



**FLORIDA VETERINARY SPECIALISTS
& Cancer Treatment Center**

Summer 2005

The Critical Care REVIEW

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Practice Update

by Neil Shaw, D.V.M., Diplomate ACVIM



Dear Friends and Colleagues,

I trust all are well. Welcome to the Summer 2005 Edition of The Critical Care Review.

Florida Veterinary Specialists and Cancer Treatment Center and Brandon Veterinary Specialists continue to expand to meet your referral needs. We have several new additions to our team of specialists available to you. Remember, we are available for your specialty case referrals to be received and managed by a specialist, 7 days a week.

Alan Spier, DVM, PhD, Diplomate of the American College of Veterinary Internal Medicine (Cardiology) is establishing our cardiology service. Alan trained at the Ohio State University College of Veterinary Medicine and most recently was faculty of the University of Missouri College of Veterinary Medicine prior to joining FVS. Not only is Dr. Spier one of the leading cardiologists in the U.S., he is a fantastic individual with whom you will utterly enjoy interacting. Dr. Spier is available for telephone consultation and referral appointments. We are fortunate to have Dr. Spier join our staff.

Chad West, DVM, Diplomate of the American College of Veterinary Internal Medicine (Neurology) is establishing the **Neurology/Neurosurgery** service. Chad is a graduate from the University of Florida College of Veterinary Medicine,

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FVS hosts "K-9 Down", a weekend seminar for firefighters, police, and other emergency rescue personnel who may respond to canine health emergencies in the field.



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Oncology Update

by Carrie Kosarek, D.V.M., Diplomate ACVIM (Oncology)

CLINICAL TRIALS IN VETERINARY ONCOLOGY

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The Oncology Service at Florida Veterinary Specialists & Cancer Treatment Center is currently participating in **two clinical trials involving canine lymphoma and canine mast cell cancer**. In collaboration with The Ohio State University's College of Veterinary Medicine, we are participating in a genetic study evaluating genes associated with chemoresistance in canine lymphoma. We are also part of a multi-institutional phase III clinical trial investigating the treatment of canine mast cell cancer with an oral tyrosine kinase inhibitor. Further information regarding the details of these trials, including inclusion and exclusion criteria, can be obtained on our website at <http://www.fvs.com>. If you have any concerns or questions regarding clinical trials or to discuss possible referral of one of your patients, please call us.

Clinical trials, conducted with volunteer clients and their pets, are research studies aimed at answering specific scientific questions; the answers to these questions may help to find better ways to prevent, screen, diagnose or treat a specific disease (such as cancer). Cancer research is a large focus of human clinical trials. In a recent review of the National Institutes of Health database (<http://www.clinicaltrials.gov>), 2,347 of the 4,482 clinical trials in the recruitment phase involve cancer research.

There are several different types of clinical trials, including prevention, screening, diagnostic, and treatment trials and genetic studies. Prevention trials investigate ways to reduce the risk of developing cancer. These types of trials are not as common in veterinary studies as in human studies. Screening trials are aimed at developing methods for detecting cancer. In people, these studies are often done in order to determine if detecting a tumor prior to the development of clinical signs increases survival time. On the other hand, diagnostic trials are typically conducted once clinical signs develop. These diagnostic studies are aimed at investigating tests or procedures that may identify cancer more accurately or at an earlier stage. Treatment trials, which are conducted with patients with cancer, test experimental treatments, vaccines, novel drugs or combination of drugs, and new approaches to surgery or radiation therapy. These trials may compare the efficacy of the new treatment versus the standard of care. Finally, genetic studies focus on how the genetic makeup can affect detection, diagnosis, or response to cancer treatment. Familial-based genetic studies are often conducted to find genetic changes that are associated with cancer. Patients may or may not have cancer in these types of studies. In veterinary oncology, investigators have identified certain breeds that may be at risk for developing specific types of cancer, such as the Bernese Mountain Dog and malignant histiocytosis. Genetic research is ongoing for certain breeds of dogs, such as the Irish Wolfhound, with bone cancer.

Clinical trials are conducted in different phases, depending on the purpose of the particular trial. Phase I trials are the first step in testing an experimental drug or treatment in a small group of patients. There are typically less than 100 participants in human phase I studies. The goals of most phase I trials are to determine a safe dose range or the maximally-tolerated dose and to identify adverse effects. In a recent 2004 veterinary phase I study, *Poirier et al* evaluated vinorelbine, a new semi-synthetic vinca alkaloid, in 19 dogs with spontaneous neoplasia. Neutropenia was found to be the dose-limiting toxicity. The investigators determined a starting dose and concluded that the drug was well-tolerated in the majority of the dogs. In addition, the authors concluded that further studies were warranted based on the clinical activity that was observed in a few dogs. In 2003, *London et al* conducted a phase I trial evaluating an oral tyrosine kinase inhibitor in dogs with various malignancies. Pharmacokinetics, toxicity and tumor response were assessed. This study provided the 1st evidence that oral kinase inhibitors exhibit activity against a variety of tumors, most notably in mast cell cancer.

In phase II trials, the experimental drug or protocol evaluated in the previous phase I study is given to a larger group of patients (usually 100-300 patients in human trials) in order to evaluate efficacy and to further evaluate safety. In veterinary medicine, phase I and II studies are often combined due to the smaller number of patients available for enrollment; it is uncommon to have studies with greater than 100 patients in veterinary clinical trials.

The purposes of phase III trials are to confirm the effectiveness of the new drug or protocol, to monitor adverse effects and to compare it to more commonly used treatments. These studies generally involve an even larger group of people (1,000 - 3,000 people). In most cases, studies move into phase III testing only if they have shown promise in phase I and II studies. Phase III studies usually are randomized, double-blinded and placebo-controlled. An example of a current phase III study in veterinary oncology is the study of tyrosine-kinase inhibitors for the treatment of canine mast cell cancer.

Finally, phase IV trials are conducted to further evaluate the long-term safety and effectiveness of a new treatment. Phase IV studies usually take place after the treatment has been approved for standard use. These studies are less common than other phase trials in human medicine.

Each study's protocol has specific guidelines, termed inclusion and exclusion criteria, which determine a patient's eligibility for a particular study. Most criteria for treatment trials require that patients have a particular type and stage of cancer. Informed consent is a process by which clients learn the important facts about a clinical trial and sign an informed consent form if participating in the study. Although clients have signed consent, they can withdraw from a study at any time at their own request.

There are several benefits for patients participating in oncology clinical trials. There may be promising new drugs for treatment of cancer in which there was no previous hope for remission or cure. Additionally, patients may have failed standard of care and their cancer has progressed. Furthermore, owners typically do not have health insurance for their pets; there may be a financial incentive for owner's that may not otherwise be able to afford treatment without the assistance of a clinical trial. On the other hand, there may be significant risks associated with some clinical studies. For example, the new drug or protocol may be less effective or more toxic than expected. In addition, patients in randomized, placebo-controlled studies may not receive active drug.

