Nonsteroidal anti-inflammatory drug-induced duodenal ulceration and perforation in a mature rottweiler

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Abstract — A mature male rottweiler was evaluated for acute collapse and abdominal pain. The history consisted of concurrent administration of meloxicam and aspirin. On exploratory laparotomy, a large perforated ulcer was discovered in the proximal duodenum, with secondary peritonitis. The pathogenesis of NSAID-induced gastrointestinal ulceration and the supposed safety of COX-2 selective agents are discussed.

Résumé — Ulcérations et perforations duodénales induites par des médicaments anti-inflammatoires non-stéroïdiens chez un Rottweiler adulte. Un Rottweiler mâle adulte a été évalué à la suite d'un collapsus aigu et d'une douleur abdominale. L'historique faisait état d'administration simultanée de méloxicam et d'aspirine. À la laparotomie exploratoire, un gros ulcère perforé a été découvert dans le duodénum proximal, accompagné d'une péritonite secondaire. La pathogénèse des ulcères gastro-intestinaux provoqués par les AINS et la prétendue sécurité des drogues COX-2 sélectives sont discutées.

(Traduit par Docteur André Blouin)

Can Vet J 2002;43:971–972

An 8-year-old, male rottweiler was sent home after surgery on a daily dose of 0.1 mg/kg bodyweight (BW) of meloxicam (Metacam; Boehringer Ingelheim, Burlington, Ontario). Ten days later, the owner noticed that the dog was restless and gave him 650 mg of coated acetosalicylic acid (Entrophen extrastrength; Merck Frosst, Kirkland, Ontario). The dog vomited that night and again the next day. He collapsed in the evening and was rushed to an emergency hospital.

The clinical signs on presentation at the emergency hospital were prostration, nonresponsiveness, and cranial abdominal pain. The dog was approximately 5% to 7% dehydrated. On radio- and ultrasonographs, fluid was visualized in the abdomen. Results from an abdominocentesis were consistent with exudate and sepsis. No significant changes were noted on a complete blood cell (CBC) count, biochemical panel, or urinalysis. The dog's condition continued to deteriorate overnight; in the morning, he was transferred to the Granville Island Veterinary Hospital. The suspected diagnosis was a perforated viscus with subsequent peritonitis. The dog was taken to surgery immediately for an exploratory laparotomy. Approximately 2.3 L of bile-stained fluid containing food particles was removed from the abdominal cavity. A large perforated duodenal ulcer, about 1.5 to 0.2 cm in diameter, was located just distal to the pylorus. The edges of the ulcer were debrided, and the defect was closed. Repeat abdominal lavage was performed and 2 passive drains were placed. Intraoperatively, premature ventricular contractions (PVCs) occurred and were controlled with a lidocaine (Xylocaine 2%; AstraZeneca, Mississauga, Ontario) infusion in balanced polyionic fluid, IV. The resected tissue from the ulcer was submitted for histopathologic examination. Abdominal fluid was sent for culture and sensitivity testing. The dog was placed in intensive care for the next few days.

Postoperative treatment consisted of balanced polyionic fluid with lidocaine (Xylocaine 2%; AstraZeneca, Mississauga, Ontario) IV; balanced polyionic fluid plus 20 mEq of KCL through a second IV line; procainamide (Pronestyl; Squibb, Montreal, Quebec), 1000 mg, PO, q4h; cefazolin (Kefzol; Lilly, Scarborough, Ontario), 1400 mg, IV, q8h; amikacin (Amiglyde; Fort Dodge, Iowa), 550 mg, IV, q8h; omeprazole (Losec; AstraZeneca), 20 mg, PO, q24h; metoclopramide (Metoclopramide HCl; Bioniche Pharma, London, Ontario), 15mg, SC, q8h; sucralfate (Sulcrate suspension; Aventis Pharma, Laval, Quebec), 1 g, PO, q8h, and ranitidine (Zantac; GlaxoSmithKline, Mississauga, Ontario), 110 mg, IV, q8h. Morphine was also given as needed. Cefazolin was later switched to choramphenicol (Chlor 1000; Vetoquinol, Lavaltrie, Quebec), 2500 mg, PO, q8h, based on culture and sensitivity results.

