

Endocrinology

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

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Feline Hypothalamic-Adenohypophyseal Tumors

Troxel MT, Vite CH, Van Winkle TJ, et al. Feline intracranial neoplasia: retrospective review of 160 cases (1985-2001). *J Vet Intern Med* 2003;17:850-859.

► INTRODUCTION:

Background: The incidence of feline intracranial tumors is believed to be 0.0035 to 2.2% of cats. Not only is the reported incidence range extremely wide, very little is known of the relative incidence of intracranial tumor types or their signs, location, and individual prognosis.

Objectives: The purpose of the study was to determine the frequency of intracranial tumors in cats and to correlate signalment, tumor size, location, and survival time for each tumor.

✦ SUMMARY:

Methods: The medical records of 160 cats with intracranial tumors that were seen over a period of 15 years were reviewed retrospectively. These were selected from among a total of 228 cats with 244 brain tumors diagnosed in this period. Parameters collected included age, sex, breed, Feline Leukemia Virus (FeLV) and Immunodeficiency Virus (FIV) status, clinical signs and duration of signs, histological tumor types and locations, imaging results, treatment, and survival times.

Results: The median age of affected cats was 11.3 ± 3.8 years. Primary tumors comprised 70.6% of cases. The third most common location was the pituitary (14, 9.3%). The median age for cats with pituitary tumors was 10.1 years, with a range of 4.2 to 17 years. More males (11 cats) were affected than females (3 cats). All, but one, was a domestic short-haired cat. All that were tested for FeLV and FIV were negative.

The most common clinical sign was blindness (35.7%), followed by altered consciousness (28.6%). Other less common or specific clinical signs observed were circling, ataxia, head pressing, head tilt, pacing, anorexia, weight loss, and polyuria and polydipsia. Associated endocrinopathies were diabetes mellitus (50%), pituitary-dependent hyperadrenocorticism (14.3%), hypoadrenocorticism (7.1%), and hyperthyroidism (7.1%).

Greater use of CT or MR imaging in suspected cases (blindness, altered consciousness, polyuria and polydipsia, or a combination) is justifiable.

The pituitary tumor in 35.7% of cats was considered incidental. The median duration of clinical signs prior to diagnosis was 37.5 days.

Eleven of 14 cats with pituitary tumors were diagnosed at necropsy. One cat was diagnosed for possible pituitary tumor using computerized tomography; two were diagnosed by magnetic resonance imaging.

Five cats were administered palliative corticosteroids. The median duration of clinical signs until death was 52.5 days, with a range of 1 to 323 days.

Conclusions: Pituitary tumors are more common among intracranial tumors in cats than previously reported. Their association with endocrinopathies is more frequent than pituitary tumors in dogs.

🌀 CLINICAL IMPACT:

The results of this 15-year-long retrospective study aid to put feline pituitary tumors into more proper perspective. Pituitary tumors in older cats are not uncommon among intracranial tumors, and more often than in dogs, they are associated with signs of endocrinopathy, especially diabetes mellitus.

The great majority of these cats had pituitary tumors diagnosed at necropsy. Greater use of computerized tomography (CT) or magnetic resonance (MR) imaging in suspected cases (blindness, altered consciousness, polyuria and polydipsia, or a combination) is justifiable for diagnostic and prognostic reasons. It is possible that external beam irradiation of tumors detected earlier could be either curative or palliate clinical signs.

Unfortunately, the tumor cell types were not reported. It is curious that acromegalic signs were not reported in any of the cats with diabetes mellitus. It is unlikely that all were associated with pituitary-dependent hyperadrenocorticism.

- ▶ Pituitary tumors comprise 8.8% of all intracranial neoplasia in cats. *J Vet Intern Med* 2003;17:850-859.
- ▶ Dynamic computed tomography may reveal pituitary adenomas or diffusely abnormal pituitary glands. *J Vet Intern Med* 2003;17:773-780.
- ▶ Aspirin therapy can markedly decrease serum total T₄ concentration in dogs. *Vet J* 2003;166:224-232.
- ▶ Multidose etodolac administration can significantly decrease serum T₄ and increase c-TSH concentrations in dogs. *Vet Therap* 2003;4:340-349.
- ▶ The arthritis management medications meloxicam and carprofen and the nutraceutical, chondroitin sulfate-glucosamine-manganese ascorbate, do not significantly alter thyroid function test results. *Can Vet J* 2003;44:474-479.
- ▶ Percutaneous radiofrequency heat ablation of the thyroid is effective only transiently for treatment of feline hyperthyroidism. *J Am Vet Med Assoc* 2003;223:1602-1607.
- ▶ Carcinoma of the apocrine glands occurs without gender predilection and has a more favorable prognosis than previously reported. *J Am Vet Med Assoc* 2003;223:825-831.
- ▶ Most owners of diabetic dogs are able and willing to perform home monitoring of blood glucose concentrations. *J Sm Anim Pract* 2003;44:298-305.
- ▶ Continuous glucose monitoring of interstitial fluid may be a valuable tool for monitoring diabetic dogs, but it may not provide an accurate parallel of blood glucose concentrations 1 to 3 hours postprandially. *J Sm Anim Pract* 2003;44:435-442.
- ▶ Increasing age, body weight less than 22.7 kg, and female gender are risk factors for diabetes mellitus in dogs. *Vet J* 2003;165:240-247.
- ▶ Darglitazone administration improves insulin sensitivity and glucose and lipid metabolism in obese cats. *Am J Vet Res* 2003;64:1409-1413.
- ▶ The alpha-glucosidase inhibitor, acarbose, and a low-carbohydrate diet reduces insulin dependence in diabetic cats. *J Fel Med Surg* 2003;5:183-189.
- ▶ Cats are not at high risk for systolic hypertension due to diabetes mellitus. *J Am Vet Med Assoc* 2003;223:198-201.
- ▶ Continuous glucose monitoring is valid for use in dogs and cats. *J Am Vet Med Assoc* 2003;223:987-992.
- ▶ Hypoglycemia from insulinoma in cats can cause irreversible neurologic complications. *J Am Vet Med Assoc* 2003;223:812-814.
- ▶ Post-ACTH stimulated plasma 17-hydroxyprogesterone concentrations vary widely, and overlap occurs between normal dogs and dogs with hyperadrenocorticism. *Vet Rec* 2003;153:771-775.
- ▶ Trilostane treatment of dogs with hyperadrenocorticism is safe and effective, although initial sensitivity to the drug wanes after the first month of treatment. *Aust Vet J* 2003;81:600-607.
- ▶ Adrenal tumor-associated vena caval thrombi can be removed at the same time as adrenalectomy without significantly increasing perioperative morbidity or mortality. *J Am Vet Med Assoc* 2003;223:654-662.
- ▶ Trilostane may be an effective medical adjunct to bilateral adrenalectomy for cats with hyperadrenocorticism. *J Sm Anim Pract* 2003;44:269-272.
- ▶ Care must be taken in the rate of correcting chronic hyponatremia in dogs with hypoadrenocorticism to reduce the risk of iatrogenic myelinolysis. *Can Vet J* 2003;44:490-492.



Dynamic CT of the Pituitary in Dogs with Hyperadrenocorticism

van der Vlugt-Meijer RH, Meij BP, van den Ingh TSGAM, et al. Dynamic computed tomography of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 2003;17:773-780.

► INTRODUCTION:

Background: Hypophysectomy is the treatment of choice in humans with pituitary-dependent hyperadrenocorticism. In dogs with pituitary-dependent hyperadrenocorticism, it has been used to a greater extent in Europe than in the USA. The success of hypophysectomy begins with accurate presurgical images of the pituitary to assess the size and location of the tumor relative to surgical landmarks.

Conventional contrast-enhanced computerized tomography (CT) does not differentiate pituitary microadenomas well from the surrounding tissue. Dynamic contrast-enhanced CT includes scans of the same slice position during and after an intravenous injection of contrast medium. Dynamic CT permits visualization of displacement, distortion, or disappearance of the pituitary perfusion ("pituitary flush") that can disclose microadenomas when present.

Objectives: The aim of this report was to report on dynamic CT of the pituitary in dogs with pituitary-dependent hyperadrenocorticism and to correlate the findings with those at transsphenoidal hypophysectomy and histopathologic examination.

✕ SUMMARY:

Methods: Dynamic CT of the pituitary was performed on 55 dogs with pituitary-dependent hyperadrenocorticism that would receive transsphenoidal hypophysectomy. Histopathologic examinations were performed on excised pituitary tissue. Dynamic CT findings and histopathologic findings were correlated.