The majority of clinical trials in veterinary oncology provide some type of funding or compensation for participation in the study. Owners may be compensated for part or the entire study. Many studies require that owners travel to the study center for participation in the trial. Multi-institutional studies are also being conducted in order to make the trial available to more patients, thereby increasing the number of enrolled patients. Information regarding current clinical trials in veterinary oncology at various universities and referral practices is available on The Veterinary Cancer Society's website <http://www.vetcancersociety.org>. ■



FVS helps raise funds for the Susan G. Komen Breast Cancer Foundation and helps increase awareness about cancer in pets.

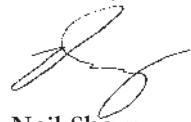
Practice Update
continued from cover

completed internship at the Animal Medical Center in NY and accomplished Neurology/Neurosurgery residency training at Washington State University College of Veterinary Medicine. Dr. West was trained with Magnetic Resonance Imaging (MRI) serving as the primary modality in assessment of the brain and spinal cord as a diagnostician and surgeon. We are excited to have his expertise in this cutting edge technology.

Melanie Otte, DVM, Diplomate of the American College of Veterinary Internal Medicine (Internal Medicine) is joining the **Critical Care** service, teaming with Dr's Hanel and Parra. Dr. Otte is a graduate of the University of Florida College of Veterinary Medicine and completed Residency at the University of Illinois College of Veterinary Medicine. Melanie grew up in Tampa, attending high school a few blocks from FVS; welcome home! Dr. Otte will further expand the Critical Care Service, providing you same day specialty emergency case transfer availability directly to a specialist, 7 days a week!

Thank you for your continued support. We look to the future of our profession with anticipation and excitement and are proud to serve as the trusted extension of your practice. Please call me if I can ever be of assistance.

Sincerely,



Neil Shaw

Diplomate of the American College of Veterinary Internal Medicine (Internal Medicine)
Medical Director

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Avian and Exotic Update

by Teresa Lightfoot, D.V.M., Diplomate ABVP (Avian)

AVIAN “ROUTINE” GROOMING PROCEDURES



Communication with the owner regarding wing trims is vital. Many owners drop off their birds for a wing trim, without indicating whether or not the bird currently has the ability to fly. These owners may assume that after a period of time has elapsed, a wing trim is required. The types of wing trims and their advantages and disadvantages should be discussed with the owner. The fact that a wing trim is a **deterrent** to flight, not a **guarantee** should be emphasized. The goal of a wing trim is to allow the bird to glide to the ground without injuring itself. This same clip may not be sufficient if the owner elects to take the bird outdoors on a windy day.

The basic types of wing trims are as follows:

- a) **Removing** four to seven of the distal primary flight feathers from both wings, below the level of the coverts. The number of feathers necessary to remove is inversely proportional to the weight of the bird.
- b) **Leaving** one to four distal primary feathers, removing the remainder of the primaries from both wings. This clip has fallen out of favor, but some owners have utilized this clip for many years. If it has worked well for their bird, it may be wise to continue its use.
- c) **Removing** a variable number of primary feathers from just one wing usually resulting in an abrupt spiral to the ground. This clip is unnecessarily severe in many cases, but some owners have found it a useful and effective deterrent to flight. Some smaller birds are able to compensate by holding their tails to the side and are still able to fly.

The record should contain a diagram or notation of the number and location of feathers that have been cut. Ask the owner to call within a day or two and report on whether or not the clip is adequate. If the bird is still flying, the owner should return to have additional feathers removed. If the clip seems a bit excessive, and the bird is dropping at a severe angle to the ground, a note can be made for the next visit to remove fewer feathers. In these cases, to avoid beak or keel trauma, the owner should be reminded to keep the bird from any great heights and away from tile or concrete floor surfaces until it regains some ability to soften its landing.

Nail trimming is often requested, usually for the owner's comfort and not due to any true overgrowth of the nails. The strong grip of many birds causes the needle-sharp points of their nails, which stabilize them well in the wild, to cause pain on the owner's skin. The owners must be cautioned that trimming these nails will lessen the bird's stability and make falling from its perch - whether that perch is in the cage or on the owner's shoulder - much more likely. Generally, a compromise can be reached by blunting the needle-like tip while still leaving sufficient nail to allow a stable grip.

Various types of equipment can be used for nail trims depending on the size of the bird. Human fingernail trimmers work well to remove the tips of the nails from very small birds. Cat claw trimmers, White's nail trimmers, and hobby drills with sanding bits are all useful. The sanding tools are also excellent for removal of excess keratin that can accumulate on the lateral surfaces of the beak. Birds with true beak deformities often have underlying nutritional deficiencies, disease or previous trauma. Normal, healthy birds that are provided with adequate environmental abrasive surfaces rarely require beak trims.

Concrete (cement) perches are now available in various sizes and textures. These can work well in medium-sized psittacines (approximately 250-700 grams) when a suitable size is selected and properly placed in the cage. These perches function efficiently to eliminate the need for both toe nail trimming and removal of excess keratin from the beak. For effective use of these perches for dulling of the nails, the perch should be placed in a location in which the bird is forced to stand for brief periods - such as in front of a food bowl or treat cup. To avoid irritation to the plantar surfaces of the feet, the concrete perch should not be the main perch on which the bird sits to preen or to sleep.

Continued on page 9

Clinical Trials Update

Canine Inflammatory Bowel Disease Study

The purpose of this clinical study is to determine the effect of a test diet on the management of idiopathic Inflammatory Bowel Disease (IBD) in dogs.

Clinical Study Overview

- > Study is conducted in 2 phases:
 - Phase I: 3-week food elimination trial
 - Phase II: Dogs not showing resolution in phase I will be evaluated for inclusion for Phase II
- > All dogs entering Phase II will received a standardized medical regimen for IBD in addition to being fed the Test diet or a positive control diet.
- > Reimbursement is offered for minimum data base and 2 endoscopic examinations and histopathological evaluations:
- > Dogs will be evaluated by Florida Veterinary Specialists at weeks 0, 3, 7, 11 during Phase I and Phase II.
- > Enrollment will begin June 2005 and continue for 4 months

A dog is eligible for participation in Phase I of the study, if the dog:

1. Is greater than 1-year of age
2. History of chronic diarrhea for a minimum of 3 weeks
3. Exclusion of other causes of chronic diarrhea including but not limited to exocrine pancreatic insufficiency, parasitism, infectious disease (fungal, bacterial, and viral), protein losing enteropathy, gastrointestinal neoplasia, histiocytic colitis, or drug-associated (e.g. NSAIDs, antibiotics, cancer chemotherapeutics) causes.

