$ -hydroxysteroid dehydrogenase.

### SUMMARY:

**Methods:** Fifteen dogs with pituitary-dependent hyperadrenocorticism were studied before, 1-2 and 3-7 weeks after administration of therapeutic dosages of trilostane. Concentrations of hormones in the steroidogenesis pathway before the action of 3- $\beta$ -hydroxysteroid dehydrogenase (17-hydroxypregnenolone and dehydroepiandrosterone; DHEA) and after (cortisol, aldosterone, 17-hydroxyprogesterone, androstenedione, 11-deoxycortisol, 21-deoxycortisol) the action of 3- $\beta$ -hydroxysteroid dehydrogenase were measured on serum samples collected before and after synthetic adrenocorticotrophic hormone (ACTH) administration. In addition, endogenous plasma ACTH concentrations were measured. Trilostane dosage was adjusted to achieve a post-ACTH cortisol concentration of 132.5  $\mu$ g/dl.

**Results:** All dogs improved clinically within the first 13 weeks of treatment. Concentrations of 17-hydroxypregnenolone and DHEA were increased as would be anticipated with inhibition of 3- $\beta$ -hydroxysteroid dehydrogenase. One of the end products of steroidogenesis, cortisol, was suppressed before and after ACTH administration while the other end product, aldosterone, had increased basal concentrations and decreased to normal concentrations in response to ACTH. Concentrations of the steroid intermediates, 17-hydroxyprogesterone, androstenedione, 11-deoxycortisol, 21-deoxycortisol were largely unchanged by trilostane treatment, although basal 11-deoxycortisol decreased and post-ACTH 21-deoxycortisol increased. The plasma ACTH concentration was significantly increased at the time of the second evaluation compared with that prior to treatment.

**Conclusions:** Based on the pattern of hormone concentrations, trilostane inhibits 3- $\beta$ -

hydroxysteroid dehydrogenase and 11- $\beta$ -hydroxylase activities in dogs with hyperadrenocorticism.

**CLINICAL IMPACT:**

The clinical response to trilostane was good in all dogs despite the finding that many of the steroid intermediates were not reduced. Importantly, serum 17-hydroxyprogesterone concentrations were not decreased by trilostane. Therefore, elevated serum 17-hydroxyprogesterone, while useful for diagnosis of hyperadrenocorticism in some cases, should not be used to monitor response to treatment. All post-treatment monitoring should be performed by measuring cortisol responses to ACTH. In addition, trilostane may not be effective treatment for atypical hyperadrenocorticism or Alopecia X associated with elevated serum 17-hydroxyprogesterone concentration.

**Note to the publisher- possible pull quote:** Trilostane inhibits 3- $\beta$ -hydroxysteroid dehydrogenase and 11- $\beta$ -hydroxylase activities in dogs@

## Glucocorticoid Therapy

### **Effect of Inhalant Corticosteroids on the Pituitary-Adrenal Axis**

Reinero CR, Brownlee L, Decile KC, et al. Inhaled flunisolide suppresses the hypothalamic-pituitary-adrenocortical axis, but has minimal systemic immune effects in healthy cats. J Vet Intern Med 2006;20:57-64.

#### INTRODUCTION:

**Background:** Although cats infrequently develop signs of iatrogenic hyperadrenocorticism when administered oral glucocorticoids, long-term administration of these agents suppresses pituitary adrenocorticotrophic hormone (ACTH) secretion and causes adrenocortical atrophy. Cats with respiratory disease are often administered corticosteroids orally, but the inhalant route of administration is becoming more common. Inhalant administration of corticosteroids is expected to reduce systemic absorption and therefore reduce the systemic adverse effects of the drugs while maintaining efficacy in respiratory disease.

**Objectives:** The purpose of this study was to compare the effects of oral prednisone and inhaled flunisolide on the pituitary-adrenal axis and on systemic immune function.

#### SUMMARY:

**Methods:** Six healthy client-owned cats were studied using a randomized, cross-over, repeated measures, placebo controlled study. Cats were randomly assigned to receive a two week course of placebo (empty inhalant chamber applied for 10 breaths), inhaled flunisolide (250 µg in an inhalant chamber for 10 breaths twice daily), or prednisone (10 mg, orally, once daily). All cats received each treatment with a four week washout period between treatments. Clinical signs, adrenocortical and immune function were evaluated immediately before and at the end of each two week treatment period. Any adverse effects including abnormal behavior, appetite, water intake, or activity and urine specific gravity were noted during each treatment. Urine cortisol:creatinine ratio, basal serum cortisol concentration, and cortisol response to ACTH stimulation were measured to evaluate adrenocortical function. Immune function was evaluated using total lymphocyte count, lymphocyte phenotype, lymphocyte blastogenesis, serum IgM and IgA concentrations, and cytokine production.

**Results:** The only potential clinical sign of hyperadrenocorticism noted was a mild to moderate increase in appetite of all cats during oral prednisone treatment. The basal serum cortisol, cortisol in response to ACTH stimulation, and urine cortisol:creatinine ratio were significantly and markedly decreased during inhalant glucocorticoid treatment but not during oral prednisone administration. The blood total lymphocyte number and the absolute number of lymphocyte subsets did not differ with either treatment compared with placebo, but the percentage of T cells and B cells were significantly lower during oral prednisone treatment than during placebo treatment. Lymphocyte blastogenesis response was decreased during oral but not inhalant glucocorticoid treatment. Serum antibody concentrations were not affected by either treatment. The only effect of treatment on cytokines was an increase in IL-10 mRNA transcription during both

glucocorticoid treatments.

**Conclusions:** Inhalant glucocorticoid treatment suppresses the pituitary-adrenocortical axis but minimal effects on the systemic immune function.

**CLINICAL IMPACT:**

The most important finding of this study is that substantial suppression of cortisol secretion is induced by two weeks of inhalant flunisolide treatment. Because much of the justification of inhalant therapy is to reduce systemic adverse effects, it is important to realize that systemic absorption of this corticosteroid is sufficient to have this effect. Therefore, if treatment is continued for four weeks or more, it would be appropriate to gradually taper the drug prior to discontinuation to avoid signs of hypoadrenocorticism. In addition, systemic glucocorticoid supplementation might be necessary if a cat receiving inhalant corticosteroids were placed in a stressful situation by illness or surgery. It is unclear why oral prednisone did not suppress the pituitary-adrenal axis, but the poor bioavailability of prednisone compared with the active compound, prednisolone, has been noted to occur in cats.

**Note to the publisher- possible pull quote:** A substantial suppression of cortisol secretion is induced by two weeks of inhalant flunisolide treatment@

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