Results: Dynamic CT of the pituitary demonstrated the presence of microadenomas

in 36 dogs by enhanced contrast pituitary flush of the neurohypophysis. Ten dogs had an enlarged pituitary and abnormal pituitary flush. Twenty-four dogs had no enlargement of the pituitary but had displaced pituitary flush consistent with an adenoma. Surgical and histological confirmation was achieved in 18 of the 24 dogs. A diffusely abnormal contrast pattern was evident in 19 dogs. The findings at surgery agreed with the CT images in 13 dogs. Histological findings agreed with CT findings in all 19 dogs.

Conclusions: Dynamic CT enables the detection of pituitary adenomas and diffusely abnormal pituitaries and therefore should be used prior to hypophysectomy.

If hypophysectomy is planned as an option of treatment, dynamic CT appears to be a beneficial preoperative evaluation.



CLINICAL IMPACT:

There is considerable difference in the morphology of the pituitary in dogs and humans. However, in both, dynamic CT is helpful in detecting an abnormal pituitary flush. Abnormal flush signifies the presence of an adenoma whether or not there is overall enlargement of the pituitary. Pituitary flush is diminished or absent when there is abnormal space occupation, i.e. a microadenoma, in the pituitary.

The value of this procedure in dogs that will be treated medically is only academic, and is not needed for formulating a treatment plan. There is practical value if hypophysectomy, or perhaps, radiotherapy may be used. The cost of the procedure relative to conventional CT was not mentioned. Again, if hypophysectomy is planned as an option of treatment, dynamic CT appears to be a beneficial preoperative evaluation.



Effect of Aspirin and Ketoprofen on Thyroid Function Tests

Daminet S, Croubels S, Duchateau L, et al. Influence of acetylsalicylic acid and ketoprofen on canine thyroid function tests. *Vet J* 2003;166:224-232.

➔ INTRODUCTION:

Background: Many drugs are known to alter thyroid function or thyroid test results. Non-steroidal anti-inflammatory drugs (NSAIDs) are among these in humans. Several new NSAIDs, including ketoprofen, have become approved for use in dogs that may alter thyroid function or thyroid test results.

Objectives: The reason for this study was to determine the effect of acetylsalicylic acid (aspirin) and ketoprofen on thyroid function test results in dogs.

✦ SUMMARY:

Methods: Eighteen spayed female beagles were randomly assigned to three treatment groups in a 3X3 crossover study. The three treatment groups were administered: (1) aspirin, 25 mg/kg, twice per day; (2) ketoprofen, 1 mg/kg, once daily; and (3) lactose placebo, once daily. Each batch of six dogs assigned to treatment group were administered the NSAID or placebo for a week followed by a three week washout period. During weeks of treatment, blood samples were taken on days 0, 1, 3, and 7. Weekly samples were taken during the washout periods. Determinations done on blood samples were for concentrations of total T_4 , free T_4 , total T_3 , canine thyroid-stimulating hormone, reverse T_3 , aspirin, and ketoprofen.

Results: Mean plasma aspirin and ketoprofen levels were within recommended therapeutic ranges during drug administration. Serum total T_4 concentrations decreased significantly within 24 hours of receiving aspirin. Normal levels were regained one week after aspirin administration was discontinued. Total T_3

decreased less and not significantly compared to placebo until the end of the week of administration. No significant changes in thyroid function were detected associated with ketoprofen administration.

Conclusions: Aspirin administration can rapidly and significantly reduce total T_4 concentrations in dogs.



CLINICAL IMPACT:

NSAIDs are capable of altering plasma protein binding. More than 99% of circulating T_4 is normally bound to plasma proteins. Although additional mechanisms may be involved, aspirin affects more binding sites on albumin than does ketoprofen and therefore displaces more T_4 as free T_4 . Free T_4 suppresses TSH and this in turn, reduces T_4 production and serum T_4 concentration.

The reason for concern about drug-induced changes in thyroid test results is that a misdiagnosis of hypothyroidism could result in an inappropriate life-long treatment of supplementation of thyroid hormone.

If principles of good endocrine diagnostics are adhered to, none of these changes will lead to a misdiagnosis. First, all current or recent medications should be investigated before endocrine testing is done and especially before results of testing are interpreted. Second, the diagnosis of hypothyroidism should not be definitive whenever clinical signs do not exist. And third, a single marginally low serum T_4 level should not be the basis for a diagnosis of hypothyroidism. Low thyroid hormone levels induced by medications are marginally and inconsistently lower than normal range (45% of T_4 concentrations measured in dogs receiving aspirin were in normal range).

Serum total T_4 concentrations decreased significantly within 24 hours of receiving aspirin.



Effect of Etodolac on Thyroid Function Tests

Ness TA, Torres SMF, Kramek EA, et al. Effect of dosing and sampling time on serum thyroxine, free thyroxine, and thyrotropin concentrations in dogs following multidose etodolac administration. *Vet Therap* 2003;4:340-349.

► INTRODUCTION:

Background: A variety of nonsteroidal anti-inflammatory drugs (NSAIDs) decrease serum T_4 concentrations in humans. In dogs, high doses of aspirin have a similar effect, but other NSAIDs have less consistent effects. Because these drugs are widely used for treatment of osteoarthritis and other disorders in dogs, it is important to understand their effects on thyroid function tests.

Objectives: The objectives of this study were to determine the effect of etodolac on thyroid function tests.

Thyroid function should not be evaluated in dogs receiving etodolac.

✕ SUMMARY:

Methods: Thirty-eight dogs that were treated, 21 medically and 17 surgically, for orthopedic disorders were studied by measuring serum T_4 , free T_4 , and canine thyroid-stimulating hormone (c-TSH) concentrations before and at the end of 14 to 19 days of etodolac administration (10 to 13.3 mg/kg, orally, once daily). To be included in the study dogs had to be free of other significant nonthyroidal illness, have not received drugs known to affect thyroid function for one month, and be free of significant complete blood count and routine serum chemistries abnormalities.

Results: In dogs that were treated only medically, the mean serum T_4 concentration decreased significantly comparing pretreatment (21.4 nmol/L) to post-treatment (17.1 nmol/L) values, but was not different in dogs that underwent surgery (23.0 nmol/L vs. 19.7 nmol/L). When all dogs were evaluated as one group, the mean serum T_4 concentration decreased significantly after etodolac administration. Serum T_4 concentration was

below the normal range (12.9 to 51.5 nmol/L) in eight (38%) dogs when receiving etodolac. The mean serum free T_4 concentration was not significantly affected in dogs in the medical or surgical group or when all dogs were evaluated as one group. Serum free

T_4 concentration was below the reference range in four dogs. The mean c-TSH concentration was significantly increased after etodolac treatment in the surgical group (0.1 ng/ml vs. 0.2 ng/ml), but not in the medically managed dogs. When all dogs were evaluated as a single group, the mean serum c-TSH increased during etodolac administration, but no dog had a level above the reference range.

Conclusions: Etodolac administration results in a decrease in serum T_4 concentrations that are frequently below the reference range, and thyroid function should not be evaluated in dogs receiving etodolac.



CLINICAL IMPACT:

The changes in mean serum T_4 concentration in this study were slight, but the finding that 38% and 11% of treated dogs had a low serum T_4 or free T_4 concentration respectively, is important. Unfortunately, a control group was not included in this study, and other variables might account for the decrease in serum T_4 concentration. A study evaluating a similar dose of etodolac to dogs in laboratory conditions did not demonstrate any effect on thyroid function tests. When evaluating thyroid function in dogs receiving etodolac, it is preferable to discontinue treatment prior to testing. If this is not possible, measurement of free T_4 concentration is preferred over total T_4 concentration.



Effect of Meloxicam, Carprofen, and a Nutraceutical on Thyroid Function Tests

Sauve F, Paradis M, Refsal KR, et al. Effects of oral administration of meloxicam, carprofen, and a nutraceutical on thyroid function in dogs with osteoarthritis. *Can Vet J* 2003;44:474-479.

➔ INTRODUCTION:

Background: Some nonsteroidal anti-inflammatory drugs (NSAIDs) alter thyroid function tests primarily through impaired protein binding, although other factors may also play a role. With the advent of many new NSAIDs and the prevalent use of this class of drugs in dogs, it is important to know their effects in order to properly select and interpret thyroid function tests in dogs receiving these agents.

Objectives: The objective of this study was to evaluate the effects on thyroid function tests of meloxicam, carprofen, and a nutraceutical purported to have beneficial effects on osteoarthritis.

✦ SUMMARY:

Methods: Sixty-two dogs with naturally-occurring osteoarthritis of the elbow, hip, or stifle were evaluated. The dogs were otherwise healthy. Blood samples were obtained for measurement of thyroglobulin autoantibodies before, and serum concentrations of total T_4 , free T_4 , and canine thyroid stimulating hormone (c-TSH) concentrations before and 30 and 60 days after treatment with carprofen (14 dogs), meloxicam (14 dogs), a nutraceutical (18 dogs), or placebo consisting of meloxicam vehicle (16 dogs). The nutraceutical consisted of a combination of chondroitin sulfate, glucosamine, and manganese ascorbate.

