

Effect of short-term sequential administration of nonsteroidal anti-inflammatory drugs on the stomach and proximal portion of the duodenum in healthy dogs

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Objective—To evaluate effects of injection with a nonsteroidal anti-inflammatory drug (NSAID) followed by oral administration of an NSAID on the gastrointestinal tract (GIT) of healthy dogs.

Animals—6 healthy Walker Hounds.

Procedures—In a randomized, crossover design, dogs were administered 4 treatments consisting of an SC injection of an NSAID or control solution (day 0), followed by oral administration of an NSAID or inert substance for 4 days (days 1 through 4). Treatment regimens included carprofen (4 mg/kg) followed by inert substance; saline (0.9% NaCl) solution followed by deracoxib (4 mg/kg); carprofen (4 mg/kg) followed by carprofen (4 mg/kg); and carprofen (4 mg/kg) followed by deracoxib (4 mg/kg). Hematologic, serum biochemical, and fecal evaluations were conducted weekly, and clinical scores were obtained daily. Endoscopy of the GIT was performed before and on days 1, 2, and 5 for each treatment. Lesions were scored by use of a 6-point scale.

Results—No significant differences existed for clinical data, clinicopathologic data, or lesion scores in the esophagus, cardia, or duodenum. For the gastric fundus, antrum, and lesser curvature, an effect of time was observed for all treatments, with lesions worsening from before to day 2 of treatments but improving by day 5.

Conclusions and Clinical Relevance—Sequential administration of NSAIDs in this experiment did not result in clinically important gastroduodenal ulcers. A larger study to investigate the effect of sequential administration of NSAIDs for longer durations and in dogs with signs of acute and chronic pain is essential to substantiate these findings. (*Am J Vet Res* 2006; 67:1794–1801)

The NSAIDs are used in a number of settings in veterinary medicine to control acute and chronic pain and inflammation. Most commonly, NSAIDs are used for managing chronic pain associated with osteoarthritis

ABBREVIATIONS

NSAID	Nonsteroidal anti-inflammatory drug
COX	Cyclooxygenase
GIT	Gastrointestinal tract

and acute pain associated with surgical procedures.¹ To varying degrees, NSAIDs inhibit COX, which is an important enzyme in the production of prostaglandins and inflammatory mediators. Studies^{2,3} have revealed the existence of at least 2 COX isoforms. Cyclooxygenase-1 is a constitutive form of the enzyme that is found in many tissues and maintains, among its many functions, the production of prostaglandins necessary for health of the GIT mucosa, platelet aggregation, and renal vasoreactivity.^{1,2}

Although COX-2 is found constitutively in some tissues, such as ovarian and renal tissues, it is not detectable in most mammalian tissues under physiologic conditions.⁴ However, production of COX-2 can increase 20-fold in these tissues when there is inflammation.¹ The end products of this upregulated COX-2 activity are prostanoids, which contribute to pain and edema associated with inflammation.^{1,2}

Aspirin (acetylsalicylic acid) is the classic NSAID; it is a nonselective COX inhibitor and therefore prevents production of homeostatic and proinflammatory prostaglandins. Inhibition of COX-1 accounts for most of the adverse effects (eg, GIT ulcers, decreased platelet function, and renal damage) reported with use of aspirin in humans and other animals. There is also a proposed direct toxic effect of compounds such as aspirin on the GIT mucosa that contributes to ulcers.⁵

A number of NSAIDs selective for COX-2, including celecoxib and rofecoxib, have been introduced for human use. Selective inhibition of the proinflammatory prostaglandins that concurrently does not inhibit production of homeostatic prostaglandins is believed to account for a decrease in adverse effects, especially gastric ulcers.^{6–8} Several NSAIDs labeled for use in veterinary medicine have revealed promise as gastric-sparing NSAIDs.⁹ Carprofen, ketoprofen, and meloxicam reportedly¹⁰ have fewer adverse effects than aspirin because of their postulated selectivity for COX-2, thereby reducing pain and inflammation while preserving the important prostaglandin production mediated by COX-1.¹⁰ In 1 study,¹¹ investigators detected fewer erosions and ulcers with etodolac or carprofen, compared with the number seen after aspirin, as determined by

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the use of endoscopic evaluation of gastric mucosa before and after NSAID administration. In vitro studies^{12,13} have revealed variable degrees of COX-2 inhibition relative to COX-1 inhibition for these drugs. For example, although carprofen is touted as a COX-2 inhibitor, in some in vitro studies,^{4,14} it appears to be an overall weak COX inhibitor with nearly equal inhibition of COX-1 and COX-2. It has been hypothesized that the analgesic and anti-inflammatory effects of carprofen are mediated by a process other than inhibition of COX, which may account for the COX-1-sparing characteristics.

