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Objective—To identify factors associated with gastrointestinal tract perforation in dogs being treated with a selective cyclooxygenase-2 (COX-2) inhibitor (deracoxib).

Design—Retrospective study.

Animals—29 dogs.

Procedure—The Novartis Animal Health pharmacovigilance database was searched for records of dogs treated with deracoxib in which gastrointestinal tract perforation was documented.

Results—16 of the 29 (55%) dogs had received deracoxib at a dosage higher than that approved by the FDA for the particular indication being treated, with 25 (86%) dogs having received deracoxib at a dosage > 2 mg/kg/d (0.9 mg/lb/d). Seventeen (59%) dogs had received at least 1 other nonsteroidal anti-inflammatory drug (NSAID) or a corticosteroid in close temporal association (within 24 hours) with deracoxib administration (ie, immediately before or following). In all, 26 (90%) dogs had received deracoxib at a higher-than-approved dosage or had received at least 1 other NSAID or corticosteroid in close temporal association with deracoxib administration. Twenty dogs died or were euthanized, and 9 survived.

Conclusions and Clinical Relevance—In dogs with gastrointestinal tract perforation and that had been treated with deracoxib, perforation was most likely attributable to a number of factors. Deracoxib should only be used at approved dosages. Corticosteroids and other less selective NSAIDs should not be administered in close temporal association with selective COX-2 inhibitors, including deracoxib. Further study is required to define this problem. (J Am Vet Med Assoc 2005;227:1112–1117)

Several new nonsteroidal anti-inflammatory drugs (NSAIDs) have recently been approved for the treatment of acute pain associated with surgery in dogs1 and chronic pain associated with osteoarthritis.1,2 Although alleviating pain in dogs is an important goal in veterinary medicine, the increase in the number of NSAIDs that are available, combined with the greater tendency to administer NSAIDs, could potentially increase the risk that adverse effects will develop.

It has been suggested that dogs are more sensitive than humans to NSAID-induced toxicoses, but data to support this contention are weak. Ulcer formation resulting from NSAID administration in dogs is reported to be common by some authors3 and uncommon by others.4 Fortunately, to our knowledge, there is no published information on the incidence of gastrointestinal perforation associated with NSAID use in dogs.

In humans, administration of NSAIDs, particularly selective cyclooxygenase-2 (COX-2) inhibitors, at higher-than-normal dosages and of multiple NSAIDs concurrently or in close temporal association with each other has been suggested to increase the risk of adverse effects.5 The newer NSAIDs approved for use in dogs tend to be COX-2 selective, and previous studies6,7 have demonstrated the possible adverse effects on gastrointestinal ulcer healing when selective COX-2 inhibitors are used in rats and mice with ongoing ulceration. This may be clinically important if selective COX-2 inhibitors are used following an episode of ulceration or following drug treatment that may induce ulceration.8

More information, therefore, is needed concerning possible adverse effects of selective COX-2 inhibitors in dogs. The purpose of the study reported here was to identify factors associated with gastrointestinal tract perforation in dogs being treated with deracoxib, a selective COX-2 inhibitor. Specific factors that were examined included dose and dosing interval of deracoxib, whether corticosteroids or other NSAIDs had been administered concurrently or in close temporal association with deracoxib administration, and whether dogs had any concurrent diseases.

Criteria for Selection of Cases

The Novartis Animal Health US Inc pharmacovigilance database was searched to identify reports of possible adverse effects in dogs being treated with deracoxib between September 2002 (when the product first became commercially available in the United States) and July 31, 2003. The database consisted of spontaneous, voluntary submissions from owners and veterinarians; all reports were subsequently submitted to the US FDA. For each incident reported to the pharmacovigilance database, the attending veterinarian was contacted to obtain specific details. For the present study, reports of possible adverse effects associated with deracoxib administration were reviewed and dogs in which gastrointestinal tract perforation had been identified were selected for inclusion.