There was no significant difference in serum T_4 , free T_4 , or c-TSH concentrations between any of the treatment groups.

Results: There was no significant difference in serum T_4 , free T_4 , or c-TSH concentrations between any of the treatment groups. Serum c-TSH concentration increased significantly over time, but the change was similar in all groups.

Conclusions: Thyroid function tests are not affected by administration of meloxicam, carprofen, or a nutraceutical in dogs with osteoarthritis.



CLINICAL IMPACT:

Although only a few NSAIDs have been evaluated for their effect on thyroid function tests, dogs appear to be relatively resistant compared with humans. This may in part be because thyroid hormone binding proteins differ considerably between these species. A previous study of a 50% higher dose of carprofen than the amount administered in this study showed a significant reduction in serum T_4 , but the decrease was slight.

The effects of aspirin, which consistently decreases serum T_4 concentrations in humans, appears to be slight at clinically applicable dosages. While the effects of some NSAIDs on thyroid function remain to be determined, it seems unlikely that this class of drugs has important effects on thyroid function in the dog.



Heat Ablation Treatment of Hyperthyroidism in Cats

Mallery KF, Pollard RE, Nelson RW, et al. Percutaneous ultrasound-guided radiofrequency heat ablation for treatment of hyperthyroidism in cats. *J Am Vet Med Assoc* 2003;223:1602-1607.

► INTRODUCTION:

Background: Hyperthyroidism is the most commonly diagnosed endocrinopathy in cats. Treatment options are traditionally medical using antithyroid medications, surgical excision of affected thyroid lobes, or radioiodine. Non-conventional treatments that have been more recently described are chemical ablation with intrathyroidal ethanol injection and percutaneous radiofrequency heat ablation.

Ultrasound-guided ethanol injection is an inexact procedure that is less likely than traditional treatments to achieve or maintain euthyroidism. It also risks chemical migration adversely affecting surrounding tissue, particularly the recurrent laryngeal nerve. Percutaneous heat ablation may be more efficacious and safe than ethanol injection.

Objectives: The purpose of this study was to determine the efficacy and safety of percutaneous heat ablation for treatment of hyperthyroidism in cats.

✕ SUMMARY:

Methods: Nine cats with hyperthyroidism based on at least three clinical signs of hyperthyroidism and two abnormally high serum T_4 and free (f) T_4 concentrations were included in the study. In addition, scintigraphy and ultrasonography of the thyroids had to indicate enlargement of at least one thyroid lobe. Heat ablation guided by ultrasound was applied to the solitary enlarged lobe or largest lobe, if both lobes were enlarged. Serum T_4 , f T_4 , and calcium concentrations were monitored daily for two days (including just before ablation), weekly for one month, and monthly after ablation. Laryngeal function and ultrasonography of the thyroid were also monitored at four and eight weeks if hyperthyroidism was not resolved within a month. A total of 14 heat ablation treatments

were administered to the nine cats.

Results: Unilateral thyroid enlargement was found in four cats by scintigraphy; five cats had bilateral involvement. Within two weeks of each treatment, serum T_4 and f T_4 concentrations decreased. One cat with unilateral involvement and two cats with bilateral involvement were treated a second time. A third bilaterally involved cat was treated three more times. In 10 of 14 treatments, the serum T_4 and f T_4 concentrations were at or below reference ranges for normal. Euthyroidism was maintained for a mean of four months (range of 0 to 18 months).

All cats became hyperthyroid again. Two cats developed transient Horner's syndrome and one cat developed laryngeal paralysis.

Conclusions: Percutaneous heat ablation for feline hyperthyroidism is only transiently effective.

Percutaneous heat ablation for feline hyperthyroidism is only transiently effective.



CLINICAL IMPACT:

Transient control of hyperthyroidism is not a bad thing. Hyperthyroid cats in this study were typical of the population at risk with a minimum age of nine years and a mean age of 13 years. Transient control of hyperthyroidism may be sufficient to allow the cat to succumb to another cause for death. Or, the owner may opt for a more effective treatment after seeing how much better the cat is when it is euthyroid.

However, there will be few if any situations where the cat's condition or a well informed owner decision leads to heat ablation as the best option for treatment. Heat ablation should never be considered in the top three treatments available for control of hyperthyroidism. It should be considered superior to ethanol injection.



Apocrine Gland Carcinoma of the Anal Sacs in Dogs

Williams LE, Gliatto JM, Dodge RK, et al. Carcinoma of the apocrine glands of the anal sac in dogs: 113 cases (1985-1995). J Am Vet Med Assoc 2003;223:825-831.

► INTRODUCTION:

Background: Random reports of dogs with apocrine gland adenocarcinomas suggest that it occurs more often in female than male dogs, is aggressively malignant with a metastasis rate of at least 50%, and produces a hypercalcemic paraneoplastic syndrome in 25% of cases.

It is considered the second most frequent cause of hypercalcemia of malignancy in dogs with lymphosarcoma being the first.

Objectives: The purpose of this study was to better characterize the signalment, clinical signs, biological effects, and response to treatment in dogs with apocrine gland adenocarcinoma of the anal sacs.

All dogs 5-years-old or more, should have their anal sacs, rectum, and iliac lymph nodes palpated and serum calcium concentration monitored during annual health examinations.



CLINICAL IMPACT:

Conclusions: Dogs with apocrine gland adenocarcinoma of the anal sacs have a better prognosis and more equal gender distribution than previously reported.

This study reports a near equal gender risk for apocrine gland adenocarcinoma of the anal sac. It also includes a dog that was 5-years-old at diagnosis. Although previous reports indicated a greater risk in older female dogs, the gender and age risk should not influence the need to investigate all dogs with perianal tumors or hypercalcemia for apocrine gland adenocarcinoma of the anal sacs.

Even with appropriate clinical sensitivity to the need to investigate suspicious cases, many cases are occult. Four in 10 cases of this report were discovered as an incidental finding. Hypercalcemia of malignancy and metastasis can occur during the occult stage. For example, some of the anal sac adenocarcinomas causing hypercalcemia were less than 1 cm².

The optimum chemotherapy for metastasis remains unknown. The results of this study indicate that all cases should undergo surgery, but whether current chemotherapy is helpful is not clear and it may detract from the quality of remaining life.

Until a more sensitive marker of the disease is found, all dogs 5-years-old, or more, should have their anal sacs, rectum, and iliac lymph nodes palpated and serum calcium concentration monitored during annual health examinations.

✕ SUMMARY:

Methods: Signalment, clinical signs, staging, and survival time were evaluated by a survey questionnaire in a multi-institutional study of 113 dogs with carcinoma of the anal sac.

Results: No gender predisposition was evident (54% females and 46% males). Perianal swelling (53%) was the most common clinical sign. No other clinical sign was detected in more than 34% of cases. Treatment was attempted in 104 cases using surgery, radiotherapy, chemotherapy, or a combination of the therapies. The median survival time was 544 days (range of 0-1,873 days). The shortest survival times were associated with chemotherapy alone, and 36% of dogs receiving chemotherapy had drug-related adverse effects. The longest survival times occurred in conjunction with surgery or surgery and other forms of treatment. Significantly shorter survival times occurred with tumors of at least 10 cm². Hypercalcemia was detected in 27% of cases. Dogs with hypercalcemia or pulmonary metastasis had shorter survival times.



Home Monitoring of Blood Glucose Concentration in Diabetic Dogs

Casella M, Weiss G, Hassig M, et al. Home monitoring of blood glucose concentration by owners of diabetic dogs. *J Sm Anim Pract* 2003;44:298-305.

► INTRODUCTION:

Background: Assessment of response to treatment of diabetes mellitus is made by evaluation of clinical signs, physical examination, blood glucose measurements, and glycated proteins such as serum fructosamine. Blood glucose curves are frequently considered the best method of determining the response to treatment. However, multiple factors, including the stress of transportation and hospitalization and differences in feeding and exercise, that accompany in-hospital evaluations may reduce the validity of glucose curves. With the advent of relatively accurate glucometers that require a very small volume of blood, monitoring of blood glucose concentrations has become practical for some pet owners.

Objectives: The objective of this study was to determine if long-term monitoring of blood glucose by owners in their homes was practical.

✕ SUMMARY:

Methods: Twelve dogs with diabetes mellitus were studied over a 16 week period, with blood glucose curves performed in the hospital on weeks 6, 9, 12, and 16. Blood glucose curves were performed at home by the owners within one week prior to hospital measurements. All blood glucose measurements were obtained using the same method. A lancet device that applies a vacuum to enhance formation of a blood droplet of adequate size was used to obtain a sample from the inner pinna. A portable glucometer was used that acquires a small sample (2 μ l) of blood from the droplet formed on the pinna and determines the glucose concentration.