Mast Cell Tumor Clinical Trial

We are currently recruiting dogs diagnosed with either grade II or grade III mast cell tumors for a clinical study investigating the safety and efficacy of a new drug.

Inclusion Criteria

- Dogs, regardless of the breed and sex.
- Owner written informed consent.
- Dogs presenting one or several histologically diagnosed measurable grade II (intermediate) or grade III (poorly differentiated) MCTs, and either recurrence after failure of surgery, or presence of non-resectable tumor.

Exclusion Criteria

- Lactating/pregnant bitches, dogs intended for breeding.
- Dogs under 6 months age.
- Dog weight strictly under 3.3 kg.
- Chemotherapy, including corticosteroids, with 2 weeks of treatment initiation.
- Surgical removal within 2 weeks of treatment initiation and/or incompletely healed surgical incisions prior to treatment initiation.
- Radiation therapy within 6 weeks of treatment initiation.
- Severe renal insufficiency or significant renal impairment.
- Presence of gastrointestinal bleeding assessed by clinical signs.
- Presence of internal metastasis.
- Presence of lymph nodes involvement.
- Absolute neutrophil count <3000 / mm³
- Other serious diseases (life expectancy less than 3 months)
- Liver transaminases >2 x N upper limit of normal and/or abnormal liver structure as assessed by ultrasound.

Canine Lymphoma Genetic Study

Introduction

The purpose of this study is to determine tumor gene expression profiles (GEP) from dogs with lymphoma (LSA) prior to treatment with chemotherapy and at 1st relapse. Specifically, we plan to identify unique GEP that may definespecific subtypes of LSA and that may impact diagnosis, treatment, response to chemotherapy, and development of new treatments.

Eligibility Requirements

- ✓ Any K9 breed, age, sex in otherwise good health
- ✓ Cytologically or histologically confirmed multicentric LSA
- ✓ No previous chemotherapy or steroids
- ✓ Staging diagnostics
- ✓ Willingness to treat with the modified Wisconsin Protocol
 - 16 treatments over a 6-month period
- ✓ Pre-treatment blood sample and biopsy
- ✓ Blood sample and biopsy at time of relapse
- ✓ Owner consent ■

Surgery Update

by Helga Bleyaert, V.M.D., Diplomate ACVS

TRIPLE PELVIC OSTEOTOMY (TPO) FOR THE CANINE DYSPLASTIC PATIENT



Canine hip dysplasia is a genetic disease that can be a distressing to owners and devastating to a dogs quality of life. Poor hip conformation results in abnormal biomechanics, articular cartilage damage and the development of progressive osteoarthritis. One of the difficulties with hip dysplasia is determining when or if the pet will suffer clinical signs of lameness.

Radiographs correlate poorly with clinical development of the disease. Numerous factors play a role in clinical progression and severity including diet, body condition, and level of exercise. Most dogs with radiographic signs of hip dysplasia will require some form of pain management during their lifetime. Many dogs can be treated medically with a combination of: strict weight control, regular exercise, non-steroidal anti-inflammatories, joint supplements and acupuncture. If there is persistence of obvious lameness or pain after approximately 2-6 months of treatment, it is an indication that surgery is necessary. Approximately 10-30% of dogs with radiographic signs of hip dysplasia will require some form of surgical intervention.

Dogs over 1 year of age with established degenerative changes that are surgical candidates have the option of either a femoral head and neck ostectomy or a total hip replacement. A total hip replacement is the treatment of choice for reestablishing normal, pain-free limb function. A high degree of success has been reported with this surgery. Most dogs ranging from 40 to 120 pounds can be fit for a prosthesis. Dogs with a total hip prosthesis will be able to carry on an excellent quality of life and it is often difficult to tell which leg underwent surgery. When a total hip replacement is not permitted due to size or cost, a femoral head and neck ostectomy can be done. This eliminates hip pain by removing the femoral head and neck and initiating the development of a fibrous false joint that permits ambulation. The false joint is less stable with a reduced range of motion which will cause a mechanical gait abnormality. Pain relief with adequate function is the goal of this surgery. The procedure can be performed in all dogs of all sizes, but there are usually better long-term success rates in smaller dogs less than 40 pounds.

Many owners, given this information early on in the disease process, prefer to take a proactive approach to treatment and avoid the risks, difficulties and discomfort associated with medical treatment. A Triple Pelvic

Osteotomy can be performed in hip dysplasia patients with no degenerative joint disease. This procedure can reestablish joint stability, encourage normal joint development and minimize abnormal biomechanical forces on the joint before osteoarthritis occurs. Waiting for clinical signs of lameness can be too late for this prophylactic procedure. Prior to clinical signs of arthritis a Triple Pelvic Osteotomy can be a very beneficial surgical procedure allowing patients full return to activity. Recovery time is about 6 weeks and a good success rate has been reported with return of normal hip function. A small number of dogs may require additional medical management or additional surgery due to continued progression of arthritis.

The surgical department at Florida Veterinary Specialists recommends that lateral and VD radiographs of the pelvis and palpation while under sedation or general anesthesia should be done on all young dogs as a screening for Hip Dysplasia. Ideally the first radiograph should be taken around 6 months of age. This can be routinely done while undergoing spay or neuter procedures. The radiographs should be reviewed by a radiologist or orthopedic surgeon. Also, an additional set of hip radiographs at 9 to 12 months of age is recommended to pick up those dogs where hip dysplasia is not evident early on. Florida Veterinary Specialists would be glad to perform radiographic interpretations or provide clients with a personal consultation to discuss options. ■



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Internal Medicine Update

by Brian Luria, D.V.M., Diplomate ACVIM

HISTIOCYTIC ULCERATIVE COLITIS: AN UPDATE



Histiocytic ulcerative colitis (HUC) is an inflammatory bowel disease that causes signs of chronic large bowel diarrhea with tenesmus, hematochezia, and profound weight loss. The disease is most commonly described in young Boxer dogs, however has been reported in other breeds as well. A single cat has been reported with the disease as well.

HUC differs from other forms of inflammatory bowel disease in dogs because it is characterized histologically by periodic acid-Schiff (PAS) positive macrophages, it is more likely to be associated with mucosal ulcerations, and it is less responsive to therapy with a poorer long-term prognosis. The disease was first described in boxer dogs by Van Kruiningen in 1965. Since that time, the gross, histopathologic, and ultrastructural findings have been well characterized. The pathognomonic lesion of HUC is the accumulation of distinctive, PAS positive macrophages (indicative of glycoprotein within the macrophages) in the lamina propria and submucosa of the colon with loss of the associated epithelial surface. Early studies on HUC proposed an infectious etiology based on the presence of Chlamydia-like organisms seen on electron microscopy in the macrophages and clinical improvement with chloramphenicol therapy. In subsequent ultrastructural studies, organisms were not conclusively demonstrated. Attempts to experimentally create the disease with mycoplasma infection failed. It has been suggested that the PAS positive material is derived from remnants of bacterial cell wall glycoprotein, and that accumulation of PAS positive material within macrophages may occur secondary to abnormal lysosomal activity, overwhelming of lysosomal activity, or inhibition of lysosomal activity by toxic substances. There has been recent evidence to support this statement both in the antibiotic responsiveness of the disease and identification of a bacterial organism within the colon of affected dogs.