Procedures

For dogs included in the study, information obtained from the database included age; weight; breed; sex; reason...
for deracoxib use (ie, disease process and whether the disease process was acute or chronic); dose, dosing interval, and duration of treatment; whether there was any history of NSAID or corticosteroid use in the 6 months before or after administration of deracoxib and, if so, the dose, dosing interval, and duration of treatment; whether any medications were administered concurrently with deracoxib; clinical signs prior to definitive diagnosis of gastrointestinal tract perforation; anatomic location of the perforation; and whether there were any concurrent diseases in addition to the condition that had resulted in deracoxib administration.

Dogs were classified as having received deracoxib for treatment of chronic pain. The approved dosage of deracoxib for dogs with chronic pain was defined as ≤ 2 mg/kg/d (0.9 mg/lb/d), consistent with the FDA-approved label dosage of deracoxib of 1 to 2 mg/kg/d (0.45 to 0.9 mg/lb/d) for treatment of osteoarthritis pain and inflammation. The approved dosage of deracoxib for dogs with acute pain was defined as ≤ 4 mg/kg/d (1.8 mg/lb/d) for a maximum of 7 days, consistent with the FDA-approved label dosage of deracoxib of 3 to 4 mg/kg/d (1.4 to 1.8 mg/lb/d) for alleviation of postoperative orthopedic pain and inflammation. For purposes of analyses, dogs treated for acute postoperative pain were grouped together, regardless of whether deracoxib had been administered following orthopedic surgery (FDA-approved indication) or soft tissue surgery (nonapproved indication).

For dogs that received deracoxib for treatment of acute pain, preoperative laboratory testing was defined as evaluation of at least total protein concentration, PCV, renal function (BUN and serum creatinine concentrations), and hepatic enzyme (alanine aminotransferase and alkaline phosphatase) activities within 24 hours of surgery. No attempts were made to evaluate management of dogs following identification of gastrointestinal tract perforation because multiple veterinary practices were involved in the treatment of these dogs and detailed information was not routinely included in the pharmacovigilance database.

Statistical analyses—Data were entered in a spreadsheet, and descriptive statistics were calculated. The chi-squared test was used to determine whether ulcer location (pylorus or proximal to the pylorus vs duodenum or jejunum) was associated with group (chronic vs acute pain). A value of $P < 0.05$ was considered significant.

Results

Twenty-nine dogs met the criteria for inclusion in the study. Mean ± SD age was $6.4 ± 3.2$ years (range, 2 to 13 years), and mean body weight was $37.1 ± 12.4$ kg ($81.6 ± 27.3$ lb; range, 12.7 to 66.5 kg [27.9 to 146.3 lb]). There were $13 (45\%)$ Labrador Retrievers, $7 (24\%)$ mixed-breed dogs, $2 (7\%)$ Bullmastiff, and $1 (3\%)$ each of the following breeds: Cocker Spaniel, Dalmatian, Great Pyrenees, Welsh Corgi, Border Collie, English Springer Spaniel, and Bouvier des Flandres. In all dogs, a perforated ulcer was identified during exploratory surgery or necropsy. Twenty of the 29 (69\%) dogs died or were euthanized, and 9 survived.

Dogs treated for chronic pain—Fifteen of the 29 dogs had received deracoxib for treatment of chronic pain. Gastrointestinal tract perforation was diagnosed by means of exploratory laparotomy in 11 of these 15 dogs and by means of necropsy in 4. In 2 of the 15 dogs, laboratory testing was performed prior to initiation of deracoxib treatment. Three other dogs had a history of an underlying medical condition (inflammatory bowel disease, hypothyroidism, and cutaneous mast cell neoplasia). In 14 of the 15 dogs, the first clinical sign associated with ulceration was vomiting; in the remaining dog, the first clinical signs were anorexia and lethargy. The perforation was located at the pylorus or pyloroduodenal junction in 8 dogs, in the body of the stomach in 3 dogs, in the duodenum in 3 dogs, and in the jejunum in 1 dog.

