Gastroprotectant and Antacid Therapy in Veterinary Medicine
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Minimally Invasive Treatment Options: The Use of Stents in the Veterinary Patient
Written by Jennifer Brisson, DVM, DACVR

“The future of gastric acid suppression in veterinary medicine may include gastrin receptor antagonists, gastrin-releasing peptide receptor antagonists and potassium-competitive acid blockers...For now, the use of PPIs appears to be the most effective and consistent form of gastric acid inhibition in both dogs and cats.”
GASTROINTESTINAL PHYSIOLOGY

The entire gastric epithelial surface is replaced every 2-3 days, with cellular production occurring in the crypts and migrating toward the lumen to be shed. A rich microcirculation is necessary to transport nutrients, oxygen and back-diffused hydrogen ions. The mucus layer protects the mucosa from digestive enzymes, acts as a mechanical barrier against abrasion and consists of viscous glycoprotein that is produced by gastric neck cells. Bicarbonate secreted into the mucus layer establishes a pH gradient and neutralizes stomach acid. Prostaglandins (from arachidonic acid and enzyme cyclooxygenase [COX]) may increase cell turnover, decrease gastric acid secretion, increase bicarbonate and mucus secretion and cause vasodilation increasing blood flow to the gastric mucosa. Medications that interfere with prostaglandin production such as non-steroidal anti-inflammatory drugs (NSAIDs) contribute to ulcer formation by interfering with all of these protective mechanisms.

CONTRIBUTORS TO ULCERATION

Prostaglandin production is significantly decreased by COX-1 enzyme inhibitors (aspirin, flunixin, ibuprofen, indomethacin, ketoprofen, naproxen, phenyl butazone, piroxicam) and therefore gastric protective mechanisms are significantly altered by these medications. COX-2 specific enzyme inhibitors [carprofen, meloxicam] have less ulcerogenic properties since eicosanoids produced by the COX-2 enzyme pathway are more responsible for pain and inflammation of the gastric mucosa. Non-specific COX inhibition increases the risk of gastric ulcers substantially.

While corticosteroids do decrease protective eicosanoid production, and are often implicated in the formation of gastric ulcers, they only contribute to ulceration when other factors are present (NSAID therapy, hypotension) or they are administered at very high doses (4-6 mg/kg/day). Other documented causes of gastric ulcer formation include infiltrative diseases such as neoplasia, pyothiosis and inflammatory bowel disease. Metabolic diseases such as renal failure and hepatopathy will cause gastric ulcers secondary to reduced renal gastrin clearance and elevated histamine levels, respectively. Pancreatitis, hypoadrenocorticism, disseminated intravascular coagulation and mechanical irritants like chemical toxins and foreign objects (if pre-existing gastritis or ulcers are present) are causes of gastric ulcers. Conditions that increase gastric acid such as a gastrinoma in the pancreas, mast cell tumors and amine precursor uptake and decarboxylation tumors (APUDomas) will contribute to ulcer formation. Since the gastrointestinal tract is the shock organ in our canine patients, hypovolemia, sepsis and systemic inflammatory response syndrome (SIRS) may be commonly overlooked causes of gastroduodenal ulceration. Any critically ill patient should be considered at risk for ulcer formation.

CLINICAL SIGNS

Clinical signs of gastric ulceration can range from mild biochemical changes to severe vomiting. Dogs do not secrete gastric acid continuously like people do, and blood from an ulcer may not always appear digested when vomited. Vomiting, inappetence and anorexia may be the most common clinical symptoms of ulceration.
Biochemical changes may include regenerative or non-regenerative anemia with, or without hypochromasia and microcytosis, and electrolyte abnormalities from severe vomiting. Melena may not be present if the blood loss is minimal, and fecal occult blood testing may be falsely positive from red meat, cauliflower or turnips (peroxidase-rich foods) in the diet. A 3-day hiatus from red meat is recommended before fecal occult blood testing is performed using any method.