Management of HUC has historically consisted of various combinations of the following treatments: dietary modifications; antibiotics such as chloramphenicol, metronidazole, and tylosin; and anti-inflammatory/immunosuppressive drugs such as sulfasalazine, prednisone, and azathiaprine. Response to treatment has generally been poor resulting in frequent euthanasia of affected animals. Any currently published textbook will report these treatment options and prognosis, however recently evidence has drastically altered our outlook on this disease process.

Dr. Grant Guilford described a Boxer dog being managed in New Zealand for HUC with high dose prednisone therapy suddenly developed a fever and became very ill (personal communication). Fearing an intestinal perforation, the dog was treated with triple antibiotic therapy consisting of enrofloxacin, amoxicillin and metronidazole. Subsequently, the fever resolved, as did all of the dog's intestinal symptoms. Within days, the previously intractable diarrhea resolved. Subsequent to this finding, other Boxer dogs were empirically managed with this triple antibiotic protocol following diagnosis of HUC with excellent success. Two recently published papers describe this treatment and suggest that the enrofloxacin alone is the effective therapy^{1,2}. These recent reports indicate resolution of clinical signs and histological lesions, including the disappearance of PAS infiltrates in response to enrofloxacin alone or in combination with amoxicillin and metronidazole.

Although not widespread throughout the general veterinary community, this therapy is now the primary recommendation for HUC without concurrent immunosuppressive therapy. The current recommendation based on this empiric treatment is to administer enrofloxacin at 5 to 10mg/kg every 24 hours for 4 weeks. Many anecdotal reports describe complete remission within days of therapy without evidence of relapse many months later.

The response to enrofloxacin supported the logical conclusion that HUC likely has an infectious etiology. Recent work presented at this year's ACVIM conference by Kenneth W. Simpson, BVMS, PhD at Cornell University has apparently uncovered the organism³. Through a combination of culture independent techniques for determining the presence of infectious agents, Dr. Simpson identified an *Escherichia coli* strain similar to one implicated in Crohn's disease in humans. Colonic biopsies from dogs with HUC (15), non-HUC (26), and normal histology (12), were examined by fluorescent in situ hybridization (FISH) with a probe against eubacterial 16srRNA. Organisms were able to be visualized within intramucosal colonic tissue in the HUC dogs in much larger numbers than in non-HUC or normal colons. Subsequently, culture, 16s rDNA sequencing, polymerase chain reaction (PCR) with broad range and pathogen specific primers and histochemistry were performed to further define the invasive flora. Ultimately, an *E. coli* isolate was identified as the offending organism.

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Internal Medicine Update
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This *E. coli* strain demonstrated virulence factors which set it apart from other strains, including an ability to invade and persist in epithelial cells. The PAS-positive material described within macrophage is thought to be degradation products from these bacterial organisms. Dr. Simpson describes this combination of a seemingly benign genotype, but pathogenic phenotype as being similar to that observed in *E. coli* strains isolated from Crohn's disease in people.

Inflammatory bowel disease is most often described as a multifactorial disease process with speculation that a combination of an exaggerated immune response against normal or overgrown bacterial flora or dietary proteins manifests in clinical symptoms. This disease seen in the boxer dog may be a genetic defect in their host defense to an otherwise normal flora or a combination of this defect with presence of a virulent bacterial organism.

1. Hostutler R et al. Antibiotic-responsive histiocytic ulcerative colitis in 9 dogs. *J Vet Intern Med.* 2004,18: 499-504.
2. Davies DR et al. Successful management of histiocytic ulcerative colitis with enrofloxacin in two Boxer dogs. *Aust Vet J* 2004, 82[1-2]:58-61.
3. Simpson KW. Histiocytic Ulcerative Colitis and Feline Cholangiohepatitis: Infectious or Immune Mediated?, in *Proceedings*. 23rd Annu ACVIM Forum 2005. ■

Avian and Exotic Update
continued from page 5

Birds may also use these concrete perches to remove excess food from their beaks after feeding. This behavior also removes any accumulation of excessive keratin on the lateral maxillary rhamphotheca. Some owners have found that hanging a small concrete perch vertically from the top of the cage allows their bird to best utilize the perch for auto grooming of the beak. (Note: these cement perches should not be confused with the sandpaper perches that were historically sold and that were generally ineffectual).

Extensive client communication and knowledge of the species and individual bird's temperament will remove much of the medical risk from these procedures and prevent them from becoming a source of client dissatisfaction. ■



The distal nine primary remiges have been cut on this Amazon parrot. Generally, only 4 - 5 feathers are cut on a bird this size to deter flight.



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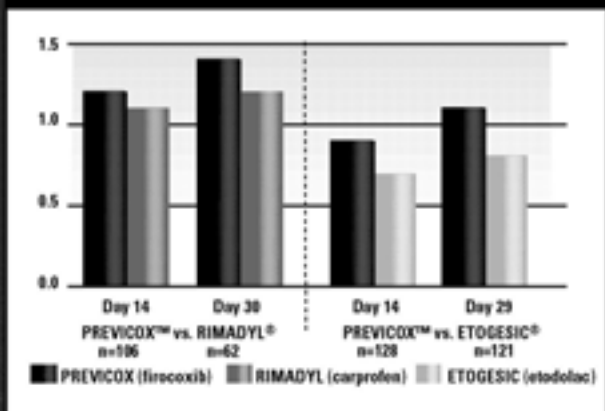
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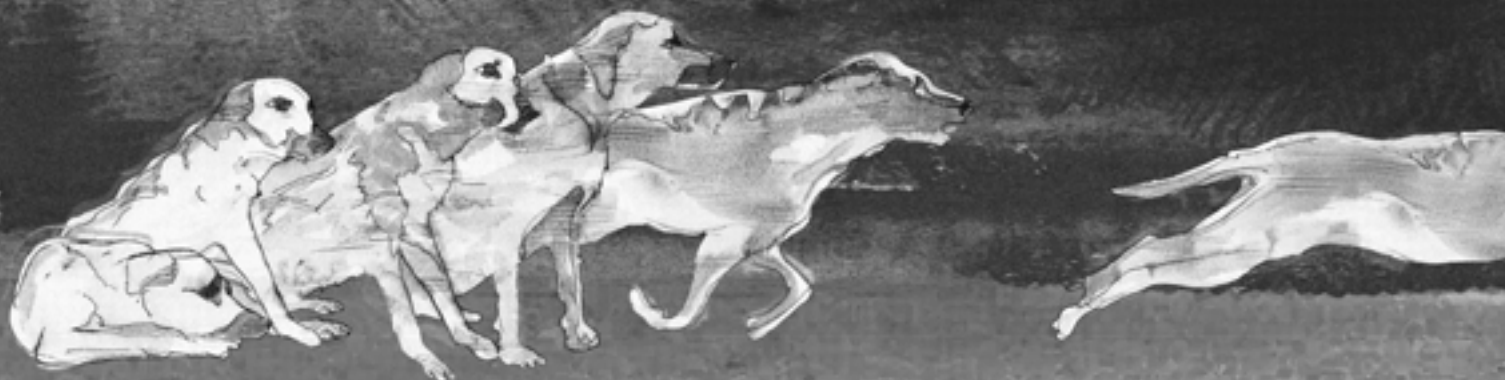
*In clinical studies, NEW
PREVICOX™ (firocoxib)
demonstrated great results.**