Twelve of the 15 dogs had been given deracoxib at a dosage higher than the approved dosage (Figure 1). Ten of these 12 dogs were treated because of osteoarthritis, 1 was treated because of osteochondrosis dissecans, and 1 was treated because of swelling of the soft tissues of a toe. Mean ± SD dosage for these 12 dogs was $3.4 ± 2.0$ mg/kg/d (1.5 ± 0.9 mg/lb/d; range, 2.3 to 6.2 mg/kg/d [1 to 2.8 mg/lb/d]), and mean duration of administration prior to identification of gastrointestinal tract perforation was $20 ± 21.5$ days (range, 3 to 70 days). Eight of these dogs died, and 4 survived.

Six of the 12 dogs that received deracoxib at a dosage higher than the approved dosage reportedly received a corticosteroid or another NSAID within 24 hours prior to initiation or after discontinuation of deracoxib treatment. All other NSAIDs were administered at an approved or generally recommended dosage. One dog received carprofen for 21 days, then deracoxib for 42 days, and then aspirin for 6 days, with ≤ 24 hours between discontinuation of 1 drug and initiation of the next. Two dogs received carprofen immediately prior to receiving deracoxib (1 for 21 days and the other for 150 days). One dog received tepoxalin for 12 days prior to receiving deracoxib, 1 dog received aspirin for 1 day prior to receiving deracoxib, and 1 dog received a low dose of dexamethasone immediately after deracoxib administration was discontinued. The latter dog had evidence of preexisting renal disease (high BUN and serum creatinine concentrations) and received a single dose of dexamethasone (0.05 mg/kg [0.023 mg/lb]).
immediately after having received deracoxib for 9 days. Mean ± SD duration of deracoxib administration in the 6 dogs that received an additional NSAID or corticosteroid was 12.8 ± 14.5 days (range, 4 to 42 days). Two of these 6 dogs had a perforation at the pylorus, 2 had a perforation in the body of the stomach, 1 had a perforation in the duodenum, and 1 had multiple perforations in the jejunum. All of these dogs died.

The remaining 6 of the 12 dogs that received deracoxib at a dosage higher than the approved dosage reportedly had not received any corticosteroids or other NSAIDs before or after deracoxib administration. One of these dogs was receiving ketoconazole (10 mg/kg [4.5 mg/lb], PO, q 24 h) concurrently to treat a fungal ear infection. Three of these 6 dogs had a perforation at the pylorus, 1 had a perforation in the body of the stomach, and 2 had perforations in the duodenum. Four dogs survived, and 2 died.

Three of the 15 dogs given deracoxib for treatment of chronic pain received an approved dose of the drug. All 3 of these dogs were given deracoxib to treat chronic pain associated with osteoarthritis. One received a single dose of dexamethasone, then deracoxib for 28 days, and then carprofen for 11 days prior to identification of gastrointestinal tract perforation. A second dog received 2 doses of aspirin prior to administration of deracoxib for 5 days. The remaining dog did not receive any corticosteroids or other NSAIDs within 7 days of the initiation of deracoxib administration. All dogs had perforations at the pylorus. One died, and 2 survived.

In 11 of the 15 dogs that received deracoxib for treatment of chronic pain, clinical signs of gastrointestinal tract perforation were first noticed < 24 hours after administration of the last dose of deracoxib. Clinical signs were first noticed within 2 to 3 days after administration of the last dose of deracoxib in 1 dog, within 4 days after administration of the last dose of deracoxib in 1 dog, within 6 days after administration of the last dose of deracoxib in 1 dog (this dog was receiving aspirin when clinical signs of perforation were first noticed), and within 11 days after administration of the last dose of deracoxib in 1 dog (this dog was receiving carprofen when clinical signs of perforation were first noticed).

Dogs treated for acute pain—Fourteen dogs had received deracoxib for treatment of acute perioperative pain; 9 of these dogs had undergone orthopedic surgery, and 5 had undergone soft tissue surgery (Figure 2). In 6 dogs, gastrointestinal tract perforation was diagnosed by means of exploratory laparotomy, whereas perforation was diagnosed at necropsy in 8 dogs. The first clinical signs associated with ulceration were vomiting in 6 dogs, vomiting and signs of generalized pain in 3 dogs (all had duodenal perforations), anorexia and lethargy in 3 dogs, diarrhea and signs of generalized pain in 1 dog (duodenal perforation), and melena in 1 dog. The perforation was located in the duodenum in 7 dogs, at the pylorus in 5 dogs, and at the junction of the pylorus and body of the stomach in 2 dogs. Incidence of duodenal perforation was significantly higher in dogs treated for acute pain (7/14) than in dogs treated for chronic pain (3/15).