**DIAGNOSIS**

Definitive diagnosis of gastric ulceration is best made with gastroscopy. Therapy, however, may be implemented based on history (NSAID administration), risk (disease process) and clinical signs. Therapeutic goals include amelioration of clinical signs, reduction of complications and prevention of recurrence. Discontinuation of ulcerogenic medications, re-perfusion by establishing adequate volume and hydration, antacid therapy and reduction of gastric acid secretion are the mainstays of therapy.

**TREATMENT OPTIONS**

Antacids such as calcium carbonate, aluminum hydroxide, sodium bicarbonate and magnesium hydroxide function by neutralizing gastric acid with a H+-binding group. This reaction produces water and a neutral salt. Antacids also increase endogenous prostaglandin secretion, bind bile acids and decrease pepsin activity in the stomach. Although very effective, side effects, palatability and frequent dosing requirements make antacid therapy difficult in our veterinary patients.

Gastric acid may be reduced medically by histamine2-receptor antagonists (H2-RA) or proton pump inhibitors (PPIs). Acid production by parietal cells of the gastric glands is diminished when the H2 histamine receptors are blocked. Additionally, H2-RAs have been demonstrated to increase mucosal blood flow, bicarbonate and mucus. A study in 2005 revealed that of all the H2-RAs used in veterinary medicine, famotidine was the only one to affect gastric acid secretion. Cimetidine and ranitidine were found to be no more effective than saline at pH reduction. An abstract recently presented at the 2010 ACVIM forum found that famotidine, even at doses of 1-1.5 mg/kg every 12 hours, was not significantly different than placebo in decreasing gastric acid when compared to omeprazole, a PPI. Both ranitidine and nizatidine have been shown to have some additional gastric promotility activity. Cimetidine must be used with extreme caution as it decreases hepatic blood flow and inhibits hepatic P-450 and P-488 enzymes. This, in turn, allows medications cleared by this pathway (cyclosporine) to accumulate in the body, reaching higher plasma concentrations. The use of cimetidine for acetaminophen toxicity in cats and dogs is also controversial as it has not been proven to be effective: recent research suggests that it inhibits beneficial hepatic biotransformation pathways. It is no longer used in human medicine for acetaminophen toxicity.

Proton pump inhibitors exert their effect by blocking the H+K+-ATPase enzyme on the gastric luminal side of the parietal cell. Acid secretion is inhibited regardless of the cause of gastric acid production (histamine, acetylcholine or gastrin). In humans, omeprazole has been shown to be more effective and consistent in acid suppression than famotidine. Current research finds this to be true in dogs as well, though higher than traditional doses may be needed for adequate suppression. Optimal gastroduodenal ulcer healing occurs at an intragastric pH of > 3 in humans. PPIs started 1-2 days prior to surgery have been shown to decrease intraoperative gastroesophageal reflux, which may minimize post-procedural complications including esophagitis and aspiration. Newer PPIs such as pantoprazole (available in an injectable form for more rapid gastric acid suppression), esomeprazole and lantoprazole are being examined for efficacy in veterinary medicine.
misoprostol's effect on corticosteroid induced injury is debated and it has been shown to not be useful if an ulcer is already present. When owners administer this medications gloves need to be worn, as it is easily absorbed through the skin and may induce abortion in pregnant women.

The future of gastric acid suppression in veterinary medicine may include gastrin receptor antagonists, gastrin-releasing peptide receptor antagonists and potassium-competitive acid blockers that block the H+-K+-ATPase by competing with potassium. For now, the use of PPIs appears to be the most effective and consistent form of gastric acid inhibition in both dogs and cats.