Dogs treated with PREVICOX at daily recommended doses had no evidence of renal or hepatic toxicity.²

PREVICOX: Improvement in veterinarian-assessed lameness was comparable to active controls in large field studies.¹



No claim of superiority can be made based on these data.



As with all drugs in this NSAID class, gastrointestinal, kidney or liver side effects may occur. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarians immediately if side effects occur. Evaluation for pre-existing conditions and regular monitoring are recommended for pets on any medication, including PREVICOX. Use with other NSAIDs, corticosteroids or nephrotoxic medication should be avoided. Refer to the prescribing information for complete details or visit www.previcox.com.

¹Data on file at Merial, PR&D Study Series 00535/00538, 00604

²Data on file at Merial, PR&D Study Series 00535/00538, 00603, 00604, 00714



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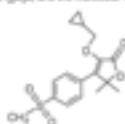
Previcox™ (firocoxib)

CHEWABLE TABLETS

For oral use in dogs only.

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

DESCRIPTION: PREVICOX™ (firocoxib) belongs to the coxib class of non-steroidal anti-inflammatory drugs. Firocoxib is a white crystalline compound described chemically as 2-(cyclopropylmethoxy)-4-[[4-methylbutyl]phenyl]-5,5-dimethylfuranone. The empirical formula is C₂₁H₂₈O₂ and the molecular weight is 336.4. The structural formula is shown below.



PHARMACOKINETICS: The absolute bioavailability of PREVICOX™ (firocoxib) is approximately 30% when administered as a 5 mg/kg oral dose to fasted adult dogs. Firocoxib is rapidly cleared from the blood via hepatic metabolism and fecal excretion (Cl_{systemic} = 0.4 L/hr/kg). Despite a high level of plasma protein binding (96%), firocoxib exhibits a large volume of distribution (V_d of total drug = 4.5 L/kg) and a terminal elimination half-life of 7.8 hours (t_{1/2} = 30%). The oral drug absorption process is highly variable among subjects. Co-administration of PREVICOX™ with food delays drug absorption (T_{max} from 1 to 5 hours) and decreases peak concentrations (C_{max} from 1.3 to 0.9 mcg/mL). However, food does not affect the overall oral bioavailability at the recommended dose.

INDICATIONS: PREVICOX™ (firocoxib) Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

DOSE AND ADMINISTRATION: Always provide Client Information Sheet with prescription. The recommended dosage of PREVICOX™ (firocoxib) for oral administration in dogs is 2.27 mg/lb (5.0 mg/kg) body weight once daily. The tablets are scored and dosage should be calculated in half-tablet increments. PREVICOX™ Chewable Tablets can be administered with or without food.

CONTRAINDICATIONS: Dogs with hypersensitivity to firocoxib or other NSAIDs should not receive PREVICOX™ Chewable Tablets.

WARNINGS: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

For oral use in dogs only. Use of this product at doses above the recommended 2.27 mg/lb (5.0 mg/kg) in puppies less than seven months of age has been associated with serious adverse reactions, including death (see Animal Safety).

All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum baseline data is recommended prior to and periodically during administration of any NSAID. Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given a Client Information Sheet about PREVICOX™ Chewable Tablets.

For technical assistance or to report suspected adverse events, call 1-877-217-3543.

PRECAUTIONS: This product cannot be dosed accurately in dogs less than seven pounds in body weight.

Consider appropriate washout times when switching from one NSAID to another.

As a class, cyclooxygenase-inhibitory NSAIDs may be associated with renal and gastrointestinal toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, or concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concomitant administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored. The concomitant use of protein-bound drugs with PREVICOX™ Chewable Tablets has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit the metabolism of PREVICOX™ Chewable Tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of PREVICOX™ Chewable Tablets in pregnant, lactating or breeding dogs has not been evaluated.

ADVERSE REACTIONS: In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated for safety when given PREVICOX™ Chewable Tablets at a dose of 5.0 mg/kg orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in U.S. Field Studies

Adverse Reactions	PREVICOX™ n=128	Active Control n=121
Vomiting	5	8
Diarrhea	1	10
Decreased Appetite or Anorexia	3	3
Lethargy	1	3
Pain	2	1
Somnolence	1	1
Hypersensitivity	1	0

PREVICOX™ (firocoxib) Chewable Tablets were safely used during field studies concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics.

CLINICAL PHARMACOLOGY: Mode of action: PREVICOX™ (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties. There are two main cyclooxygenase enzymes, COX-1 and COX-2, and a newly discovered third enzyme, COX-3, which has yet to be fully characterized. Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiologic processes, e.g., platelet aggregation,

gastric mucosal protection, and renal perfusion.² It also is constitutively expressed in the brain, spinal cord, and reproductive tract.¹ Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators, but it is also constitutively expressed in the brain, spinal cord and kidneys.^{4,11} Cyclooxygenase-3 (COX-3) is also constitutively expressed in the canine and human brain and also the human heart.⁸ Results from *in vitro* studies showed firocoxib to be highly selective for the COX-2 enzyme when canine blood was exposed to drug concentrations comparable to those observed following a once daily 5 mg/kg oral dose in dogs.¹ However, the clinical significance of these findings has not been established.

EFFECTIVENESS: Two hundred and forty-nine dogs of various breeds, ranging in age from 11 months to 20 years, and weighing 13 to 175 lbs, were randomly administered PREVICOX™ or an active control drug in two field studies. Dogs were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall improvement in a non-inferiority evaluation of PREVICOX™ compared with the active control. At the study's end, 67% of the owners rated PREVICOX™ treated dogs as improved. Eighty-eight percent of dogs treated with PREVICOX™ were also judged improved by the veterinarians. Dogs treated with PREVICOX™ showed a level of improvement in veterinarian-assessed lameness, pain or palpation, range of motion, and owner-assessed improvement that was comparable to the active control. The level of improvement in PREVICOX™ treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control.