Owners completed a questionnaire regarding technical aspects of sampling

including operation of the lancet and glucometers, adequacy of blood droplet, tolerance of the dog to the procedure, and overall feasibility of the procedure. Comparisons between the hospital and home blood glucose curves were evaluated using the nadir, maximum, and mean blood glucose concentrations. In addition, the decision to adjust the insulin dose was evaluated using hospital and home generated curves with a dose decrease planned when the nadir was less than 72 mg/dl, no change planned when the nadir was 72 to 180 mg/dl, and a dose increase indicated when the nadir was more than 180 mg/dl.

Results: Ten of the 12 owners were able to perform blood glucose measurements on their dogs. Initial problems encountered by owners included trouble producing negative pressure with the lancet device, dog restraint, generation of an adequate blood drop, uptake of blood into the glucometer strip, and use of glucometers and test strips. These problems were resolved after telephone consultation or further training. Only one dog required restraint by a second individual for sampling beyond the first glucose curve. Production of negative pressure by the lancet device continued to be a minor problem with three owners. The mean and maximum blood glucose concentrations for the hospital samples were significantly lower than the home samples on the first two glucose curves. There were no significant differences in any of the glucose measurements on the third and fourth glucose curves. The decision to change the insulin dosage based on home and hospital glucose curves was in agreement in 22 of 38 pairs of data.

Conclusions: Most owners are capable of and willing to perform blood glucose curves on their diabetic dogs.



CLINICAL IMPACT:

Home monitoring of glucose by owners has owner advantages of convenience and reduced cost and for the animal, eliminating the need for a visit to a veterinary clinic. However, considerable training is necessary for owners to become competent at testing and difficulties are frequently encountered early in the process, so owners must be committed to using the technique. The veterinarian will have to continue to assist owners in timing and interpretation of glucose curves.

Interestingly, the influence of stress due to hospitalization was not apparent in the glucose curves. This may be dependent on the temperament of the dogs studied, but also potentially negates one of the reasons for home glucose testing. Because considerable variation occurs in glucose curves from one day to the next, such information should be interpreted in light of other clinical and biochemical markers of glycemic control.

Owners must be committed to using the technique.



Continuous Glucose Monitoring in Diabetic Dogs

Davison LJ, Slater LA, Herrtage ME, et al. Evaluation of a continuous glucose monitoring system in diabetic dogs. J Sm Anim Pract 2003;44:435-442.

► INTRODUCTION:

Background: The diagnosis of diabetes mellitus in dogs and cats is usually based on two or more, fasting blood glucose concentrations of 140 mg/dl or higher. However, during the initial management of diabetics with insulin therapy, repeated blood glucose concentrations must be determined. This may be done on blood samples taken twice per day to every two hours depending on the difficulty in control or wishes of the clinician in charge. Frequent sampling of blood can cause phlebitis and anticipatory fear in the patient.

A continuous glucose monitoring system has been developed which uses a 22-gauge needle that is placed subcutaneous to provide 72 hour access to interstitial fluid. The needle is attached to a small monitor that is strapped to a patient harness. A continuous glucose monitoring system determines glucose concentration in interstitial fluid every 10 seconds, averages, and records the results every 5 minutes. Within a lag of 10 minutes, interstitial fluid and blood glucose concentrations correlate well. A continuous glucose monitoring system might provide more information with less stress on diabetic pets.

Objectives: The purpose of this study was to evaluate the clinical accuracy and practicality of using a continuous glucose monitoring system in diabetic dogs.

✦ SUMMARY:

Methods: Ten diabetic dogs on insulin and in poor control were hospitalized for at least 30 days and administered their routine insulin dosage and feedings. Serum fructosamine and glycosylated hemoglobin concentrations were measured. Blood glucose concentrations were measured and plotted every one to three hours for at least 28 hours.

Results: None of the dogs had any problems tolerating the harness nor with the subcutaneous sensor needle. All dogs had a serum fructosamine concentration above normal (greater than 400 $\mu\text{mol/l}$). The interstitial fluid and blood glucose concentrations had a significant correlation of 0.81. The greatest differences in values were in the one to three hour period after eating.

Conclusions: Continuous glucose monitoring is a valuable means of monitoring and managing canine diabetics, but early postprandial concentrations may differ between the blood and interstitial fluid.



CLINICAL IMPACT:

Continuous glucose monitoring system is preferable to drawing multiple blood glucose concentrations in diabetics because it provides more useful information and greater accuracy with less stress to the patient. Cost may be a prohibitive factor. However, this could be minimized by short term leasing from a veterinary hospital.

Most diabetic dogs do not require repeated or continuous monitoring.

Of those that do require repeated blood testing, continuous glucose monitoring is preferable to multiple intravenous blood draws per day. However, continuous glucose monitoring apparatus may not be well tolerated by dogs less than 15 lbs.

Continuous glucose monitoring is preferable to multiple intravenous blood draws per day.



Risk Factors for Diabetes Mellitus in Dogs

Guptill L, Glickman L, Glickman N. Time trends and risk factors for diabetes mellitus in dogs; analysis of veterinary medical data base. Vet J 2003;165:240-247.

▶ INTRODUCTION:

Background: Diabetes mellitus is one of the three most commonly diagnosed endocrinopathies in dogs. Risk factors have been reported to be advancing age, female gender, and certain breeds such as poodles, terriers, sled breeds, and other small- to medium-sized dogs.

Objectives: The purposes of this study were to investigate recent trends in the prevalence of diabetes mellitus in dogs and risk factors for diabetes mellitus.

✕ SUMMARY:

Methods: The medical records of 6860 dogs diagnosed with diabetes mellitus at multiple institutions over 30 years were reviewed retrospectively and evaluated for changing trends over time. The records of 6707 dogs with diabetes mellitus and 6707 dogs with diagnoses other than diabetes mellitus seen in the same institutions during the same time periods were compared for contrasts.

Results: The rate of diagnosis of diabetes mellitus per 10,000 admissions per year increased significantly from 19/10,000 (0.2%) in 1970 to 64/10,000 (0.6%) 30 years later. During the same period, fatality rates for dogs with diabetes mellitus declined from 37% to 5%. Advancing age, female gender, and body weight of less than 22.7 kg were and remained significant risk factors over the 30 year study. The breed with the highest incidence of diabetes mellitus was the Australian terrier. Castrated male dogs were at significantly higher risk than intact male dogs, but there was no significant difference in the risk for diabetes mellitus between intact and spayed females. No seasonal pattern in the incidence of diagnosis was detected.

Conclusions: The incidence of diabetes mellitus in dogs has increased and the mortality rate has decreased.



CLINICAL IMPACT:

The population studied in this report were primarily referral cases. An increase in the number of cases with diabetes mellitus over 30 years does not necessarily mean an increase in the incidence. A few of the other factors which could increase the percentage of diabetic referrals could be a relative decline in other referrals, an increase earlier diagnosis of diabetes and increase in the survival rates leading to more patients with diabetic complications needing referral services.

Many findings of most previous reports diabetes mellitus in dogs were substantiated by this study, i.e. older female dogs of small to medium size are at significantly higher risk for becoming diabetic than the general population of dogs. Although seasonal incidence occurs in Type 1 diabetes in humans and seasonal incidence has rarely been suggested in dogs, most clinicians have not observed a seasonal incidence of diabetes in dogs and neither did the results of this study.

Both spayed and intact female dogs are at significantly higher risk for developing diabetes mellitus. Gonadal hormones do not appear to be involved in the cause for female dogs having an increased susceptibility to diabetes. Castrated male dogs were found to have a significantly higher risk than intact males in this study and another using the same database. However, other retrospective and prospective studies have not reported this observation. Castrated males would be more likely to become obese which could increase the susceptibility and severity of diabetes mellitus requiring referral, but the status of

body condition was not evaluated in this study.

Survival rates for referred diabetic dogs increased 3-fold over 30 years. This is gratifying news for internists, but not surprising considering the advances in fluid therapy, low-dose insulin administration, and many other improvements from the time before the American College of Veterinary Internal Medicine even existed (circa 1970).

Survival rates for referred diabetic dogs increased 3-fold over 30 years.



Effect of Darglitazone on Glucose Clearance in Cats

Hoening M, Ferguson DC. Effect of darglitazone on glucose clearance and lipid metabolism in obese cats. Am J Vet Res 2003;64:1409-1413.