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An in-house CBC count and biochemical panels were run. Results were as follows: severe leukocytosis (31.5×10^9/L; reference range, 6 to 16.9×10^9/L), severe neutrophilia (26.2×10^9/L; reference range, 3.3 to 12.0×10^9/L), hyperfibrinogenemia (375 g/L; reference range, 1 to 2.5 mg/L), severe hypoalbuminemia (12 g/L; reference range, 27 to 38 g/L). Five hundred milliliters of colloids were given to treat the hypoproteinemia.

Histopathologic results of the excised ulcer evaluated the maturity of the granulation tissue at different depths throughout the ulcer. The granulation tissue was more immature on the serosal surface than in the submucosa and muscle layers of the duodenum. This suggested that the initial injury to the duodenal mucosa had occurred days prior to the perforation.

The dog continued to improve after surgery. He gained rapidly in strength and alertness, and was sent home 8 d after the surgery. Meloxicam is a cyclooxygenase (COX)-2 selective NSAID that has shown a very low frequency of inducing gastrointestinal lesions. In this case, however, the combination of meloxicam with a single dose of aspirin resulted in an acute intestinal perforation.

Several components may be involved in the pathogenesis of NSAID-induced small intestinal lesions: elevations in enteric bacterial numbers, increased epithelial permeability of the small intestine, enterohepatic recirculation of the NSAID, and influx of neutrophils into the mucosa in response to the initial tissue injury (1). Initial changes in the epithelial permeability are probably caused by topical irritation (1). The change in permeability enables more hydrogen ions to penetrate the protective mucous layer (2), leading to more tissue damage over time.

Enterohepatic recirculation results in repeated exposure of the intestinal mucosa to the NSAID (1), increasing the risk of injury. In addition, combination of an NSAID with bile appears to be much more damaging to the mucosa than does an NSAID alone (3). Elevations in enteric bacterial numbers seem to occur only with NSAIDs that undergo enterohepatic recirculation (1). Increased numbers of bacteria exacerbate the initial injury caused by the NSAID (1). Therefore, the use of NSAIDs that undergo enterohepatic recirculation may increase the likelihood of intestinal ulceration (1).

Inhibition of COX does not seem to be a major contributing factor in the pathogenesis of NSAID-induced small intestinal injury (1). Consequently, COX-2 selective inhibitors (meloxicam), which spare gastrointestinal prostaglandin production, may not prevent NSAID-induced injury to the small intestine (1).

Meloxicam is eliminated from the body mainly through the biliary system (75%), with 25% excreted via the kidney (4). Enterohepatic recirculation is likely due to its high rate of elimination in the bile. In this case, the meloxicam may have been responsible for the initial injury to the duodenum, as the erosive lesions in the mucosa had occurred some time prior to those in the serosa. Healing of ulcers and maintenance of mucosal integrity are partially attributable to the action of prostaglandins derived from COX-2 (5). Therefore, the COX-2 selectivity of meloxicam may have actually been detrimental in this situation.

Aspirin is not excreted in bile, and in one study, aspirin administration did not cause detectable small intestinal damage (1). It is, however, a potent inhibitor of COX-1 and COX-2 (1). Suppression of prostaglandin synthesis via inhibition of COX can cause an increase in gastric acidity (4), and a decrease in gastric and duodenal secretion of bicarbonate (2). In addition, aspirin is especially known for its ability to cause local toxicity through a mechanism known as ion trapping, in which the drug becomes concentrated in the mucosa (6). In this case, the aspirin may have caused further damage by increasing the overall acidity in the proximal duodenum, and through topical irritation. Since the defense mechanisms of the intestine had already been breached, the injured area would have been much more vulnerable to these effects. The aspirin may have caused the final insult, resulting in perforation of the ulcerated region.

In summary, histopathologic examination of the ulcer suggested that the initial injury to the duodenal mucosa had occurred some time prior to the perforation. Given the history, meloxicam administration of approximately 10 d duration was likely responsible for the initial lesion. Concurrent administration of the aspirin may have caused additional damage to the compromised mucosa, resulting in a large perforation and subsequent peritonitis. This case serves as a useful reminder of the potentially harmful effects of NSAID usage, and the contraindications of using 2 NSAIDs concurrently.

Acknowledgments

The author thanks Dr. Dennis Jackson for his guidance with this case, and Dr. Trish Dowling for her valuable advice while composing this case report. CVJ

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