PALATABILITY: PREVICOX™ Chewable Tablets were rated both convenient to administer (83.2%) and palatable to the dog (89.5%) by owners in multi-center field studies involving client-owned dogs of various breeds and sizes.

ANIMAL SAFETY: In a target animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment-related adverse events. Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group. One dog in the 3X dose group was diagnosed with juvenile polyarthritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one 5X dog. This dog also had a decreased serum albumin which returned to normal by study completion. One control and three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control, one 3X, and three 5X dogs. Mean ALP was within the normal range for all groups but was greater in the 3X and 5X dose groups than in the control group. Transient decreases in serum albumin were seen in multiple animals in the 3X and 5X dose groups, and in one control animal.

In a separate safety study, firocoxib was administered orally to healthy juvenile (10-12 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated 150 dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal periportal hepatic fatty change. On histopathologic examination, one control, one 1X, and two 5X dogs had diffuse slight hepatic fatty change. These animals showed no clinical signs and had no liver enzyme elevations. In the 2X dose group, one dog was euthanized because of poor clinical condition (Day 63). This dog also had a mildly decreased serum albumin. At study completion, out of five surviving and clinically normal 3X dogs, three had minimal periportal hepatic fatty change. Of twelve dogs in the 5X dose group, one died (Day 82) and three moribund dogs were euthanized (Days 31, 71, and 78) because of anorexia, poor weight gain, depression, and in one dog, vomiting. One of the euthanized dogs had ingested a toy toy. Two of these 5X dogs had mildly elevated liver enzymes. At necropsy all five of the dogs that died or were euthanized had moderate periportal or severe periportal hepatic fatty change, two had duodenal ulceration, and two had pancreatic edema. Of two other clinically normal 5X dogs (out of four euthanized as comparators to the clinically affected dogs), one had slight and one had moderate periportal hepatic fatty change. Drug treatment was discontinued for four dogs in the 5X group. These dogs survived the remaining 14 weeks of the study. On average, the dogs in the 3X and 5X dose groups did not gain as much weight as control dogs. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs. Thalamic vacuolization was seen in three of six dogs in the 3X dose group, five of twelve dogs in the 5X dose group, and to a lesser degree in two unmedicated controls. Diarrhea was seen in all dose groups, including unmedicated controls.

In a separate dose tolerance safety study involving a total of six dogs (two control dogs and four treated dogs), firocoxib was administered to four healthy adult Beagle dogs at 50 mg/kg ten times the recommended daily dose for twenty-two days. All dogs survived to the end of the study. Three of the four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption than control dogs. One of these dogs had severe duodenal ulceration, with hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, lethargy, and mild elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One of the two control dogs and three of the four treated dogs exhibited transient increases in ALP that remained within normal range.

STORAGE: Store at room temperature, between 59°-86° F (15°-30° C). Brief periods up to 104° F (40° C) are permitted.

To request a Material Safety Data Sheet (MSDS), call 1-877-217-3543.

HOW SUPPLIED: PREVICOX™ is available as round, beige to tan, half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. Each tablet strength is supplied in 10-count and 30-count blister packages and 80-count bottles.

For customer service, please contact Merial at 1-888-637-4251.

¹ Wiloughby DA, Moore AP and Coville-Nash PR. COX-1, COX-2, and COX-3 and the future treatment of chronic inflammatory disease. *Lancet* 2008;355:646-648.

² Smith, et al., *Pharmacological Analysis of Cyclo-oxygenase-1 in Inflammation*. Proc. Natl. Acad. Sci. USA, *Pharmacology* 1998; 95:12913-12916.

³ Jones CJ and Blumberg SC. Physiologic characteristics and clinical importance of the cyclooxygenase isoforms in dogs and cats. *JAVMA* 2000;217(5):721-729.

⁴ Zhang, et al., *Inhibition of Cyclo-oxygenase-2 Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin G₂ Production*. *JPEI* 1987; 2(3):1089-1095.

⁵ Jones and Blumberg, pp. 721-729.

⁶ Zhang, et al., pp. 1089-1095.

⁷ Chandrasekaran M, Dai H, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure and expression. *Proc. Natl. Acad. Sci. USA*, 2002;99(1):1303-1309.

⁸ Data on file.

Merial Limited
2329 Satellite Blvd.
Duluth, GA 30096-6040
U.S.A. 1-877-217-3543
U.S. Patent Nos. 5,961,576; 6,541,646; and 6,677,373
NADA 141-238, Approved by FDA



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PVX-ADS-5-SINGLEPTRADE.

Employee Spotlight

Beth Faiola, CVT
Surgical Technician



Beth Faiola likes the fact that a day in the surgery department is never routine. Every day is different and brings new challenges, which require her to use all of her training and experience. She assists in the surgeries, takes radiographs, meets clients, maintains inventory and coordinates surgical schedules and duties. Beth always wanted to work in

the veterinary field and graduated from Wilson College with her A.S. in Veterinary Medical Technology in 1991. She worked in Pennsylvania as a technician from 1988-1991 and was a technician with the United States Army from 1991-2001. In 2001, she joined FVS. Beth has always had animals including a baby fawn when she was growing up. Now, she has (brace yourself!) 8 horses, 8 dogs, 3 cats, 1 rabbit and a bird! Outside of work, she enjoys barrel racing and team roping (with the horses), any activities involving animals and spending time with her family. Since getting married last month, Beth is taking the time to settle into her new family and working on getting back into competitive barrel racing. Her one piece of advice to someone going into the field is that "the day is best if you start each day fresh and charged. Challenge yourself in everything you do and make sure you do it the best you can. No getting stuck in the rut of just getting the job done." Way to go Beth! We are very happy you are a part of our team! ■

Rachel Bedford
Front Desk Supervisor



Rachel Bedford is FVS' Front Desk Supervisor. She joined the practice in 2003 with five years of general practice experience behind her. Rachel has tried several other professions but always knew she wanted to be in the veterinary field. She graduated in 2000 as a licensed massage therapist specializing in therapeutic modalities such as mofascial release,

craniosacral therapy and lymphatic drainage and several of us can attest to her miraculous ability to relieve a headache or sore muscle! Rachel was born and raised in Tampa. She states that she "certainly loves the animals but is a 'people person' too. Just taking a little extra time to get to know the client and offer a little TLC can mean so much to them. It is very rewarding when they thank you and tell you what a difference you made during a stressful time." Outside of work she enjoys gardening, spending time with her husband and friends, shopping with her mom, arts and crafts and time spent with her pets. She has 3 Chihuahuas - Corona, Tequiza and Cuervo, 2 cats - Chloe and Hailey Cooper and 2 tortoises - Violet and Veruca. She just started her own business with her husband and is celebrating her 9th wedding anniversary this month. People who know her might be surprised to know that she plays the violin and piano and collects succulents and cacti! Her advice to someone entering the field is to never forget what it is like to be the client. "It is easy for us to become accustomed to the emergencies and critical pets we see every day. Always put yourself in the clients shoes and strive to be compassionate no matter what the situation." ■

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Neil Shaw, DACVIM
Florida Veterinary Specialists, Tampa

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Tech Tips

An interview with Terry Besnier, Radiograph Technician, and Jeff Fox, Operations Manager

DIGITAL RADIOGRAPHY (DR)

At Florida Veterinary Specialists, our team has recently implemented a paperless, filmless Digital Radiography, Ultrasound, CT, and PACS solution from Sound Technologies. The process of "going digital" has delivered some impressive results, and learning opportunities. Sharing their experiences for Florida Veterinary Specialists were Terry Besnier, Radiography Technician and Jeff Fox, Operations Manager for Florida Veterinary Specialists.