➔ INTRODUCTION:

Background: Diabetic cats develop diabetes mellitus as a gradual onset insulin insufficiency. Medications that increase endogenous insulin secretion, sensitize insulin receptors, or impair simple carbohydrate absorption which are effective adjunct treatment to dietary control in insulin-insufficient diabetic humans may be effective in some diabetic cats. Glipizide is the only oral hypoglycemic that has been used on a large scale in cats. Its effectiveness has been marginal.

A new class of antidiabetic drugs has been introduced for human insulin-insufficient diabetics. The new class, called thiazolidinediones, are believed to sensitize insulin receptors and to alter lipid metabolism resulting in lowered plasma free fatty acid concentrations and redistribution of intracellular lipids from insulin responsive organs to peripheral fat stores.

Objectives: The purpose of the study was to evaluate darglitazone on glucose clearance and lipid metabolism in obese cats.

✦ SUMMARY:

Methods: Eighteen obese and four lean neutered female cats were each administered intravenous (IV) glucose tolerance tests. Serum concentrations of glucose, insulin, nonesterified fatty acids (NEFA), cholesterol, triglyceride, leptin, and glycosylated hemoglobin were determined before and 42 days after the oral administration of darglitazone (2 mg/kg, once daily) to nine obese cats and a placebo to the other nine obese cats and four lean control cats.

Results: Obese cats that received darglitazone had significantly lower serum cholesterol, triglyceride, and leptin concentrations than the placebo-treated obese cats and tolerated darglitazone well. The area under the curve for nonesterified fatty acids, glucose, and insulin during an IV glucose tolerance test decreased significantly in cats that received darglitazone. No change in food intake occurred in association with darglitazone administration.

Conclusions: Darglitazone increases insulin sensitivity and lipid metabolism in obese cats.



CLINICAL IMPACT:

The results of this study confirm that darglitazone administration in obese cats can cause increased uptake of glucose into cells without adverse effects.

Insulin sensitivity increases while insulin concentrations decline. Darglitazone was also demonstrated to suppress serum NEFA, cholesterol, and triglycerides.

Darglitazone may be an alternative or a replacement for the use of glipizide in insulin insufficient diabetic cats.

Darglitazone may be an alternative or a replacement for the use of glipizide in insulin insufficient diabetic cats.



Alpha-Glucosidase Inhibitor and Low-Carbohydrate Diet Treatment of Diabetes Mellitus

Mazzaferro EM, Greco DS, Turner AS, et al. Treatment of feline diabetes mellitus using an alpha-glucosidase inhibitor and a low-carbohydrate diet. *J Fel Med Surg* 2003;5:183-189.

► INTRODUCTION:

Background: Many cats with diabetes mellitus are thought to have a form similar to type 2 diabetes in humans, where a combination of insulin resistance and inadequate beta-islet cell function result in hyperglycemia and other metabolic aberrations. One factor in the pathogenesis of type 2 diabetes is glucose toxicity, whereby severe, chronic hyperglycemia reduces insulin secretion and results in permanent dysfunction of beta-islet cells. If the demand for insulin secretion is reduced by decreasing carbohydrate content of the diet, cats may recover sufficient insulin secretion to recover from their hyperglycemic state.

Objectives: The objective of this study was to determine the efficacy of a low carbohydrate diet combined with an α -glucosidase inhibitor (acarbose) for treatment of diabetes mellitus in cats.

✦ SUMMARY:

Methods: A total of 24 otherwise healthy cats with diabetes mellitus, including 20 cats that had received insulin for two weeks to three years yet were poorly controlled and four cats that had not previously been treated, were studied. All cats were overweight or had a history of being overweight prior to development of diabetes. All cats were treated with twice daily PZI or Lente insulin, except for one that was on glipizide orally. A low carbohydrate canned diet consisting of 7% carbohydrate, 49% protein, and 36% fat was fed twice per day to all cats. In addition, 18 cats were administered 12.5 mg acarbose orally with each meal while six cats acted as untreated controls. Body composition was evaluated using dual-energy X-ray absorptiometry (DEXA) before and after four months of treatment. Control of hyperglycemia was assessed monthly by measurement of a single blood glucose concentration two to four hours after a meal and serum fructosamine. Cats were classified as either nonresponders, where insulin administration was necessary for glycemic

control and serum fructosamine was more than 400 $\mu\text{mol/L}$, or as responders where exogenous insulin administration was not required and serum fructosamine was normal (less than 400 $\mu\text{mol/L}$).

Results: Fifteen cats were considered responders, maintaining normal serum fructosamine concentrations despite discontinuation of insulin administration. The median insulin dose in cats in the nonresponder group decreased from 10 units/day to 2 units/day. Acarbose administration had no effect on response. Lean body mass increased during treatment in both groups of cats, although no difference in lean body mass was found when responders and nonresponders were compared.

Prior to treatment, cats in the responder group had a significantly higher body fat content (39%) compared with nonresponder cats (17%).

Conclusions: Feeding a low carbohydrate diet to cats with diabetes mellitus decreases insulin dependence within four months.

Feeding a low carbohydrate diet to cats with diabetes mellitus decreases insulin dependence within four months.



CLINICAL IMPACT:

The use of low carbohydrate diets has become widespread in the management of feline diabetes mellitus. In this study, 62.5% of cats fed a low carbohydrate diet no longer required exogenous insulin demonstrating the benefits of dietary control. The finding that obese cats were more likely to respond to treatment may be related to increased insulin sensitivity concurrent with decreased adiposity.

In addition to feeding a low carbohydrate diet, strict control of the blood glucose concentration is likely to play a role in resolution of diabetes mellitus. Twice daily insulin treatment and subsequent dosage adjustments done in this study to improve glycemic control may have contributed to the remission of diabetes in some cases, although details of treatment and response were not included. Acarbose has no apparent beneficial role in controlling diabetes in cats.



Systolic Blood Pressure in Diabetic Cats

Sennello KA, Schulman RL, Prosek R, et al. Systolic blood pressure in cats with diabetes mellitus. *J Am Vet Med Assoc* 2003;223:198-201.

► INTRODUCTION:

Background: Hypertension is a common complication of diabetes mellitus in humans and appears to be prevalent in diabetic dogs. Because hypertension can contribute to development of nephropathy, cardiac changes, microvascular disease, and insulin resistance, it is important to determine if alterations in blood pressure occur in cats with diabetes mellitus.

Objectives: The objective of this study was to determine the frequency of systemic arterial hypertension in cats with diabetes mellitus.

✦ SUMMARY:

Methods: Indirect systolic arterial blood pressure was measured using a Doppler flow device in 14 diabetic cats without other significant illness likely to cause hypertension and 19 healthy cats. Adequacy of control of blood glucose in diabetic cats was determined by measurement of serum fructosamine concentration within 12 months preceding the study or the mean blood glucose concentration during a 24 hour glucose curve, or both. The average of five consistent blood pressure readings obtained over a 5 to 10 minute period was used. Ophthalmic examinations were performed on all cats and echocardiograms were performed in 13 cases with emphasis on changes associated with hypertension. Hypertension was diagnosed if systolic blood pressure was more than 180 mm Hg and ophthalmologic or echocardiographic changes compatible with hypertension were found.

Results: Diabetes mellitus had been present for 1 week to 62 months in 11 cats and had occurred intermittently in three other cats. Control of blood glucose was considered poor in three cats, fair to poor in one, fair in six, fair to good in one, and good in three. None of the cats (diabetic or control) were found to be hypertensive. The mean systolic blood pressure

was not different when control cats (157 mm Hg) and diabetic cats (161 mm Hg) were compared. One diabetic cat had left ventricular hypertrophy, but the systolic pressure in this patient was 174 mm Hg so it was not considered hypertensive. In addition, four diabetic cats had left atrial enlargement. None had hypertensive retinopathy or proteinuria.

Conclusions: Hypertension does not occur or occurs only rarely secondary to diabetes mellitus in cats.

Because diabetic nephropathy rarely becomes a clinical problem in cats, they may be resistant to development of diabetes-induced hypertension.



CLINICAL IMPACT:

Although the number of diabetic cats studied was small, control of blood glucose concentrations was at best fair in 10 of the 14. Therefore, it seems likely that hypertension is not a common complicating factor related to poor control of diabetes mellitus in cats. However, cats with significant proteinuria were excluded from the study. In humans, nephropathy, rather than control of blood glucose, is related to hypertension. Because diabetic nephropathy rarely becomes a clinical problem in cats, they may be resistant to development of diabetes-induced hypertension.



Continuous Glucose Monitoring in Dogs and Cats

Wiedmeyer CE, Johnson PJ, Cohn LA, et al. Evaluation of a continuous glucose monitoring system for use in dogs, cats, and horses. *J Am Vet Med Assoc* 2003;223:987-992.