Clinicians have empirically recommended various washout periods, ranging from 24 hours to 7 days, after use of an NSAID before administration of another NSAID or a glucocorticoid. Although analysis of serum half-lives of the NSAIDs indicate that they would be cleared within 8 to 12 hours, there is a prolonged clinical effect of analgesia for many of these medications.^{15,16} Pharmacokinetics of deracoxib reveal a serum half-life of 3 hours but a clinical efficacy that permits once-daily dosing.¹⁷ Presumably, the wide ranges for washout periods have been recommended out of concern for an increase in adverse effects for overlapping NSAIDs, which is reinforced by a report¹⁸ on a case series of dogs with GIT perforation after they were administered multiple NSAIDs sequentially. However, to the authors' knowledge, there have been no controlled studies testing this hypothesis. Therefore, this assumption causes a dilemma for many veterinarians who want to provide perioperative pain management with an injectable NSAID (eg, carprofen or ketoprofen) but continue the pain management after surgery by administration of an oral preparation of an NSAID (eg, carprofen or deracoxib).

The purpose of the study reported here was to evaluate adverse GIT effects in healthy dogs after injection of an NSAID followed within 24 hours by oral administration of an NSAID. The study did not attempt to simulate long-term NSAID use or to replicate the acute or chronic pain typically found in clinically affected dogs. We hypothesized that in this experimental setting, there would be no increased incidence of adverse effects in the dogs.

Materials and Methods

Animals—Six sexually intact female purpose-bred Walker Hounds were acclimated and socialized for 2 weeks prior to the start of the study to decrease stress-induced GIT problems. The dogs were housed in indoor runs, exercised daily, and fed a maintenance diet.³ Food and water were available ad libitum throughout the study. At the end of the study, all dogs were adopted to private homes. The study was approved by the Colorado State University Animal Care and Use Committee.

Experimental protocol—The study comprised four 1-week treatment periods with a washout period of 16 days between successive treatments. A randomized, crossover design was used whereby each dog was administered each of 4 treatments and served as its own control animal. All treatments were administered by 2 investigators (KRM and SRU). Throughout the study, none of the investigators were aware of the treatments administered to the dogs.

The 4 treatments were as follows: treatment 1, SC injection of carprofen^b (4 mg/kg) followed 24 hours later by oral administration of an inert substance^c (q 24 h for 4 days); treatment 2, SC injection of saline (0.9% NaCl) solution followed 24 hours later by oral administration of deracoxib^d (4 mg/kg, q 24 h for 4 days); treatment 3, SC injection of carprofen (4 mg/kg) followed 24 hours later by oral administration of carprofen^c (4 mg/kg, q 24 h for 4 days); and treatment 4, SC injection of carprofen (4 mg/kg) followed 24 hours later by oral administration of deracoxib (4 mg/kg, q 24 h for 4 days). Thus, SC injections for each treatment were administered on day 0, and oral administration of NSAIDs was performed on days 1 through 4.

Two days before start of the study, endoscopy and a test to detect fecal occult blood^f were performed on each dog. The stomach and proximal portion of the duodenum were endoscopically examined. An endoscopic biopsy specimen was obtained from the cardia region of the stomach. The biopsy specimen was placed into a urease-containing slant gel^g and observed for 24 hours for a color change indicative of *Helicobacter* spp. Fecal samples were submitted to the Colorado State University Diagnostic Laboratory for acid-fast staining for detection of *Cryptosporidium* spp and an ELISA^h to detect clostridial enterotoxin. A CBC and serum biochemical analysis were also performed for these baseline assessments.

During each treatment week of the study period, dogs were observed 4 times daily by 2 investigators (KRM and SRU). Adverse effects (eg, excessive salivation, vomiting, anorexia, lethargy, or restlessness) detected during these observation times were recorded. In addition, temperature, pulse rate, and respiration rate of each dog were measured twice daily, and body weight of each dog was recorded at the beginning and end of each treatment week. A CBC, serum biochemical analysis, and fecal ELISA^h to detect clostridial enterotoxin were repeated on day 7 of each treatment period.

Dogs with hematemesis or overt melena were to be withdrawn from the study and treated with appropriate antiulcer medications, including sucralfate and misoprostol. Dogs that developed a gastroduodenal perforation as a result of the treatments were to be euthanized.

During each treatment week of the study period, a test to detect fecal occult blood was performed on days -2 (baseline), 1, 2, and 5. Endoscopic examination of the stomach of each dog was performed on days -2, 1, 2, and 5. On days -2 and 5, the proximal portion of the duodenum was also endoscopically examined. The duodenum was evaluated only twice during each week-long treatment period to avoid undue iatrogenic lesions that may have resulted from excessive passages of the endoscope through the pylorus.

