Case Report: Three Dogs on Ultra-Short Term Firocoxib Developing Gastrointestinal Perforations

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ABSTRACT

We present three cases of young, healthy dogs which developed gastrointestinal perforations, two of which were fatal, following ultra-short courses of an appropriate dose of Firocoxib. These dogs did not receive any concurrent medications that are commonly considered as increased risk factors for such complications. Another interesting observation is that despite the fact that Carprofen is sold in Israel about 4 times more often than Firocoxib (according to main local wholesalers) we did not encounter gastrointestinal perforations, in our referral hospital, related to the use of Carprofen over the study period. Given the fact that this a commonly used drug, this rare complication is likely to be encountered in clinical practice and clinicians should be made aware of this and advise owners of signs to watch for. Even though the dogs presented in this paper received Firocoxib, it is possible that a similar occurrence may occur with other COX2 preferential nonsteroidal anti-inflammatory drugs (NSAIDs) used in general practice.

Key Words: NSAIDs; Firocoxib; Gastrointestinal perforations.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular for their anti-inflammatory, analgesic, and antipyretic effects on acute and chronic pain in both human and veterinary medicine (1).

NSAIDs' primary mechanism of analgesia is by inhibiting the enzyme cyclooxygenase (COX) in the arachidonic acid (AA) pathway, thus impairing the production of pro-inflammatory mediators. The AA pathway is initiated by cell membrane damage resulting in AA release. AA can serve as a substrate of 4 groups of enzymes (cyclooxygenase (COX), 5-lipoxygenase (5-LO), 12-lipoxygenase (12-LO), and 15-lipoxygenase (15-LO)). Through a series of cascade reactions, groups of eicosanoid mediators are formed (prostaglandins, thromboxane A2, leukotrienes, and lipoxins A and B). NSAIDs block the rate-limiting step in this pathway at the site of COX, inhibiting the conversion of arachidonic acid to prostaglandins (PGs) (1, 2, 3).

COX exists in two isoforms: COX-1 and COX-2. COX-1 is present in most cell types (excluding erythrocytes) and is associated with physiological activities, including platelet aggregation, gastric protection and electrolyte balance in the kidney. The COX-2 isoform is present in low concentrations under basal conditions in monocytes, macrophages, smooth muscle cells, fibroblasts, and chondrocytes and was also identified in the canine ovary, liver, lung, cerebral cortex and Gastrointestinal (GI) tract. COX-2 is rapidly expressed at inflammatory sites, in infections, and neoplasia. A third COX isoform, COX-3, which is a spliced COX-1 variant, was identified in the CNS of the dog and may account for central analgesia (3).

NSAIDs are divided into nonselective inhibitors (aspirin, phenylbutazone, ketoprofen, meclofenamate), preferential COX-2 inhibitors (meloxicam, carprofen, and etodolac), and selective COX-2 inhibitors (deracoxib and firocoxib). Another classification is the COX-3 preferential drugs,

such as paracetamol and the Pyrazolone derivative dipyrone (metamizole) (3,4).

Many of the adverse effects of the nonselective NSAIDs (that inhibit both COX-1 and COX-2 isoforms) have been attributed to inhibition of the constitutive COX-1 (mainly gastric irritation and ulcers, development of protein-losing enteropathy, hepatic and renal damage, articular degradation and prolonged bleeding time). As a result, COX-1–sparing drugs have been preferred for use in both veterinary and human medicine. However, COX-1–sparing drugs still produce adverse effects, as described by Luna *et al.*, 2007 (1).

Firocoxib (brand names: Previcox®, Equioxx®) is a potent NSAID developed specifically for veterinary use with COX-2 selectivity and little impact on COX-1 activity (5). Firocoxib is generally considered to be well-tolerated in dogs, with few drug-related adverse effects reported in previous studies (4, 6, 7, 8,).

A large-scale study of 1002 dogs conducted by Ryan *et al.* (2006) reported a 2.9% withdrawal rate associated with gastrointestinal side effects, with no reports of serious drug-related adverse events (8). The side effects reported in the study included vomiting in 1.9% of the dogs and diarrhea in 0.6%. Elevated laboratory values mainly increased Blood urea nitrogen (BUN) were reported in 1.2% of the dogs. A small-scale study of six dogs presented no clinical effects necessitating long-term treatment. Moreover, none of the dogs had positive fecal occult blood, and no endoscopic GI lesions were observed (4).

Studies aimed to compare firocoxib to other NSAIDs typically indicate a low morbidity rate in patients treated with firocoxib. Clinical signs are usually classified as mild and are commonly GI-related. A comparison of firocoxib to carprofen by Pollmeier *et al.* (2006) demonstrated fewer health problems related to the treatment. 1.8% of the dogs treated with firocoxib showed clinical signs of emesis, while 7.5% of the dogs treated with carprofen presented various clinical signs (adipsia, anorexia, diarrhea, emesis, and polydipsia) (7). Another study (Hanson *et al.,* 2006) (6), aimed to present the efficacy and safety of firocoxib in comparison to etodolac, had a 0.8% incidence rate of firocoxib treatment-related clinical signs (vomiting), in comparison to 4.1% in patients treated with etodolac (vomiting, inappetence, diarrhea, and abdominal pain). However, recent study on gastric and duodenal perforations (GDP) following therapeutic NSAID administration found firocoxib to be associated with 28% of GDPs in dogs and only second in occurrence to Meloxicam (that was associated with 44.4% of the GDPs) (9).

