Tess is Blessed

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most used classes of pharmaceuticals in canine medicine. Oral NSAIDs in veterinary practice are primarily marketed for chronic pain in small animals and are widely used for their proven efficacy as analgesic, anti-pyretic, and anti-inflammatory agents. NSAIDs are broadly classified as derivatives of salicylate or carboxylic acid including indoles (eg, indomecthacin), propionic acids (eg, carprofen), fenamates (eg, mefenamic acid), oxicams (eg, meloxicam), pyrazolones (eg, phenybutazone), and coxibs (eg, robenacoxib). The general mechanism for NSAID efficacy is through inhibition of prostaglandin synthesis from arachidonic acid through blockade of cyclooxygenase enzymes (COX-1 and/or COX-2)[2]. Gastrointestinal toxicosis through altered integrity of the gastrointestinal mucosal barrier as a consequence of COX inhibition and prostaglandin synthesis has been the most widely accepted pathophysiology for NSAID adverse reactions. Carprofen is one of the most widely used NSAIDs in canines due to extensive evidence for its preferential inhibition of COX-2,, limiting gastrointestinal adverse effects[3,8, 10]. However, reports of acute adverse reactions to appropriately administered NSAIDs are absent in the literature. This case further describes the severe acute gastrointestinal effects NSAIDs had on one canine patient postoperatively.

History and presentation

Tess was a 1.5-year-old female spayed Welsh Pembroke Corgi, that presented to the MSU-CVM Surgery Service on 2/13/20 for progressive left pelvic limb lameness since August 2019 with no response to medical management with Vetprofen, methocarbamol, gabapentin, and cage rest. Tess was administered cetirizine (Zyrtec) daily for allergies and had a history of food allergies and episode of angioedema after administration of rabies vaccine the previous year as a

puppy. Tess was otherwise healthy with no other major medical history or health concerns. On presentation to MSU Surgery Department on 2/13/20, Tess exhibited moderate left pelvic limb lameness with left stifle effusion and mild muscle atrophy of the left pelvic limb. She had a positive sit test on the left pelvic limb with pain elicited in hypertension and cranial tibial thrust. Tess weighed 14.8kg with a body condition score of 8/9 (obese). Tess was diagnosed with a left cranial cruciate ligament tear and was kept overnight for surgical management with a left stifle arthrotomy and tibial plateau leveling osteotomy (TPLO) planned for the following day. During initial hospitalization Tess ate well and was started on oral Trazodone at 3.5 mg/kg, Gabapentin at 7 mg/kg, and Maropitant at 2 mg/kg. A pre-operative complete blood count and chemistry profile was performed indicating no abnormalities. Tess was placed under general anesthesia and a 4.4 mg/kg dose of Carprofen subcutaneously and a caudal epidural on 2/14/20. Tess's TPLO surgery was successful with appropriate implant placement and she was administered Cefazolin IV at 22mg/kg every 90 minutes and Nocita (liposomal bupivacaine) intraoperatively. Post-operative pain was controlled with intravenous 0.1 mg/kg Hydromorphone administered every 4 hours. Tess was bright and energetic the night of her surgery and the following morning. She ate her food readily and ambulated well post-operatively with use of her left pelvic limb the morning after surgery. Tess appeared relatively comfortable with her pain control plan, and her incision site was clean with no signs of infection or dehiscence. Tess was administered oral Carprofen 1.8 mg/kg, Acetaminophen/codeine (Tylenol 4) with codeine dosed at 2 mg/kg, Trazodone, and Gabapentin as previously described with food. She was discharged the morning of 2/15/20 and at that time, with the exception of her TPLO surgery and expected post-operative abnormalities and her demeanor being bright, though slightly less perky, her physical exam was normal. She was discharged with instructions to continue her Tylenol 4, Trazodone and Gabapentin orally every 8

hours, and Carprofen orally every 12 hours with food. Instructions were emphasized to watch for side effects of medications and Tess's owners were instructed to keep Tess's activity strictly restricted with cage confinement. Passive range of motion and weight shifting exercises were demonstrated to her owner with instructions to perform them and cold pack her incision 2-3 times per day. A weight loss plan was also extensively discussed for Tess to decrease arthritis and other health complications.