The mucosal protectant, sucralfate, is a sulfate disaccharide with aluminum hydroxide groups. When ingested it dissociates to aluminum hydroxide (which buffers H+) and sucrose octasulfate, which combines with hydrochloric acid to become a paste-like substance that adheres to damaged mucosa. The necessity of hydrochloric acid activation in the stomach explains the minimal effect sucralfate has on oral or esophageal ulceration when regurgitation or vomiting is controlled. The adhered substance minimizes further mucosal damage by bile, acid and/or pepsin. Administration of H2-RA and PPIs do not impact the efficacy of sucralfate as it continues to work at a near neutral pH. A two hour separation from other drug administration is recommended as sucralfate can greatly affect gastric drug absorption. Like sucralfate other mucosal protectants such as bismuth subsalicylate, kaolin-pectin and products containing barium may bind bacteria and their toxins, while simultaneously coating the intestinal tract.

Misoprostol, a synthetic prostaglandin E1 (PGE1) acts similarly to endogenous prostaglandins to increase cell turnover, decrease gastric acid secretion, increase bicarbonate and mucus secretion and vasodilate the vessels increasing blood flow to the gastric mucosa. In order to have an effect, misoprostol must be absorbed into the systemic circulation. While demonstrated to potentially be protective against damage by NSAIDs,
Tracheal collapse is graded on a scale of I-IV, with grade I being mild and less than 25% occlusion of the lumen, and grade IV being complete luminal occlusion. Clinical signs range from a chronic non-productive cough and exercise intolerance, to severe dyspnea and cyanosis. Stress can exacerbate the clinical signs and lead to patient collapse.

Diagnosis of tracheal collapse occurs through the use of thoracic radiographs and fluoroscopic evaluation of the airways. Bronchoscopy may be performed concurrently and is useful to assess the presence of disease or collapse in the lower airways, as well as, to obtain a cytologic sample (see fig. 1).

Medical management for tracheal collapse involves bronchodilators, anti-inflammatories, cough suppressants, sedation and weight management. Medical management can be effective for dogs with mild to moderate clinical signs; however some dogs with severe clinical signs and/or complete luminal occlusion require either surgery or alternative intervention. Surgical procedures are available for both cervical and intrathoracic tracheal collapse, however they are associated with complications and increased patient morbidity when compared with the placement of an intraluminal tracheal stent with fluoroscopic guidance. This minimally invasive alternative for these patients is associated with reduced morbidity and mortality and shortened hospital stays.

Patients are administered oxygen, bronchodilators, cough suppressants, and sedation as needed pre-procedurally. The patient (either awake or with mild sedation) undergoes fluoroscopic evaluation of the upper airway, trachea, mainstem bronchi and diaphragm. The patient is then anesthetized and radiographs are obtained under positive pressure and negative pressure ventilation, to measure minimal and maximal tracheal luminal diameter. If the patient is diagnosed with severe tracheal collapse, or the severity of clinical signs warrant, a stent can be placed. With fluoroscopic guidance, the stent is introduced into the endotracheal tube via a bronchoscopy adaptor and advanced into the trachea. The stent length is chosen to span the majority of the tracheal length to avoid progressive tracheal collapse cranial and caudal to the stent. The stent is then deployed into the tracheal lumen with simultaneous extubation.

The majority of patients exhibit a significant immediate improvement in respiratory function as the upper airway obstruction is relieved. A cough may still be present and must be managed medically as appropriate to the patient’s needs. The persistence of cough is attributed to the chronic nature of the disease, a chronic inflammatory response already being present at the time of diagnosis and stent placement, and concurrent lower airway disease if present (see fig. 2).

Tracheal stenting may also be used in the cases with static tracheal narrowing, as can be seen with tracheal stenosis or tracheal stricture following previous tracheal surgery or secondary to malignancy.

Dr. Jennifer Brisson practices at Massachusetts Veterinary Referral Hospital in Woburn, MA.