► INTRODUCTION:

Background: Blood glucose monitoring is an important tool in proper management of diabetes mellitus. It is accomplished by measuring glucose in blood samples obtained by either venipuncture or cutaneous pricks using a lancet. These techniques require restraint and sometimes discomfort that limits the number of blood samples and may affect the blood glucose concentration.

Recently, a continuous blood glucose monitoring device has been developed and approved for use in humans. This device measures glucose in the interstitial fluid using a small subcutaneous sensor that is placed subcutaneously and connected to a automatic glucose monitor strapped to the thorax.

Objectives: The objective of this study was to determine if a continuous glucose monitoring system would be effective, well-tolerated, and practical for use in dogs and cats.

✕ SUMMARY:

Methods: A commercial continuous glucose monitoring system was evaluated in three normal cats, four normal dogs, and seven normal horses, as well as two cats, three dogs, and one horse with diabetes mellitus. The monitoring system was comprised of a sensor, a recording device, and a cable connecting the two. The sensor was inserted percutaneously in the lateral thoracic region using a stylet that was then removed leaving the sensor tip in the subcutaneous tissue.

The sensor was attached to the skin using a cyanoacrylate adhesive and the cable connecting the sensor to the recording device was attached. The recording device (9 X 6.5 X 2 cm, 170 g) was attached to dogs using a harness and to cats by applying a bandage.

The continuous glucose monitoring system is valid for use in dogs and cats.

Following a 1 hour initialization period, the recording device was activated and three blood glucose samples were obtained over a 24 hour period to calibrate the system.

The blood glucose concentrations were then compared with glucose values measured by the monitoring system. The system measured glucose concentrations every 5 minutes. Dogs and cats were released to their owners overnight after placement of the system and initiation of recording, and presented again the following day for completion of the 24 hour glucose monitoring. The maximum glucose concentration measurable by the system was 400 mg/dl.

Results: Sensor placement was tolerated with minimal discomfort. No evidence of inflammation was noted at the sensor site and there was no evidence of irritation based on behavior of animals. Removal was associated with mild discomfort and slight redness was noted at the insertion site. Recordings were obtained successfully in all cases for approximately 24 hours. Three dogs and one cat with diabetes mellitus were determined to be poorly controlled based on blood glucose concentrations exceeding 300 mg/dl for most of the monitoring period. The interstitial glucose and blood glucose concentrations were highly correlated.

Conclusions: The continuous glucose monitoring system is valid for use in dogs and cats and appeared to be well-tolerated.

🌀 CLINICAL IMPACT:

The potential advantages of the continuous glucose monitoring system tested in this study are that the frequency of sampling precludes the possibility that a brief episode of hypoglycemia would be overlooked, only three blood glucose concentrations in 24 hours are

needed, and in-hospital stresses are avoided. Some of these advantages can be accomplished by a much simpler and less costly method of at-home blood glucose monitoring. The use of the glucose monitoring system will be restricted to research applications or clinical cases that cannot be monitored by less intensive and expensive means.



Irreversible Neurologic Complications Associated with Hypoglycemia in a Cat

Kraje AC. Hypoglycemia and irreversible neurologic complications in a cat with insulinoma. *J Am Vet Med Assoc* 2003;223:812-814.

► INTRODUCTION:

Background: Insulinomas are rare in cats. Clinical signs generally include seizures, weakness, ataxia, disorientation, and collapse from hypoglycemia. The diagnosis is typically based on demonstration of hypoglycemia concurrent with inappropriately normal levels or abnormally high levels of fasting serum insulin activity. Treatment is surgical excision of the primary tumor.

Persistence of seizures after surgical excision of the primary tumor may indicate recurrence of the tumor, growth of metastasis sites, or persistent brain injury from hypoglycemia.

Objectives: The objective of this report was to report an insulinoma in a cat that developed hypoglycemia and irreversible neurologic problems.

✦ SUMMARY:

Case Report: A 14-year-old, spayed female, domestic shorthaired cat was presented with weakness, lethargy, poor appetite, diarrhea, and weight loss that had been developing for 2 to 3 weeks. Grand mal seizures occurred the day of initial examination. Ten days earlier, she had been evaluated by another veterinarian. The serum chemistries then revealed hypoglycemia (38 mg/dl) and azotemia (44 mg/dl). The hemogram was within normal limits. Serum T₄ concentration was low (less than 0.2 µg/dl).

Physical examination revealed depression, weakness, disorientation, and hypothermia (98.3°F). Serum glucose was low (20 mg/dl) and the blood urea nitrogen was high (35 mg/dl). The hemogram was within normal reference ranges. Serum for fasting insulin activity was mishandled and a measured

activity of 0.9 µU/ml (normal, less than 0.1 to 8.0 µU/ml) may have been inaccurately low but still inappropriately within normal range for concurrent hypoglycemia.

An insulinoma was suspected and symptomatic treatment was administered consisting of polyionic intravenous solutions with added glucose and an external heat source. Prednisone (0.5 mg/kg once or twice/day, orally) and frequent forced feedings were added to the treatment protocol. A laparotomy was performed and a pancreatic tumor was removed. A gastrostomy tube was also placed. Post-surgery, the blood glucose was within normal range.

Seven days after the surgery, the cat was disoriented and paced intermittently.

Appetite was poor. The cat had an inconsistent menace response and aggressive behavior one month after surgery. Its serum insulin and glucose concentration were normal. The cat was euthanized at the owners request, and necropsy was not permitted.

Conclusions: Chronic hypoglycemia in cats can cause irreversible brain damage.

If seizures or neurologic deficits persist without recurrence of hypoglycemia, neurologic injury as a sequella to earlier hypoglycemia is highly probable.



CLINICAL IMPACT:

Hypoglycemia from an insulinoma should be suspected whenever seizures or neurologic deficits develop in an older dog or cat. If an insulinoma is removed and seizures or neurologic deficits persist without recurrence of the hypoglycemia, neurologic injury as a sequella to earlier hypoglycemia is highly probable. Clinical signs of hypoglycemia-induced neurologic injury in addition to seizures can include weakness, ataxia, mental depression, disorientation, and possibly amaurosis. Aggression was also attributed to hypoglycemia-induced neuropathy in the cat of this report.



Pre- and Post-ACTH Serum 17-Hydroxyprogesterone for the Diagnosis of Hyperadrenocorticism

Chapman PS, Mooney CT, Ede J, et al. Evaluation of the basal and post-adrenocorticotrophic hormone serum concentrations of 17-hydroxyprogesterone for the diagnosis of hyperadrenocorticism in dogs. *Vet Rec* 2003;153:771-775.

► INTRODUCTION:

Background: Diagnosis of hyperadrenocorticism can be difficult because of the lack of a gold standard for diagnosis. Screening tests such as the urine cortisol/creatinine ratio and low-dose dexamethasone suppression test are very sensitive but are not specific, while the adrenocorticotrophic hormone (ACTH) response test suffers from suboptimal sensitivity yet is more specific than other screening tests.

Recently, a number of cases of hyperadrenocorticism have been reported to have a normal ACTH response test when serum cortisol was measured, but an increase in non-cortisol steroid hormones such as progesterone and 17-hydroxyprogesterone. If measurement of serum 17-hydroxyprogesterone increased the sensitivity of the ACTH response test without a loss in specificity, it would improve the utility of this test.

Objectives: The objective of this study was to evaluate the sensitivity and specificity of measurement of serum 17-hydroxyprogesterone concentrations during ACTH response tests in diagnosis of hyperadrenocorticism.

✕ SUMMARY:

Methods: Three groups of dogs, 27 healthy controls, 19 dogs with nonadrenal illness, and 46 dogs with hyperadrenocorticism, were studied. Hyperadrenocorticism was diagnosed based on compatible clinical findings, lack of suppression on a low-dose dexamethasone suppression test, and an adequate response to appropriate treatment. Dogs with nonadrenal illness were included if hyperadrenocorticism was suspected but another disease was diagnosed and hyperadrenocorticism was effectively ruled out and if they had a normal low-dose dexamethasone suppression test. ACTH response tests were performed by

obtaining blood samples before and one hour after administration of 250 µg of synthetic ACTH. Receiver operator curves (ROC) were determined for basal and post-ACTH serum cortisol and 17-hydroxyprogesterone in order to optimize the sensitivity and specificity.

Results: The 19 dogs in the nonadrenal illness group were diagnosed with neoplasia (5 dogs), urinary tract disease (5 dogs), diabetes mellitus (2 dogs), hypothyroidism (2 dogs), dermatologic disease (2 dogs), diabetes insipidus (1 dog), hepatic disease (1 dog), and gastrointestinal disease (1 dog). Pituitary-dependent hyperadrenocorticism was diagnosed in 43 dogs and adrenal tumors were found in the three other dogs with hyperadrenocorticism.