CASE DESCRIPTION

The first dog was a 6-year-old, female neutered Rottweiler, which was presented to the rDVM for acute unspecified pain on walking. On physical examination moderate lumbar pain was observed and the dog was started on Firocoxib 7.57mg/kg PO SID (Previcox® Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rein, Germany), the pain improved but 3 days later started vomiting. The owner was instructed to stop the medication, but the dog continued to vomit and became anorexic and lethargic. On recheck examination at the referring veterinarian (rDVM) the dog was depressed, 7-10% dehydrated, febrile and had a painful abdomen. Bloodwork revealed azotemia (Creatinine 2.6 mg/dl), the dog received 30ml/kg of Lactate Ringers (LRS) (Baxter Healthcare Ltd., Thetford, UK.) and was referred to an emergency center. On arrival, the dog was barely ambulatory, heart rate (HR) 180 per minute, respiratory rate (RR) 32 per minute, hyperemic mucous membranes and painful abdomen. A focused abdominal ultrasound scan revealed free abdominal fluid mostly in the cranial abdomen and sampling revealed marked neutrophilia demonstrated intra-cellular rods and cocci and a total protein of 4.5 mg/dL. Lactate levels were >12 mmol/L. ECG revealed occasional VPC's. After another 30ml/kg of Lactate Ringers solution (Baxter Healthcare, LTD,. UK) and amoxi-clavulonic acid (Laboratory Reig Jofre, S.A., SPAIN) 15mg/kg IV the dog was taken to surgery. In surgery, a perforating ulcer was observed in the duodenum near the pancreatic papilla. The dog was unstable during surgery and despite attempts to stabilize the blood pressure the dog arrested and died.

The second dog was an overweight 6-year-old female neutered Labrador presented 5 months earlier with acute vomiting, showing a complete CBC and Chemistry panels that were within normal limits. On abdominal ultrasound a focal thickening of the stomach wall was observed as well as a reactive area around the thickened stomach. Due to a concern of an impending perforation the dog was taken for an exploratory laparotomy. In surgery, there was no perforation. The thickened area of the stomach was biopsied and a diagnosis and a diagnosis of "Severe ulcerative eosinophilic

gastritis" was made. Since *Spirocerca Lupi* has been implicated in such lesions in Israel, the dog was treated post operatively with Duramectin 0.4mg/kg SQ weekly injections for 10 weeks (Dectomax, Inovat Industria Farmaceutica LTDA, San Paulo, Brazil)) as well as standard treatment with Misoprostol and Omeprazole orally. The dog made a full recovery. In the current event, the dog was also diagnosed with a torn cruciate ligament and treatment with firocoxib 6.7mg/kg PO SID (Previcox® Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rein, Germany) was initiated. Three days after the initiation of treatment, the dog presented for vomiting and lethargy. On physical examination it was dehydrated 5%, tachycardic 240 bpm/min, suffered from acute abdomen and was febrile (39.7^{o}C). Bloodwork revealed leukopenia (1.59 K/μL) and hyperlactatemia (4.55 mmol/L). A focused abdominal ultrasound scan revealed moderate amount of abdominal effusion. The fluid was sampled and upon analysis neutrophils with intra-cellular rods were observed. On exploratory laparotomy, a 1.5 cm full thickness-perforating ulcer was seen in the proximal duodenum and several gastric mucosal erosions. A histologic examination revealed focal transmural necrotizing enteritis with focal mural round cell infiltration with small number of eosinophils. Toluidine blue stain was negative for metachromatic granules (negative for mast cells). During hospitalization the dog gradually improved and was released after 4 days of hospitalization. No records of ulcerations were recorded during a time span of 2 years from the surgery.