Question: "Has 'going digital' in radiography changed the dynamics of how FVS performs and delivers imaging within its hospital to FVS doctors?"

A: (Terry Besnier) Yes, in many ways. For example, studies are much quicker to perform and post for the Doctors with Digital Radiography, CT, and ultrasound. With instant images and rapid throughput, more exams and more views per exam are often ordered in medicine, surgery, and other specialties. Study images are instantly posted and available throughout the hospital for review as they are being taken. No more 'pit stops' in the radiology room to see if a particular study is done."

A: (Jeff Fox) "We have experienced a 30% increase in radiographs and other digital images. For those contemplating a conversion to digital imaging, beware of this good news, bad news growth. By increasing the numbers of images, you also increase the amount of image data. This data must be stored and protected for the life of the medical-legal record in a PACS software server. In meeting this challenge, Florida Veterinary Specialists has significantly increased Information Technology, computer, VetPACS, and server infrastructure to support this volume of electronic data.

Question: "By no longer generating a film, how has FVS changed how it communicates radiographic study images to referring clients and pet owners?"

A: "Today, we communicate digital images throughout the hospital on computer screens. While at FVS, clients benefit from seeing images with magnification, exposure, and measurement tools throughout the hospital. For those outside of our FVS facility, such as our referring doctors, we now burn studies to compact disc (CD). Our latest capability is to provide radiographic images on CD using VetPACS-Vu, an embedded image viewer and enhancement program on each CD. Doctors and clients simply insert the CD into any computer, click on the case name, and begin viewing the study images with the same tools and enhancements we use inside FVS." ■

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Dermatology Update

by Heather Willis-Goulet, D.V.M., Diplomate ACVD

THE ITCH IS IN THE BITE - FOOD ALLERGY IN THE DOG AND CAT



Food allergies are the result of immunologic reactions to proteins or less commonly, carbohydrates or preservatives eaten in the diet. These reactions may be type 1 to 4 hypersensitivities. Research has shown that serologic and intradermal skin tests for food allergens are not reliable due to numerous false positives and negatives. A recent prospective study performed at North Carolina State University College of Veterinary Medicine revealed that food allergies are more common than we used to think. The results further identified that many atopic animals also have a food allergic component that could not be predicted by clinical signs. At FVS we encourage food exclusion trials in all of our non-seasonal allergic patients.

When should I consider food allergy?

- NON-SEASONAL pruritus
 - one of the most pruritic skin diseases
 - rule out scabies, bacterial and yeast infection, flea allergy
 - can be ears only, ears and rear, generalized
- Develops at ANY AGE to proteins consumed for some time
- Relapsing pyoderma/yeast infections of the skin or ears
- In cats
 - non-seasonal pruritus (generalized, head and neck)
 - eosinophilic granuloma complex
 - symmetrical alopecia
 - miliary dermatitis

How do I diagnose food allergies?

- Treat infections of the ears and skin before starting the food trial
- Rule out scabies, flea allergy and other parasitic or infectious diseases
- Perform strict elimination diet (food exclusion trial)
- Research has shown that serology or intradermal skin testing for food allergens in pets is unreliable
- In order to diagnose atopy, a food trial should be performed in ALL non-seasonally pruritic animals. Remember, unless you have seasonality, atopy is a rule out diagnosis.

How do I perform a food trial?

- "No pain...No gain" This is difficult for pet owners, but I try to get them to understand that this is a diagnostic "test" that I am sending them home to perform. Also, if their pet is only food allergic they can actually control the exposure to the allergen and, therefore, their pet "may" be normal again.
- Obtain a complete dietary history
 - Before starting the food trial, have the client record what the pet eats for 1 to 2 weeks
- Ideally, home cooking is recommended with a novel protein and carbohydrate source for 12 weeks. We can provide balanced recipes if your client chooses to do this.
- Other popular options include limited antigen or hydrolyzed diets, such as Hill's z/d. Hydrolyzed protein diets take a protein and make it smaller so that the immune system should not recognize or react to it. We may repeat a food trial if other diets are used, food allergy is highly suspect, or if there is minimal response to immunotherapy.

- All medications should be non-flavored
 - o such as Heartgard or Interceptor/Sentinel (beef/ pork and soy protein flavorings)
- NOTHING ELSE, except ingredients in the diet, should enter the animals mouth
- NO rawhides, toothpaste, bones, hooves, broths, tuna juice, licking other animals bowls/litter boxes, meds should not be given in anything but the diet, etc....

How do I rechallenge and confirm the diagnosis?

- If there is resolution of clinical signs on the diet, slowly wean onto the regular diet
 - Most animals will relapse in a few days, but this can take a couple of weeks.
- If there is no reaction, place back onto trial diet for 1 week and then in 2 week intervals (one to two weeks of challenge ingredient, one week only trial diet) go back through the diet history and challenge with other allergens that the pet has been consuming...raw hides, treats
- If the pet reacts to the regular diet, the owner may elect to challenge each individual allergen in 1 to 2 week intervals as above.
- The most common proven allergens in the dog are beef/milk, chicken/eggs, corn, wheat and soy. In the cat, fish and milk products. Remember, that some allergens may cross-react such as all products from the cow, chicken, poultry, etc. Therefore, another diet may be trialed.
- If the clients do not wish to rechallenge the limited antigen or the balanced home-cooked food trial diets can be used as a maintenance diet
- Remember that there may be only partial response if the pet has concurrent atopy and/or flea allergy.

Food allergies can be a blessing when easily controlled, but can also be confusing and frustrating for the client and veterinarian. Please don't hesitate to call the dermatology department at FVS with any consultation when ever necessary. ■



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Acupuncture & Rehabilitation Medicine Update

by Felicity Talbot, D.V.M., Certified Veterinary Acupuncturist

ACUPUNCTURE AND YOUR PATIENTS



Acupuncture is becoming an increasingly popular treatment modality in veterinary medicine. Acupuncture can help a wide variety of conditions, from acute onset diarrhea to chronic degenerative disease like arthritis. Many clients have had acupuncture on themselves and feel that their pet can benefit from similar treatments.