Basal and post-ACTH serum cortisol and 17-hydroxyprogesterone concentrations were positively correlated. Basal and post-ACTH serum 17-hydroxyprogesterone concentrations were significantly higher in dogs with hyperadrenocorticism than dogs without the disease. The ROC was most favorable for measurement of post-ACTH cortisol, followed in order by basal cortisol, post-ACTH 17-hydroxyprogesterone, and basal 17-hydroxyprogesterone. A cut off value of 8.5 nmol/L maximized the sensitivity and specificity of post-ACTH hydroxyprogesterone at 71%. An increase in sensitivity to 90% resulted in a specificity of 40% while an increase in specificity to 90% reduced sensitivity to 47%. Post-ACTH serum cortisol concentration was less than 600 nmol/L (not clearly diagnostic of hyperadrenocorticism) in 17 dogs with hyperadrenocorticism. Using the optimized cut-off, nine of this subgroup had abnormal post-ACTH serum 17-hydroxyprogesterone concentrations, while five dogs had abnormal results using the cut-off with 90% specificity.

Conclusions: Although many dogs with hyperadrenocorticism have elevated serum 17-hydroxyprogesterone, there is considerable overlap between values of normal dogs and

those with nonadrenal illness with that of dogs with hyperadrenocorticism. Post-ACTH serum 17-hydroxyprogesterone concentration is not recommended as a screening test for hyperadrenocorticism.

🌀 CLINICAL IMPACT:

This study demonstrated limitations associated with the use of serum 17-hydroxyprogesterone concentration, namely the low specificity in diagnosis of hyperadrenocorticism. The low sensitivity (63%) of post-ACTH serum cortisol concentrations for diagnosis of hyperadrenocorticism shows limitations of this test as well. The low-dose dexamethasone suppression test, while quite sensitive, has poor specificity.

Knowledge of the limitations of adrenal function tests makes accurate interpretation of other clinical information crucial when considering a diagnosis of hyperadrenocorticism. A substantial proportion of dogs with hyperadrenocorticism that were not positively diagnosed using serum cortisol concentration had elevated serum 17-hydroxyprogesterone concentration. Therefore, measurement of this hormone should be considered when the standard ACTH response test measured by serum cortisol is normal or inconclusive and hyperadrenocorticism is still suspected.

Post-ACTH serum 17-hydroxyprogesterone concentration is not recommended as a screening test for hyperadrenocorticism.



Trilostane Treatment of Dogs with Pituitary-Dependent Hyperadrenocorticism

Braddock JA, Church DB, Robertson ID, et al. Trilostane treatment in dogs with pituitary-dependent hyperadrenocorticism. *Aust Vet J* 2003;81:600-607.

➔ INTRODUCTION:

Background: Trilostane has recently been identified as an effective drug for management of pituitary-dependent hyperadrenocorticism. A competitive antagonist of 3 β -17-hydroxysteroid dehydrogenase, trilostane inhibits synthesis of sex steroids, cortisol, and possibly mineralocorticoids.

Objectives: The objectives of this study were to evaluate the clinical and biochemical response of dogs with pituitary-dependent hyperadrenocorticism to trilostane administration.

✦ SUMMARY:

Methods: Thirty dogs with pituitary-dependent hyperadrenocorticism diagnosed by low-dose dexamethasone suppression testing, abdominal ultrasound, and plasma adrenocorticotropic hormone (ACTH) concentration were studied. Dogs were initially administered trilostane once daily at the following dosages: less than 5 kg, 30 mg; 5-20 kg, 60 mg; and more than 20 kg, 120 mg.

Dogs were evaluated approximately on days 10, 30, and 90 of treatment and then every three months. Evaluations included water consumption over the previous 24 hours, history, physical examination, urine cortisol:creatinine ratio (UCCR), and ACTH response test. Dosage adjustments were made based primarily on results of ACTH response test and UCCR. Control of hyperadrenocorticism was considered acceptable (post-ACTH cortisol 75-125 nmol/L), tight control (post-ACTH cortisol 25-75 nmol/L or UCCR less than 15×10^{-6}), or excessive control (post-ACTH cortisol less than 15 nmol/L). If a change in the trilostane dose was made, the dog was evaluated again within two to four weeks.

Results: Control of hyperadrenocorticism, based on ACTH response tests, was present in 40% of dogs on day 10, 30% at day 30, 57% at day 90, and 79% at day 180. Excessive control was noted in 7 to 10% throughout

the study. Urine cortisol:creatinine ratios frequently did not agree with ACTH response test results, with a concordance of less than 50% at each evaluation. The final median dose of trilostane was 17 mg/kg, with a range of 5 to 50 mg/kg.

At the end of the 180 day study period, 22 of 24 owners with dogs still alive or not lost to follow-up, elected to continue treatment with trilostane while the remaining two owners stopped treatment for reasons other than dissatisfaction with response to treatment. During treatment with trilostane, four dogs developed clinical signs of hypoadrenocorticism from 17 to 22 months after initiating treatment. The plasma cortisol response to ACTH was suppressed for up to four months after cessation of trilostane administration, but treatment was re-instituted in all cases. Laboratory evidence of mineralocorticoid and glucocorticoid deficiency was present in one dog. No other adverse effects were attributed to trilostane treatment.

Conclusions: Trilostane is a safe and effective treatment for pituitary-dependent hyperadrenocorticism in dogs, and dosage increases are frequently necessary.



CLINICAL IMPACT:

The target for control of hypercortisolemia in this study was a lower post-ACTH plasma cortisol concentration than attempted with previous evaluations of trilostane. Despite this, adverse effects were uncommon and reversible on discontinuation of treatment. The infrequent development of

hypoadrenocorticism probably indicates that mineralocorticoid secretion is affected to a lesser degree than glucocorticoids.

Adrenal gland necrosis has recently been reported in a dog treated with trilostane. This may account for the prolonged control of hyperadrenocorticism and suppression of plasma cortisol concentration in dogs that developed signs of hypoadrenocorticism during treatment.

Trilostane is safe and effective, but the expense of treatment is 2 to 5 times greater than with mitotane. It also must be administered more frequently than mitotane.

Trilostane is a safe and effective treatment for pituitary-dependent hyperadrenocorticism in dogs.



Surgical Excision of Adrenal Gland Tumors With and Without Tumor Thrombi in Dogs

Kyles AE, Feldman EC, De Cock HEV, et al. Surgical management of adrenal gland tumors with and without associated tumor thrombi in dogs: 40 cases (1994-2001). *J Am Vet Med Assoc* 2003;223:654-662.

► INTRODUCTION:

Background: When possible, unilateral adrenalectomy is the treatment of choice for dogs with an adrenocortical tumor. Due to the location and invasive nature of some adrenocortical tumors, extension of the neoplasm into the phrenicoabdominal vein or caudal vena cava (tumor thrombi) commonly occurs. Invasion of the caudal vena cava complicates surgery. If complete excision is to be accomplished after vena caval invasion has occurred, resection of a portion of the vena cava after occlusion of blood flow is required. This is a technically demanding procedure requiring special expertise.

Objectives: The objectives of this retrospective study were to describe clinical findings and results of adrenalectomy in dogs with adrenal tumors with or without tumor thrombi.

✦ SUMMARY:

Methods: Medical records of 40 dogs with adrenal gland tumors that underwent adrenalectomy were reviewed retrospectively. In dogs with tumor thrombus in the caudal vena cava, a venotomy was performed and the thrombus was removed. Dogs with adrenocortical tumors were administered heparin at a low dose for three to four days and dexamethasone followed by prednisone for glucocorticoid deficiency. Dogs undergoing bilateral adrenalectomy were also treated with desoxycorticosterone pivalate. Disease recurrence and survival time was determined by telephone interview with the owner.

Results: Of the 40 dogs that underwent adrenalectomy during the eight year study period, 28 had an adrenocortical tumor and 11 had a pheochromocytoma.

Tumor type was not determined in one dog. Twenty-six dogs with adrenocortical tumors had hyperadrenocorticism. Eight dogs with pheochromocytoma had clinical signs compatible with the disease while the other three had an adrenal mass identified incidentally. Bilateral adrenocortical tumors were found in three dogs.

A tumor thrombus was identified at surgery in 13 dogs: six with adrenocortical tumors, six with pheochromocytoma, and one that was unidentified. The phrenicoabdominal vein alone was affected in three dogs, a local vena cava thrombus was present in eight dogs, and an extensive thrombus (extending into the intrahepatic portion of the caudal vena cava) was found in two dogs at surgery.

Abdominal ultrasound examination revealed an adrenal mass in 38 dogs. Tumor thrombus of the caudal vena cava was determined to be present in 11 dogs on ultrasound examination, but was present in only eight of these dogs at surgery. A grossly visible tumor was excised in 38 dogs. Major intraoperative complications developed in six dogs (eventually fatal in two), and only one of the nine dogs that had a caval venotomy performed was in this group.