The third dog was a one-year-old female neutered Malinois that underwent routine OHE by referring veterinarian (rDVM). Pre-operative CBC and Chemistry panels were with no remarkable findings. The dog was discharged home with Firocoxib 7. 7mg/kg PO SID (Previcox® Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rein, Germany), for post-operative pain relief, as well as preventive antibiotic treatment with Amoxi-clavulanic acid (Synolux® Zoetis, Surrey UK) at 17 mg/kg BID. On the second post operative day of treatment, the dog presented with acute vomiting, anorexia, and lethargy and was attended by a rDVM. Complete CBC and Chemistry panels were performed and found to be unremarkable. The dog was treated with Maropitant (Cerenia® Zoetis, Girona, Spain) 1 mg/kg and released home. At home the dog presented with excessive salivation and abdominal distention, and was admitted to the rDVM 1-2 hours later, when the dog collapsed. On a focused abdominal ultrasound scan a large volume of free abdominal fluid was observed. The dog received 30ml/kg of Lactated Ringers and was referred to the emergency center. On arrival the dog was depressed, non-ambulant, HR 144 per/min, pale mucous membranes, 10-12% dehydrated, with weak femoral pulses and a painful abdomen. Lactate levels were 11.5mmol/L, albumin levels 2.1 g/dL, and blood pressure (BP) of 104/61. On abdominal ultrasound, the pancreas was prominent and hypoechoic, surrounded by echogenic tissue. Multiple small bowel segments were viewed to be corrugated with evidence of echogenic mucosa and prominent muscularis with large volume of free abdominal fluid observed. Analysis of the fluid revealed a thick and purulent discharge, with glucose reading of 20<mg/dL, marked neutrophilia, and large amounts of intra-cellular rods. The dog was treated with 30 ml/kg of Lactated Ringers and broad-spectrum antibiotics; ampicillin (Penibrin® Laboratory Reig Jofre S.A. Toledo, Spain) 25 mg/kg IV, enrofloxacin (Baytril® Bayer Animal Health GmbH, Leverkusen, Germany) 10 mg/kg IV, and metronidazole (B. Braun Melsungen AG, Melsungen, Germany) 15 mg/kg IV and was taken for an exploratory laparotomy. The surgery revealed a perforating ulcer in the duodenum near the pylorus. Following surgery, the dog was markedly depressed, and hypotensive with bloodwork showing severe hypoalbuminemia (1.3 g/dL). After hours of intensive care, the dog arrested and died.

DISCUSSION

It is a well-documented fact that NSAIDs have the potential to cause gastrointestinal ulcerations and perforations in humans and small animals. There are numerous anecdotal reports in veterinary forums about dogs that received short or long courses on NSAIDs developing gastrointestinal perforations with varied outcomes.

However, on reviews of journal articles and clinical conference notes we could find only one, long term (52 weeks) safety study (10) on the use of Previcox which documented 1 dog out of 39 in the study which developed a fatal gastrointestinal perforation.

While many conference' notes mention the potential of NSAIDs to cause a gastrointestinal perforation, they all suggest that it usually happens when a COX1 NSAIDs is used, an inappropriate dose is used, a combination of NSAIDs are

used, a combination of NSAIDs and a steroid are used or the patient has a co-morbidity.

We present three cases of relatively young dogs, two of them without additional risk factors, which developed gastrointestinal perforations after extremely short periods (all three dogs were treated for less than a week) of firocoxib at the recommended dose. The second case described did have a history of gastric ulcer that was tentatively related to *Spirocerca Lupi* aberrant migration (which was not proven). However, *S. lup*i was considered an unlikely cause of perforation due to the location of the perforation, and since the dog completed an acceptable treatment protocol for *S. lup*i infection. All dogs presented clinical signs of lethargy and vomiting, two of the dogs were anorexic. All three dogs were dehydrated and suffered from abdominal pain. Two dogs were febrile. The first dog presented only had bloodwork after it developed vomiting and anorexia. Given the fact that it was clinically dehydrated, it is likely that the azotemia was pre-renal but this assumption is not certain. Urine specific gravity was not assessed. The 2nd dog did not have current bloodwork, but a previous blood profile was within normal limits. The 3rd dog also had a normal blood profile prior to firocoxib administration as well as after initiation of clinical signs. All dogs had free abdominal fluid that was diagnosed as septic. Two dogs had duodenal ulcers and one dog had jejunal ulcer. All ulcers were discovered during surgery. Only one of the three presented dogs survived. The first dog died during exploratory laparotomy surgery, and the last dog died within 12 hours after laparotomy. All dogs did not receive any gastro-protectant medications together with the Firocoxib. Although there are anecdotal reports about the use of H2 Blockers and prostaglandins as "protection" against NSAIDs induced gastrointestinal ulceration and perforation, we did not find any evidence basis in the literature for their use as a preventive measure in these cases.

The true prevalence of gastrointestinal perforation related to the use of NSAIDs is unknown. Given the fact that millions of doses of NSAIDs are administered daily it is probably very low. Even though this is a rare complication, veterinarians and pet owners need to be more aware of this potential life-threatening complication even when these drugs are given short-term treatment and at an appropriate dose. Owners should be advised to stop these drugs immediately and arrive for a follow up examination if vomiting develops.

SUMMARY

We presented 3 cases of young, healthy dogs which developed gastrointestinal perforations, 2 of which fatal, following ultra short courses of an appropriate dose of Firocoxib. These dogs did not receive any concurrent medications that are commonly considered as an increased risk factors for such complications. Given the fact that this a commonly used drug, this rare complication is likely to be encountered in clinical practice and clinicians should be aware of them and advise owners of signs to watch for. Even though the dogs presented in this paper received Firocoxib, it is likely that similar occurrence may occur with other COX2 preferential NSAiDs.

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