**Minimally Invasive Treatment Options: The Use of Stents in the Veterinary Patient**

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**TRACHEAL STENTING** is performed in patients with dynamic tracheal collapse. The syndrome of dynamic tracheal collapse occurs most commonly in the middle-aged to older toy breed canine patient (Yorkshire Terriers, Pomeranians, Poodles, Chihuahuas) as a result of weakening of the tracheal cartilage. This may be the result of a degenerative process or secondary to congenital chondrodysplasia. There is ventral deviation of the dorsal tracheal membrane, along with deformation of the tracheal cartilage shape (flattening of C-shaped cartilage), resulting in occlusion of the tracheal lumen.

Jennifer O. Brisson, DVM, DACVR

Minimally Invasive Treatment Options:
The Use of Stents in the Veterinary Patient
CHOOSING A PALLIATIVE TREATMENT PLAN

Stenting of malignant obstructions is a broad way to think about stenting applications. Currently stents are being placed as palliative treatment for obstructions in the nasopharynx, esophagus, trachea, urethra, ureters, colon, and vasculature in the veterinary patient. This is being carried out both in patients who have exhausted standard treatment options and in those for whom the owner is seeking a less invasive alternative.

URETHRAL STENTS

Dogs with urethral, prostatic and pelvic tumors can develop partial or complete urethral obstructions. The most common tumor type causing urethral obstruction is transitional cell carcinoma (TCC). TCC is reported with greater occurrence rates in smaller breed female dogs (Scottish Terriers, Shetland Sheepdogs and Beagles). Clinical signs may include dysuria, stranguria, pollakiuria, hematuria and incontinence. For the patient with a chronic partial urethral obstruction, the clinical signs can significantly reduce a patient’s quality of life and bear a burden on the owner. These patients are often treated with anti-inflammatories and chemotherapy to slow tumor progression. For patients with complete urethral occlusion secondary to neoplasia, surgical options are often limited and include placement of a permanent cystostomy tube. A cystotomy tube requires a significant commitment on the part of the owner to maintain daily cleanliness and consistent emptying of the tube.

Diagnosis of a malignant urethral or urinary bladder trigonal obstruction is often initially made by ultrasound examination. The patient then undergoes a retrograde cystourethrogram to assess and measure the length and diameter of the stenosis or occlusion. With fluoroscopic guidance, a urethral stent is introduced retrograde into the urethra and placed to span the extent of the stenosis, with an attempt made to avoid the urethral sphincter and spare normal mucosa when possible. It is estimated that fewer than 20% of patients with indwelling urethral stents, have permanent incontinence post-procedurally. This is even less for males than females when further divided by sex of the patient. Placement of a urethral stent can extend a patient’s survival time with a good quality of life, and minimal daily commitment on the part of the owner. Most patients are able to void voluntarily immediately following the procedure. Persistent clinical signs are attributed to the primary disease and chronic inflammation, rather than to the stent itself.

As mentioned previously, the application of stents to relieve malignant obstructions can be utilized in a variety of anatomical locations in a patient. This course of therapy is for palliative treatment as it does nothing to treat the underlying disease, but seeks to reduce the severity of clinical signs and improve quality of life. Stenting is often employed in conjunction with chemotherapy and other medical therapies (see fig. 3).

Stents can be deployed in the cranial or caudal vena cava to relieve caval obstructions, such as can occur with adrenal or hepatic tumors. Vascular caval stents are used also to facilitate coil embolization of intrahepatic portosystemic shunts.
INTRAHEPATIC PORTOSYSTEMIC SHUNT COIL EMBOLIZATION

Intrahepatic portosystemic shunts (IHPSS) occur predominantly in large breed dogs (Labrador Retrievers, Irish Setters and Irish Wolfhounds). The most common type of IHPSS is a left divisional shunt resulting from a patent ductus venosus. The ductus venosus should attenuate naturally within the first few days after birth.

Surgical attenuation of such vascular anomalies requires hepatic parenchymal dissection to isolate the vessel of interest, and is associated with high morbidity and mortality as a result of hemorrhage or acute rise in portal pressure.