Seven of the 9 dogs treated for acute pain following orthopedic surgery died, and 2 survived. Results of preoperative laboratory testing were unremarkable in all 8 dogs in which testing had been performed.

Of the 9 dogs treated with deracoxib following orthopedic surgery, 6 were given deracoxib at the approved dosage (ie, ≤ 4 mg/kg/d for a maximum of 7 days) or at a lower dosage (≤ 2 mg/kg/d for > 7 days). Of these, 5 received another NSAID within 24 hours prior to initiation of deracoxib treatment or were receiving a corticosteroid concurrently. In 2 of these dogs, a single injection of ketoprofen (2 mg/kg) had been administered postoperatively, and in 1 dog, naproxen had been administered for 3 weeks prior to surgery, with the last dose of naproxen administered 24 hours prior to the initiation of deracoxib administration. One dog received a single dose of carprofen (2.2 mg/kg [1 mg/lb]) postoperatively 1 week prior to administration of deracoxib. Laboratory testing revealed that this dog had high BUN and serum creatinine concentrations just prior to initiation of deracoxib treatment, although results of preoperative laboratory testing had been normal. One dog was receiving prednisone at an anti-inflammatory dosage because of allergic dermatitis concurrent with deracoxib treatment. Four of these 6 dogs had a perforation in the duodenum, 1 had a perforation at the pylorus, and 1 had a perforation at the junction of the pylorus and body of the stomach. Four dogs died, and 2 survived.

The remaining 3 dogs treated with deracoxib following orthopedic surgery were given deracoxib at a dosage for a duration greater than that approved for treatment of postoperative pain. One received deracoxib at a dosage of 3 mg/kg/d for 9 days, 1 received deracoxib at a dosage of 2.5 mg/kg/d (1.1 mg/lb/d) for 10 days, and 1 received deracoxib at a dosage of 3.3 mg/kg/d (1.5 mg/lb/d) for 46 days. None of these dogs received any other NSAIDs or corticosteroids while being treated with deracoxib. Two had perforations of the duodenum, and 1 had a perforation at the pylorus. All 3 died.

Four of the 5 dogs treated for acute pain following soft tissue surgery died, and 1 survived. Results of preoperative laboratory testing were unremarkable in the 3 dogs in which testing had been performed. In 4 of these 5 dogs, deracoxib was administered at the approved dosage, whereas in 1 dog, the dosage was...
The incidence of gastrointestinal tract ulceration associated with NSAID use in dogs is not known. In a study of gastrointestinal ulceration (defined as a mucosal defect extending to the muscularis) in 23 dogs with a single predisposing ulcerogenic factor, 4 had been treated with an NSAID, corticosteroid, or both. However, of the 17 dogs with 2 or more predisposing factors, 13 had received an NSAID or corticosteroid. However, this referenced study did not evaluate which NSAIDs or how many different NSAIDs were administered in those dogs or what dosages were used. With the greater availability and use of NSAIDs in veterinary medicine in recent years, there has been an increase in the awareness of possible adverse effects. Also, the availability of multiple NSAIDs increases the likelihood that patients may receive multiple NSAIDs concurrently or in close temporal association, as was true for many dogs in the present study. Although there are no pharmacokinetic, chemical, or pharmacodynamic data to predict or evaluate the effects of these multiple-drug treatments, use of multiple NSAIDs may be an important risk factor for the induction of ulceration.