Postoperative complications developed in six of nine dogs with thrombi and 14 of 30 without. No significant difference in survival was noted between dogs with tumor thrombi and those without. Perioperative death occurred in three of 10 dogs with thrombi and in six of 30 dogs without thrombus. Of five dogs with adrenocortical tumors surviving the perioperative period, two had recurrence of signs of hyperadrenocorticism, and one had pulmonary thromboembolism and cranial

vena cava thrombosis three months after surgery. No dog without a tumor thrombus had recurrence of hyperadrenocorticism. Recurrence of clinical signs or tumor-related death was not seen in any of the nine dogs with pheochromocytoma.

Conclusions: Vena cava tumor thrombosis is not associated with an increased perioperative mortality rate, provided surgery is performed by an individual with appropriate experience.



CLINICAL IMPACT:

Adrenalectomy is a risky procedure as documented by the 21% mortality in dogs of this study. Although few dogs died because of direct complications associated with venotomy, the skill of the surgical team is a major factor in the success reported in this study. Survival rates are likely to be lower at many practices. Abdominal ultrasound and computerized tomography were not able to reliably distinguish tumor thrombus from local compression of the caudal vena cava in a number of cases. So, the surgeon should be prepared for addressing tumor invasion into major veins at the time of surgery.

Vena cava tumor thrombosis is not associated with an increased perioperative mortality rate.



Trilostane Treatment of Cats with Pituitary-Dependent Hyperadrenocorticism in a Cat

Skelly BJ, Petrus D, Nicholls PK. Use of trilostane for the treatment of pituitary-dependent hyperadrenocorticism in a cat. *J Sm Anim Pract* 2003;44:269-272.

► INTRODUCTION:

Background: Feline hyperadrenocorticism is a life-threatening disease that often results in diabetes mellitus, thin, fragile skin that lacerates easily, infection, and poor wound healing. Medical management of feline hyperadrenocorticism is poorly described and a consistently effective long-term treatment has not been described. Trilostane is a competitive antagonist of 3 β -17-hydroxysteroid dehydrogenase and inhibits cortisol synthesis and secretion.

Objectives: The objective of this report was to describe the response to trilostane administration of a cat with pituitary-dependent hyperadrenocorticism.

✦ SUMMARY:

Case Reports:

Hyperadrenocorticism was diagnosed in a 7-year-old, neutered male cat with clinical findings consisting of polyuria and polydipsia, seborrhea, alopecia, recurrent abscesses over the hocks, a plantigrade stance, thin skin with some tears, muscle wasting, and hepatomegaly. Additional complications of the hyperadrenocorticism included diabetes mellitus and a *Candida albicans* urinary tract infection. Results of an adrenocorticotropic hormone (ACTH) response test were equivocal. Bilateral adrenomegaly was documented on abdominal ultrasound. Treatment for the diabetes mellitus and abscesses was instituted with PZI insulin, ampicillin, and enrofloxacin.

A tentative diagnosis of pituitary-dependent hyperadrenocorticism was made and treatment with trilostane (30 mg, orally, once daily) was instituted. After three weeks of treatment, the abscesses and skin tears had improved

considerably, polyuria and polydipsia had decreased, and urine sediment examination was unremarkable. Results of an ACTH response test demonstrated a reduction in the pre- and post-ACTH plasma cortisol levels. After an adjustment of the insulin dose, the diabetes mellitus was well controlled on 1 unit, twice per day. The dose of trilostane was increased to 30 mg, twice per day, in an attempt to improve healing of the skin tears. After an additional 30 days of treatment, clinical improvement continued, and plasma cortisol levels were lower than at 21 days of treatment.

After 6 months of treatment, polyuria and polydipsia worsened, one kidney was noted to be small, and *Candida albicans* was again cultured from the urine. The cat was treated with itraconazole and fluconazole for the yeast infection without success. Renal failure developed 10 months after initiating trilostane, and the cat was euthanized after failing to respond to treatment consisting of discontinuation of trilostane and conventional fluid therapy. Necropsy revealed a large pituitary mass identified as a chromophobe adenoma, fungal pyelonephritis, and adrenocortical enlargement.

Conclusions: Trilostane was partially successful in controlling hyperadrenocorticism in a cat.

🌀 CLINICAL IMPACT:

The optimal treatment of pituitary-dependent hyperadrenocorticism in cats is not known. Bilateral adrenalectomy is effective, but involves perisurgical risks in a cat that may be debilitated and more susceptible to poor wound healing and infection. Medical control of hyperadrenocorticism indefinitely or just prior to surgery is preferable.

In this case, trilostane was effective in

reducing plasma cortisol concentrations and in controlling the most severe clinical signs of hyperadrenocorticism. However, further reduction of plasma cortisol secretion might have improved control. It appears that trilostane is less effective for controlling hyperadrenocorticism in cats than in dogs.

Trilostane was partially successful in controlling hyperadrenocorticism.



Neurologic Complications of Treatment for Hypoadrenocorticism

MacMillan KL. Neurologic complications following treatment of canine hypoadrenocorticism. *Can Vet J* 2003;44:490-492.

► INTRODUCTION:

Background: Myelinolysis is a noninflammatory demyelination of the central pontine regions of the brain. It is induced by rapid correction of severe hyponatremia. Gradual development of hyponatremia permits the brain to suppress production of idiogenic osmoles and adapt to the change in osmotic pressure due to hyponatremia, thereby the risks of cerebral edema are lessened.

Objectives: This case was reported to describe a dog that developed apparent myelinolysis during the correction of hyponatremia from primary hypoadrenocorticism.

If serum sodium concentration is less than 110 mEq/L, caution must be exercised in the speed of correction.

an adrenocorticotropic hormone (ACTH) stimulation test was performed. Following the ACTH test, isotonic saline, dexamethasone, and prednisolone sodium succinate were administered intravenously (IV). Oat bags and blankets were provided in an attempt to raise the body temperature. Very low serum cortisol concentrations before and after ACTH stimulation were detected consistent with the diagnosis of hypoadrenocorticism.

Hydrocortisone and isotonic saline were administered intravenously. The serum sodium concentration rose, but the dog became weak again. On day 7, fludrocortisone and prednisone were given orally and isotonic saline continued IV. On

day 8, the serum sodium concentration was near normal (137.6 mEq/L). Neurologic signs were present, including intermittent muscle tremors of the head and urinary incontinence. Severe depression to stupor was present during days 9 to 11 along with posterior ataxia, quadraparesis, and intermittent dysphagia. During the next 2.5 weeks, the dog gradually improved with occasional periods of head pressing. It was then discharged without neurologic signs to the owner with instructions to continue treatment for hypoadrenocorticism.

Conclusions: Based the neurologic sign associated with rapid recovery from hyponatremia in this dog, myelinolysis was diagnosed.



CLINICAL IMPACT:

Most dogs with primary hypoadrenocorticism are diagnosed when the serum sodium

concentration is between 120 to 140 mEq/L with little to no risk of myelinolysis from correction of the hyponatremia. However, if serum sodium concentration is less than 110 mEq/L, caution must be exercised in the speed of correction of the low serum sodium concentration. Gradual correction over three or more days of treatment is advised, or a rise of no more than 10 mEq/L/day.

✕ SUMMARY:

Case Report: An 18-month-old, male West Highland white terrier was presented with a history of vomiting and anorexia. Physical findings were depression and dehydration. The hemogram revealed mild lymphocytosis. Serum chemistry results included the abnormalities of mild azotemia and a slight elevation of alanine aminotransferase. Thoracic and abdominal survey radiographs were within normal limits. Lactated Ringers solution was administered, the dog's condition improved, and it was released.

Within a few hours after release, the dog was depressed with dark red gums. The dog later stood with an arched back and tucked abdomen. Four days after first presentation, lethargy, weakness, dehydration, hypothermia, and hematochezia were noted. On day 5, serum chemistries revealed hyperkalemia, hypochloremia, hypocholesterolemia, and extreme hyponatremia (97.7 mEq/L).

Hypoadrenocorticism was suspected and

Thyro-Tabs[®]

(levothyroxine sodium tablets, USP)

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

Description:

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

Indications:

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

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

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

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

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

Mode of actions:

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

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

Hypothyroidism in the dog:

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

Clinical signs:

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

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

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

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

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

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

Contraindications:

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

primary hypertension, euthyroidism, and pregnancy.

Precautions:

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

Adverse reactions:

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

Dosages:

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

Administration:

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

How supplied:

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

Storage:

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

References: See package insert.



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Journals examined by the editors for article inclusion:

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

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