After discharge Tess's owners noted throughout the day Tess became lethargic and exhibited signs of nausea. Around 4 pm on 2/15/20, Tess would not take her medications in food and approximately one hour later vomited a large amount of food and bile. Tess's owners contacted MSU-CVM's Emergency Service and was advised to offer a bland diet of chicken and to not give her Carprofen unless she was eating. Tess's vomited two more times and she became severely lethargic with an increased respiratory rate. After consultation via telephone, Tess's owners were advised to come in by the MSU-CVM Emergency Service.

On presentation to MSU-CVM Emergency Service the evening of 2/15/20, Tess exhibited a dull mentation and signs of hypovolemic shock. Tess vomited a large amount of what appeared to be lining of her entire stomach with evident gastric ruggae on presentation. She was hypothermic with a temperature of 94.7*F and was tachycardic (211 bpm) and tachypneic (48 brpm). She was also hypotensive, and a blood pressure was not readable when she initially presented. Her pulse oximetry was 97%. Her mucous membranes were pink and tacky with a capillary refill time of 2-3 seconds. Tess exhibited normal palpebral and menace response bilaterally. Tess's respiratory rate and effort was noticeably increased, but no crackles, wheezes, murmurs, or arrhythmias were appreciated with normal thoracic auscultation. On abdominal palpation, Tess was tense but non-painful. Peripheral pulses were weak. TFAST revealed no

evidence of pericardial or pleural effusion and AFAST revealed no evidence of free abdominal fluid. The remainder of her physical exam was within normal limits for being 1day post TPLO surgery.

Diagnostics

Diagnosis of gastric ulceration is based on history, physical exam findings, and diagnostic imaging. Most commonly clinical signs of acute gastric ulceration are vomiting, melena, hematemesis, and abdominal discomfort. Laboratory and radiographic findings are rarely diagnostic for gastric ulcers but can be used to indicate both severity of disease and presence of gastric perforation. Ultrasonography allows for observation of gastric wall thickening and gastric wall lesion as well as evaluating motility and evidence of foreign bodies. However, endoscopy is the preferred method to evaluate gastric ulceration and observe gastric mucosa[7]. Because Tess vomited up her gastric mucosa, it allowed for definitive diagnosis of gastric ulceration.

Upon initial presentation to MSU-CVM Emergency Service, Tess's triage examination indicated she was experiencing compensatory hypovolemic shock. iStat parameters indicated a metabolic acidosis with a venous blood pH of 7.17 (7.35-7.45), bicarbonate value of 6.3mEq/L (22-27), and a base excess -22mEq/L (+2.5- -2.5). Venous partial pressure of carbon dioxide was decreased at 17.3mmHg (35-45) with a partial pressure of oxygen at 51mmHg (49-54). Hematocrit measured greater than 75% (35-55) with a pact cell volume of 82% indicating dehydration and hypovolemia. Total solids were unable to be measured. Hyperglycemia at 230ul/dL (75-125) and hyponatremia 142mmol/L (143-153) were noted with a normal potassium and ionized calcium. A lactate was unable to be measured due to persistent machine error. Abdominal radiographs showed heterogeneous, foamy, soft tissue opaque material and gas

within the stomach. The right lateral projection indicated a thin strip of gas possibly outlining ingesta within the wall of the pylorus. The gastric wall appeared thickened and there was a small volume of gas appearing to dissect the wall of the stomach within the area of the fundus. Radiographic findings suggested gastric ulceration with gastric pneumatosis or gastritis but no sign of gastric perforation. Additional iStat measurements were obtained following initial stabilization with medical and fluid therapy. Resolution of metabolic acidosis and dehydration were noted at approximately 8am on 2/16/19. Tess's hypovolemic shock was consistent with severe dehydration from severe gastric ulceration due to NSAID administration.