Chinese theory involves the idea that the life force energy, or Qi, flowing through energetic channels called meridians can become blocked or stagnant. When this occurs, pain and dysfunction are the result. When certain points are stimulated by acupuncture needles, the energy is released and able to flow freely, helping the body to heal itself. The scientific explanation of acupuncture allows for the release of endorphins, serotonin and other neurotransmitters in response to the needles, providing pain control for chronic conditions.

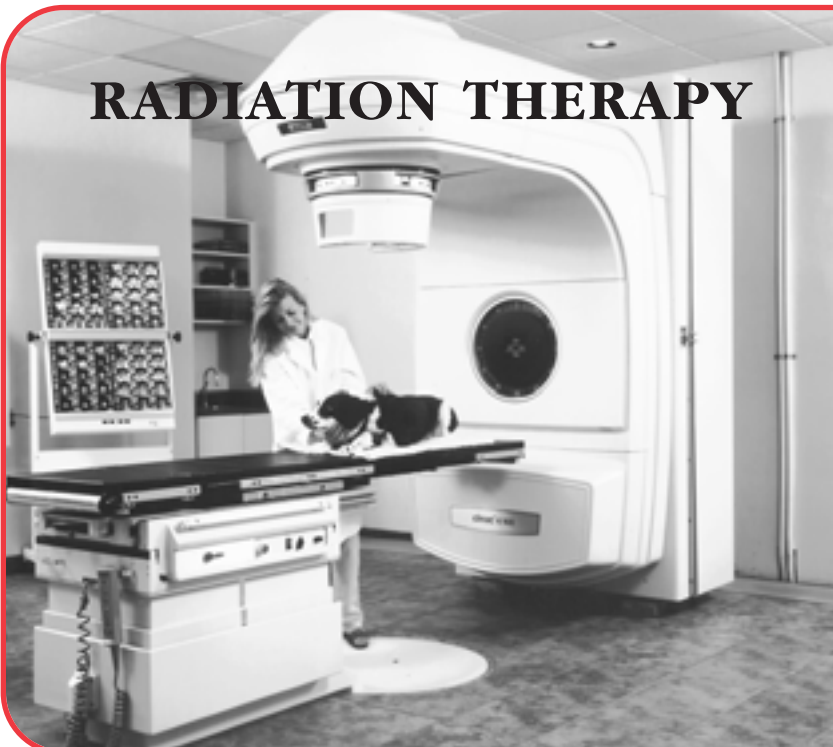
Amber is a 13 year old FS Cocker Spaniel that presented to FVS for severe degenerative lumbo-sacral disease. She is owned by a veterinarian from the Orlando area who decided to give acupuncture a try. Since acupuncture isn't usually a fast treatment like conventional medications, it can take a few treatments to have an effect. But with Amber, the results were significant after

the very first treatment. Not only did acupuncture improve her energy level and ability to move around, but it also ceased her nocturnal urination for which she no longer needs medication. The owner is convinced of the benefits of acupuncture.

Another case example is a 3 year old, FS Dachshund who became paraplegic with no deep pain before and after surgery. Acupuncture treatments began 2 weeks post-operatively as the dog still had no motor in her hind legs. Acupuncture points proximal and caudal to the lumbar disc lesion were chosen and electrodes were attached to these points. Electro-acupuncture is a great way to help stimulate the nervous system and to help restore neurological function. Other points used were those that help control the bones and joints and to help reduce pain. In addition to the acupuncture, rehabilitative exercises were shown to the owners, including assisted standing exercises in water, weight-shifting exercises on a therapy ball, and massage with range of motion. After two acupuncture treatments the Dachshund began to take a few steps and was walking after 5 treatments. The owners were extremely pleased.

Acupuncture has great potential to help control painful conditions and improve function. The overall improvement in a pet's quality of life is the part that gains most pet owner's satisfaction. ■

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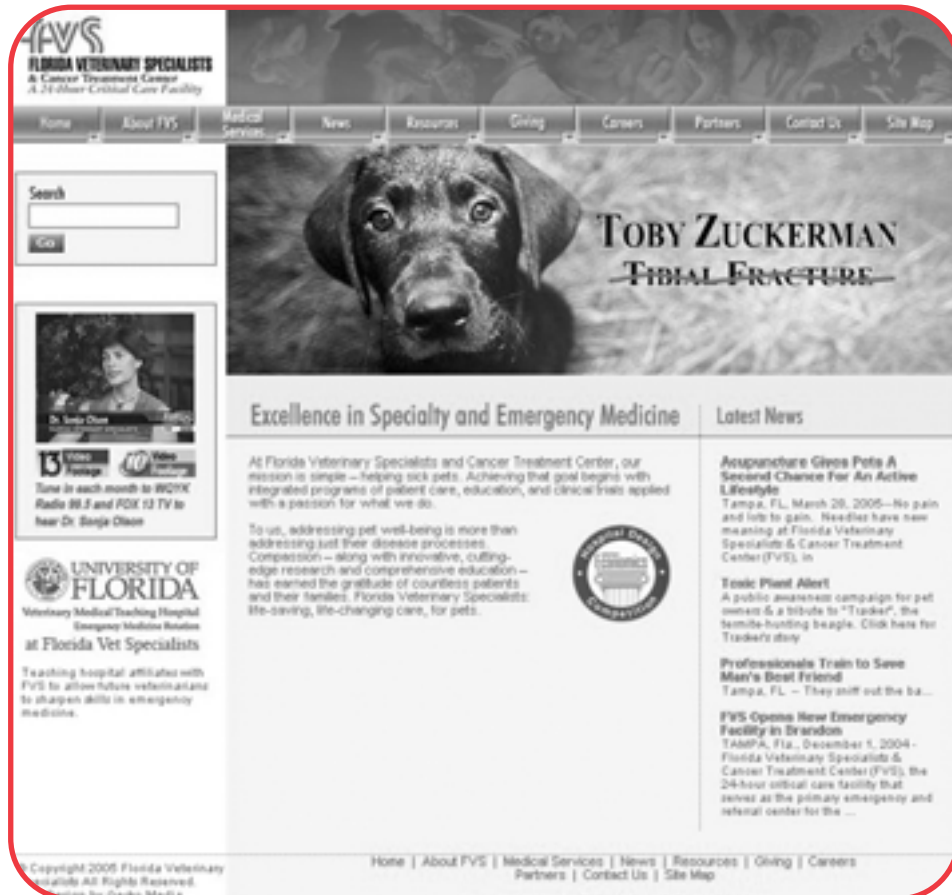


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