Anesthesia and instrumentation—Dogs were anesthetized for each endoscopic evaluation. Approximately 30 minutes before induction of anesthesia, each dog was administered acepromazine maleate (0.05 mg/kg, SC). An 18-gauge catheter was then inserted in a cephalic or lateral saphenous vein, and anesthesia was induced by administration of propofol (4 to 8 mg/kg, IV) to achieve a plane of anesthesia sufficient for endotracheal intubation. Dogs were intubated, and anesthesia was maintained throughout the procedure by administration of isoflurane.

Dogs were instrumented with ECG leads for continuous ECG monitoring, and pediatric blood pressure cuffs with Doppler crystals were placed over a pedal artery. Heart rate, respiration rate, and indirect arterial blood pressure were obtained every 5 minutes during the endoscopic procedure.

Endoscopy—A 1.0-m flexible endoscope with optic capabilitiesⁱ was used for the procedures. The distal esophageal sphincter and stomach, including the cardia, fundus, and pyloric antrum, were evaluated during each endo-

scopic examination. Videotape images of each examination procedure were recorded. Digital photographs of 5 specific gastric regions (distal portion of the esophagus that included a view of the distal esophageal sphincter, fundus or greater curvature, pyloric antrum that included a view of the pyloric sphincter, retroflexed view of the lesser curvature, and the cardia) were obtained during endoscopy. During baseline endoscopy and on day 5 of each treatment, an additional image of the proximal portion of the duodenum was obtained.

For each endoscopic procedure, dogs were placed in left lateral recumbency. The esophagus and distal esophageal sphincter were evaluated and images acquired. The stomach was entered and distended with air until rugal folds were minimized. The fundus was evaluated, which was followed by evaluation of the pyloric antrum. The endoscope was then retroflexed to allow evaluation of the lesser curvature and cardia. On days on which the proximal portion of the duodenum was evaluated first, the esophagus, pyloric antrum, and duodenum were evaluated, and the stomach was then distended with air to complete the evaluation of the fundus, lesser curvature and cardia, and decrease the likelihood of iatrogenic pyloric antral lesions when intubating the duodenum. After completion of each endoscopic examination, suction was used to remove air from the stomach and esophagus. Investigators were careful to avoid creating iatrogenic lesions.

Scoring of lesions—To prevent bias, lesions were not evaluated at the time of each endoscopic examination. At the completion of the study, still images and videotapes were randomized and reviewed by a board-certified specialist in veterinary internal medicine (KLD). Lesions in each of the 5 regions were evaluated by use of a scoring system (Appendix).¹⁰

Statistical analysis—Data were analyzed by use of a mixed ANOVA for repeated measures.¹ Effects of treatment, time (ie, day), and the treatment-by-time interaction on body weight, temperature, pulse rate, respiration rate, and serum biochemical variables were analyzed. The effects of week (ie, period), treatment, time, and the treatment-by-time interaction on endoscopic scores were analyzed. Restricted maximum likelihood analysis was performed by use of a mixed ANOVA. Autoregressive error terms were considered, when appropriate, for each response to detect patterns within a day, but significant effects were not detected. No adjustments were made for multiple comparisons because specific a priori comparisons were made among treatments and over time. When there was a significant effect for the treatment-by-time interaction, pairwise *t* tests were performed to detect differences among treatments at specific time points as well as within a treatment over time. Satterthwaite adjustment of denominator degrees of freedom was applied to the analyses of endoscopic evaluations because comparisons were made among treatments at specific time points.

Values were reported as adjusted means. Values of *P* < 0.05 were considered significant.

Results

Animals—All dogs completed the study without clinical adverse effects necessitating treatment. No major clinical adverse effects (vomiting, diarrhea, anorexia, anxiety, restlessness, or melena) were observed throughout the study in any dogs for any treatment. None of the dogs were euthanized.

Before the start of the study, all dogs had positive results when tested for *Helicobacter* spp on urease-containing slant gels. All dogs had negative results when tested for *Cryptosporidium* spp by use of acid-fast stains and for clostridial endotoxins by use of an ELISA.

Clinical evaluation—Significant differences attributable to treatment, time, or the treatment-by-time interaction were not detected for body weight, temperature, and respiration rate. However, there was a significant (*P* = 0.001) effect of time on pulse rate. The adjusted least-squares means revealed a gradual decrease in pulse rate with each successive day, regardless of treatment. This probably reflected the fact that dogs were becoming more accustomed to the examinations during the treatment week.

Clinical pathology variables—Hematologic variables from the CBC that were analyzed included total nucleated cell count, platelet count, PCV, and total protein concentration. Variables in the serum biochemical analysis that were analyzed included concentrations of albumin, BUN, creatinine, and total bilirubin and activities of alkaline phosphatase, alanine transaminase, aspartate transaminase, and γ -glutamyltransferase.