Pathophysiology

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long shown damage of the gastrointestinal tract causing damage to gastric and intestinal mucosa and integrity. Mechanisms of damage are related to activity of prostaglandin-endoperoxide synthesis (COX 1 and COX 2). Gastric mucosa is highly glandular with oxyntic (gastric) glands, pyloric glands, mucus and neuroendocrine cells dispersed to control secretion of gastric acid. To protect against acid injury, the gastric epithelial mucosal layer consists of tight junctions and is covered by a thick buffered mucosal layer and phospholipid monolayer along the mucosal surface. The abundant presence of prostaglandin in this gastric mucosal layer inhibit acid secretion, stimulate mucus and bicarbonate secretion, and alter blood flow to protect against acute mucosal damage. NSAIDs interact with the superficial phospholipid layer to uncouple tight junctions with mitochondrial oxidative phosphorylation and interfere with the cyclo-oxygenase (COX) pathways disrupting prostaglandin synthesis and thus mucosal protection through maintenance of mucosal blood flow and cellular oxygen and nutrient delivery[2,4]. COX-1 is expressed in most tissues including the stomach, duodenum, platelets, and kidneys and has an important housekeeping role to maintain

effective mucosal bicarbonate barrier. COX-2 is normally undetectable in tissues but can be induced rapidly in large quantities through the presence of inflammatory cytokines[6]. Adverse gastrointestinal damage is primarily due to inhibition of COX-1, however, studies suggest interference with both COX isoenzymes are required to cause gastric ulceration and complete disruption of the gastric mucosal barrier, leading to gastrointestinal mucosal sloughing and ulceration[6]. Carprofen has been shown to primarily select for COX-2 in canines, and is widely used for its decreased susceptibility to cause gastric upset[3,10]. Multiple studies have shown carprofen administered to healthy dogs have a very low incidence of clinically significant adverse reactions, however studies have yet to report acute canine sensitivity to NSAIDs in post-operative or stress-induced cases. Acute or chronic stressors have long been reported to similarly disrupt gastrointestinal membrane integrity though oxidative and inflammatory stress causing vasoconstriction and tight junction dysfunction of the gastric enterocyte membrane[5]. In this case, Tess presented with a chronic history of pain and previous short-term administration of oral Vetprofen, thus exposure to chronic, intraoperative, or post-operative hemodynamic stressors could have had predisposed Tess to having a breakdown of her enterocyte tight junctions which was then exacerbated by additional NSAID administration ultimately causing severe gastric ulceration and shock.

Treatment

Compensatory shock is the earliest stage of hypovolemic shock and presents from decreased blood volume through hemorrhage, third space fluid distribution, or dehydration. Patients exhibit normal to low temperature, tachycardia, normal to pale mucous membrane color with normal to slightly prolonged capillary refill time, tachypnea, normal to slight hypotension, and responsive mentation. Treatment is aimed at increasing oxygen perfusion and circulating

fluid volume with administration of balanced isotonic crystalloids (Plasmalyte, Norm-R, or LRS) as the most recommended initial therapy[9]. Tess presented with clinical signs of compensatory hypovolemic shock and received 2 one-quarter (300ml) shock doses (20-30ml/kg) of balanced isotonic crystalloids (Plasmalyte) and was immediately started with a constant rate infusion of intravenous Plasmalyte at 125ml/kg/day or 2.5 times maintenance. After initiation of fluid resuscitation, Tess was closely monitored and her mentation, temperature, blood pressure, heart rate, respiratory rate and effort improved dramatically from initial presentation.