Sixteen of the 29 (55%) dogs in the present study were administered deracoxib at a dosage higher than the approved dose for the indication being treated. One reason for the overdosage of some of these dogs may have been confusion caused by the 2 approved dosage regimens. Rofecoxib, a coxib that until recently was available for treatment of acute and chronic pain in humans, also had 2 approved dosage regimens, with the dosage approved for treatment of acute pain (50 mg daily for a maximum of 5 days) being twice the dosage approved for long-term treatment of chronic pain (25 mg daily). A recent study found that 17% of patients being treated with rofecoxib long-term were treated at a dosage higher than the approved dosage, compared with only 1% of patients being treated with celecoxib, for which only a
single dosage regimen has been approved. The investigators attributed this difference to the fact that some physicians appeared to be using the dosages approved for treatment of acute pain and chronic arthritis interchangeably and warned of the risks of adverse effects when the incorrect dosage regimen is used. In safety studies performed for FDA approval, vomiting, melena, and reduced body weight did not occur until deracoxib was administered to dogs at dosages ≥ 23 mg/kg/d (11.4 mg/lb/d) for 14 days, suggesting that there is a reasonable margin of safety for deracoxib in healthy dogs. However, little is known about COX selectivity of NSAIDs in the mucosa of the gastrointestinal tract in dogs or requirements for COX-2-derived products in normal or compromised mucosa. Reduced selectivity in vivo may decrease the safety margin of deracoxib, and selectivity is reduced at higher dosages. Thus, we suggest that to reduce the incidence of adverse effects, veterinarians adhere to approved dosage regimens for deracoxib. On the other hand, because the present study only evaluated dogs with gastrointestinal tract perforation, the overall clinical tolerance of higher dosages of deracoxib cannot be ascertained.

The present study revealed a high frequency of administration of multiple NSAIDs in close temporal association. Other NSAIDs administered prior to administration of deracoxib were all less selective NSAIDs, at least as defined by in vitro assays (ketoprofen, aspirin, naproxen, and carprofen). Studies in dogs have confirmed that ketoprofen, aspirin, and carprofen can all be associated with erosive lesions in the gastric mucosa; however, the clinical importance of these lesions has been debated.[24] In rodents with chemically induced gastric ulceration, administration of a selective COX-2 inhibitor delayed or prevented healing of the ulcers,[16] and analysis of COX-2 expression and localization indicated that COX-2 expression was upregulated during injury and was localized to reparative epithelium at the periphery of the wound. A more recent study[25] has shown that specific COX-2 inhibitors impair the healing of acid-induced gastric lesions in rats. It seems possible, therefore, that some of the dogs in the present study had preexisting damage to the stomach, whereas ulcers associated with hepatic disease occur more often in the duodenum. In the present study may be that the newer NSAIDs treatment or stress associated with anesthesia and surgery and that administration of deracoxib inhibited healing of these preexisting erosions and ulcers. On the other hand, in a study[26] of rodents with duodenal ulceration induced by serosal application of acetic acid, ulcers were able to heal despite administration of rofecoxib, a selective COX-2 inhibitor, and in a study[27] of pigs with ischemia-induced small intestinal ulcers, lesions were able to heal despite administration of selective COX-1– or COX-2–inhibiting drugs. In the authors’ experience, switching from 1 NSAID to another or initiating administration of 1 NSAID following administration of a different NSAID is common in veterinary practice, often with ≤ 24 hours allowed to elapse between drugs, even though there is little information on the safety of such practices. Results of the present study suggest that switching between NSAIDs should be done cautiously and the cumulative effects of all NSAIDs being administered should be considered.

Possible risk factors for gastrointestinal tract ulceration in dogs include NSAIDs, hepatic disease, mastocytosis, uremia, stress, and various systemic diseases (eg, disseminated neoplasia, sepsis, and disseminated intravascular coagulation).[12,13] The incidence of preexisting disease among dogs in the present study was not high (1 dog had preexisting renal insufficiency, and 1 had a history of recent mastocytosis), although all dogs undergoing surgery probably had some degree of stress. Thus, preexisting risk factors did not appear to play an important role in gastrointestinal tract perforation, suggesting that perforation was a direct result of NSAID administration or a result of administration of deracoxib in close temporal association with other NSAIDs or corticosteroids.