IHPSS are initially diagnosed by ultrasound examination. It is recommended that patients are on medical management for hepatic encephalopathy for at least 6 weeks prior to shunt coil embolization, or have achieved the majority of skeletal growth (8-10 months of age). For shunt size and morphology assessment, a computed tomography (CT) - portogram is usually performed. The axial imaging provided by CT allows for enhanced understanding of the shunt morphology prior to catheterization and for caval diameter measurements.

A transjugular venous approach has been developed to attenuate a portocaval shunt from the point of communication of the shunting vessel and the intrahepatic portion of the caudal vena cava. Diagnostic angiographic catheters are introduced into intrahepatic caudal vena cava via the jugular vein. Dual caval venography and shunt portography is performed to demonstrate shunt morphology. A vascular stent is introduced into the caudal vena cava and is deployed to span to foramen of the shunt at the junction with the caudal vena cava. Thrombogenic coils are then introduced into the shunt vessel through the interstices of the stent. Portal pressures are measured in conjunction with coil deployment to assess for portal hypertension (and to decrease risk of this complication). Attenuation of the foramen of the shunt occurs secondary to thrombus formation around the intravascular coils. This minimally invasive treatment option can significantly reduce patient morbidity and mortality when compared with traditional surgical treatment.

The use of stents in the veterinary patient is constantly expanding. Requests from owners for minimally invasive treatment options and palliative care options are steadily increasing. We are now offering these procedures, as well as a wide range of fluoroscopic diagnostic procedures and fluoroscopic guided cardiovascular interventions, at Massachusetts Veterinary Referral Hospital in Woburn.

REFERENCES AVAILABLE UPON REQUEST
IVG is dedicated to providing referring veterinarians and their clients with an unparalleled range of emergency and specialty services.

References for all articles available upon request.

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DID YOU KNOW?

We are proud to announce that in August the cardiology service at Mass Vet in Woburn will expand to five days per week. In September it will further expand to six days per week.

MEET THE CARDIOLOGY TEAM:

John MacGregor, DVM, DACVIM (Cardiology)
Dr. MacGregor received his DVM from Cornell University, College of Veterinary Medicine in 1998. In 1999, he completed an Emergency and Critical Care internship at Tufts University School of Veterinary Medicine. Dr. MacGregor was a staff veterinarian at Andover Animal Hospital and Sudbury Animal Hospital from 1999 to 2001. Between 2001 and 2004, Dr. MacGregor was a resident in cardiology at Tufts University, School of Veterinary Medicine. He became board certified by the American College of Veterinary Internal Medicine in 2004. Dr. MacGregor joined IVG in July 2008.

Trey Schutrumpf, DVM, DACVIM (Cardiology)
Dr. Schutrumpf received his DVM at the University of Florida in 2005. He then went on to complete a rotating internship in Small Animal Medicine and Surgery at Cornell University between 2005 and 2006. After working for one year at the Friendship Hospital for Animals in Washington, D.C. Dr. Schutrumpf moved to Columbia, Missouri to enter a cardiology residency starting in 2007. He completed his residency at the University of Missouri in 2010, and became board certified by the American College of Veterinary Internal Medicine in the summer of 2010. Dr. Schutrumpf joins the cardiology team at IVG in August 2010.

Laura Hatton, DVM, (practice limited to Cardiology)
Dr. Hatton received her Doctorate in Veterinary Medicine at The Ohio State University School of Veterinary Medicine in 2006. She then went on to complete a small animal rotating internship in medicine and surgery at the Veterinary Referral and Emergency Center in Norwalk, CT. From 2007 to 2010, Dr. Hatton was a resident in cardiology at the Animal Medical Center in New York City. Her professional interests include echocardiography, treatment of congestive heart failure, and interventional cardiac procedures. Dr. Hatton joins IVG in September 2010.

Examples of cardiac and vascular procedures available at Mass Vet include:

- Occlusion of Patent Ductus Arteriosus (PDA)
- Balloon Valvuloplasty for Valvular Stenosis
- Pacemaker Placement
- Stenting of Vascular Obstructions