Medical therapy of gastric ulceration is centered around administration of mucosal protectants to maintain mucosal perfusion, decrease gastric acidity, and correct secondary conditions (eg. shock, anemia, dehydration, etc.)[7]. Initial management requires withholding food to avoid stimulation of gastric acid and pepsin secretion. Histamine blocking agents reduce hydrochloric acid production by parietal cells in the gastric mucosa. Proton pump inhibitors (eg Pantoprazole, Omeprazole) decrease hydrochloric acid production from parietal cells by inhibiting the hydrogen/potassium ATPase pump within parietal cells and show marked efficacy when given every 12 hours versus more frequent dosing intervals[1]. Cytoprotective medications such as sucralfate are administered to protect ulcerated tissue from further damage. Sucralfate binds to injured mucosa and acts as a buffer and a barrier against penetration of gastric acid, pepsin, and bile salts. Additional therapies such as prostaglandin analogues (eg, Misoprostol) increase mucosal circulation and vascular permeability and are often the drug of choice for treating and preventing NSAID induced ulceration compared to other pharmaceuticals[6]. Tess was medically managed with intravenous Maropitant at 1mg/kg once daily, Pantoprazole 1mg/kg IV q 12 hours, and Sucralfate 0.5gram orally as a slurry every 8 hours. She was also administered Methadone at 0.2mg/kg intravenously upon initial presentation for pain management with

subsequent doses given every 4 hours at 0.1mg/kg. Food and water were withheld from Tess at that time, and her left pelvic limb was cold packed every 6 hours with monitoring of her incision site.

The morning of 2/17/20 Tess was transferred to the MSU-CVM Surgery Department for continuation of gastric ulceration treatment and recovery from her recent left TPLO. Her treatment was continued as previously described with the addition of misoprostol 3 µg/kg orally every 8 hours and intravenous fluids were reduced to maintenance rate (50ml/kg/day). That evening, Tess was bright and alert with no episodes of vomiting and improved mentation. She was started on Purina EN at half her daily metabolic caloric requirement and water was also reintroduced to her every 4 hours. Tess ate and drank, was ambulatory on all four legs with almost full weight bearing on her left pelvic limb and appeared comfortable and non-painful. Tess was urinating and defecating soft but formed stools and was transitioned to oral medications of Omeprazole at 1.5 mg/kg every 12 hours, Acetaminophen/codeine 2mg/kg every 8 hours, with discontinuation of intravenous Pantoprazole, Methadone, and Maropitant in the evening of 2/17/20.

Case Outcome

On 2/18/20 Tess was discontinued from intravenous fluids and maintained in ICU on oral medications. On 2/19/20 Sucralfate was discontinued and Tess was moved to surgery wards and discharge from MSU-CVM Surgery Department that afternoon. Tess was discharged with 7 days of Omeprazole, and a case of canned Purina EN food. Continuation of previously prescribed Gabapentin, Tylenol 4, and Trazodone and initial instructions from her TPLO surgery discharge were discussed. Instructions were given to maintain Tess on a bland diet of Purina EN for the next 5 days with slow gradual incorporation of her normal diet over the preceding few days. A

weight loss plan was also extensively discussed for Tess to decrease potential future health complications. Tess's owners were strictly informed to never administer NSAIDs to Tess due to her severe episode of NSAID sensitivity.

On 2/24/20 Tess re-presented to MSU-CVM Surgery Department for an episode of acute diarrhea. Tess's owners noticed Tess was constipated on 2/21/20 and started to have watery diarrhea for the next few days and they worried she may have eaten something in the yard. On presentation Tess was bright and active with all physical examination parameters within normal limits. No evidence of diarrhea was found on rectal palpation and normal formed feces were observed. Tess was diagnosed with presumptive gastroenteritis and discharged with oral omeprazole and metronidazole for 7 days with continuation of her bland diet of Purina EN with Fortiflora. Tess returned to MSU-CVM Surgery and Dermatology Department on 5/20/20 for her 8-week post-operative recheck from her left TPLO surgery in combination with atopic dermatitis. Tess was healing well from her surgery with radiographic evidence of complete healing of her TPLO and was advised to gradually return to normal activity over the next 4 weeks. Tess's atopic dermatitis continue to be managed by MSU-CVM Dermatology department, but she has otherwise continued to do well at home with no further orthopedic or gastrointestinal issues.

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