Three dogs in the present study had received corticosteroids either before, after, or concurrently with treatment with deracoxib. Although no studies have been performed evaluating the effects of coadministration of corticosteroids and deracoxib, endoscopically visible lesions increased in severity when prednisone was administered with the NSAID flunixin meglumine[16] and dexamethasone was administered with meloxicam[27] in dogs. There is no information available on the preferred washout interval between corticosteroid and NSAID administration.

In a previous study[28] of gastrointestinal tract perforation in 16 dogs, the authors suggested that young (< 5 years old) Rottweilers were overrepresented; however, the breed distribution of dogs with perforation was not compared with the breed distribution for the hospital population. A separate study[29] suggested that German Shepherd Dogs had greater susceptibility to ibuprofen-induced gastrointestinal tract ulceration. No obvious breed overrepresentation was seen in the present study; however, conclusive statements cannot be made, as breed distribution for the population these dogs came from is unknown. There is no information regarding breed-specific differences in the pharmacokinetics of deracoxib or the risk of adverse effects. Age range for dogs in the present study was similar to ranges reported in previous studies[12,13] of gastrointestinal tract perforation.

In the present study, the incidence of duodenal perforation was significantly higher in dogs treated for acute pain (7/14) than in dogs treated for chronic pain (3/15). Previous studies[12,13] have suggested that NSAID-associated ulcers occur most often in the pylorus or antral region of the stomach, whereas ulcers associated with hepatic disease occur more often in the duodenum. In the present study, results of laboratory testing performed prior to deracoxib administration were within reference limits in all 11 dogs with acute pain that were evaluated, suggesting that the higher incidence of duodenal perforation was not attributable to preexisting disease. One possible explanation for the higher incidence of duodenal perforation in the present study may be that the newer NSAIDs approved for use in dogs, particularly the coxibs, cause ulcers in different locations than do the less selective NSAIDs because of differences in chemical structure or selectivity. Alternatively, changes associated with anesthesia and surgery may have predisposed dogs treated with deracoxib for acute pain to develop duodenal ulcers.
In 23 of the 29 dogs in the present study, vomiting was the first clinical sign associated with gastrointestinal tract perforation, and vomiting has been a common finding in previous studies\(^2,3\) of dogs with gastrointestinal tract ulceration. Thus, we suggest that any dog that vomits while being administered an NSAID be carefully evaluated. However, the incidence of vomiting in dogs being administered an NSAID is not known nor is the sensitivity of this behavior as a clinical indicator of problems. Interestingly, all 3 dogs in which the first clinical sign was that of generalized pain were found to have duodenal perforations.

Twenty of the 29 (69%) dogs in the present study died or were euthanatized. Similarly, 50% and 75% of dogs in 2 previous studies\(^4,5\) of gastrointestinal tract ulceration or perforation died. Both of these previous studies have found that even with access to sophisticated supportive care, mortality rate for dogs with gastrointestinal tract perforation ranges from 30% to 70%. The severe nature of gastrointestinal tract perforation is supported by the number of dogs in the present study that died without undergoing surgical repair of the perforation and without being euthanatized.

Of the 29 dogs in the present study, only 3 did not have additional risk factors for gastrointestinal tract perforation. In the remaining 26 dogs, perforation was most likely attributable to a number of factors, including administration of deracoxib at a higher-than-approved dosage, administration of corticosteroids or other NSAIDs in close temporal association with administration of deracoxib, and concurrent diseases. These cases do not reveal a simple picture of gastrointestinal tract ulceration attributable to deracoxib administration but do indicate that a better understanding of gastrointestinal tract physiology, especially related to COX, is required to understand the risk of NSAID-associated injury in dogs. Results of the present study suggest that the approved dosage regimens should be followed carefully, deracoxib should be used cautiously in dogs likely to have gastrointestinal tract injury, and a better understanding of NSAID pharmacology is required so that the issue of washout can be clinically addressed.

a. Deramexx, Novartis Animal Health, Greensboro, NC.

b. Excel, Microsoft Corp, Mountain View, Calif.

References