Of these variables, only PCV and total protein concentration changed significantly over time. The PCV decreased significantly (by 3.3%; *P* = 0.002) from baseline to day 5. When analyzed for a treatment-by-time interaction, there were no significant overall changes for PCV. However, there were significant differences within specific treatments. The PCV decreased significantly from 47% to 42% for treatment 3 (*P* < 0.001), from 42% to 38% for treatment 4 (*P* = 0.004), and from 44% to 40% for treatment 1 (*P* = 0.002). The only significant between-treatment differences were between treatments 3 and 4, with PCV for treatment 3 significantly (*P* = 0.008) higher than the PCV for treatment 4. A specific comparison of the effects of the treatment-by-time interaction on PCV between treatments in which carprofen and saline solution were injected SC revealed that there was no significant difference (*P* = 0.066). These changes should be interpreted with caution because there was no overall significant effect of treatment (*P* = 0.054) or treatment-by-time (*P* = 0.260) on PCV. Despite these significant differences, all of the values for PCV were within the reference range for the laboratory.

Analysis of total protein concentrations indicated a significant decrease from baseline to day 5 that ranged from 0.1 to 0.43 g/dL. Despite these significant differences, all of the total protein concentrations were within the reference range for the laboratory.

Scores of lesions—The esophagus did not appear to be affected by any of the treatments, with only 2 dogs (1 for treatment 2 and 1 for treatment 3) having a score > 0. The lesions in those 2 dogs were at the distal esophageal sphincter and were a direct result of mild irritation from the endoscope after the dogs reached a light plane of anesthesia, which necessitated removal of the endoscope temporarily and reintroduction of the endoscope after a deeper plane of anesthesia was achieved.

Scores for the cardia and proximal portion of the duodenum did not differ significantly within or among treatments. However, scores for the cardia were significantly higher with each successive treatment, except they decreased slightly for the last treatment. It should

be emphasized that the mean lesion score for the cardia never exceeded 0.7. The proximal portion of the duodenum was only analyzed before and on day 5 of each treatment. The mean score for the proximal portion of the duodenum decreased from 1.3 to 0.6 for treatment 1, increased from 0 to 1.2 for treatment 2, increased from 0.0 to 0.8 for treatment 3, and decreased from 0.3 to 0 for treatment 4; however, none of these differences were significantly affected by time or among treatments.

Gastric regions with the highest lesion scores for all treatments were the fundus, antrum, and lesser curvature. Scores for the fundus revealed a significant ($P = 0.020$) effect of the treatment-by-time interaction (Figure 1). Scores for treatment 3 initially had a non-

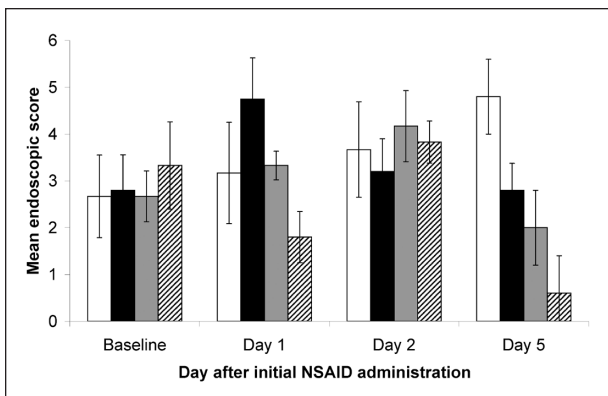


Figure 1—Mean \pm SD lesion scores of the fundus of the stomach determined by use of endoscopy in dogs administered each of 4 NSAID treatments (treatment 1, SC injection of carprofen [4 mg/kg] followed 24 hours later by oral administration of an inert substance [q 24 h for 4 days; white bars]; treatment 2, SC injection of saline [0.9% NaCl] solution followed 24 hours later by oral administration of deracoxib [4 mg/kg, q 24 h for 4 days; black bars]; treatment 3, SC injection of carprofen [4 mg/kg] followed 24 hours later by oral administration of carprofen [4 mg/kg, q 24 h for 4 days; gray bars]; and treatment 4, SC injection of carprofen [4 mg/kg] followed 24 hours later by oral administration of deracoxib [4 mg/kg, q 24 h for 4 days; diagonal-striped bars]). Lesions were scored on a scale of 0 (no visible lesions) to 6 (visible ulcers). Values represent results for 6 dogs for treatments 1, 3, and 4 but only 5 dogs for treatment 2. Day of SC injection for each treatment was designated as day 0. Baseline represents values obtained on day -2. There was a 16-day washout period between successive treatments.

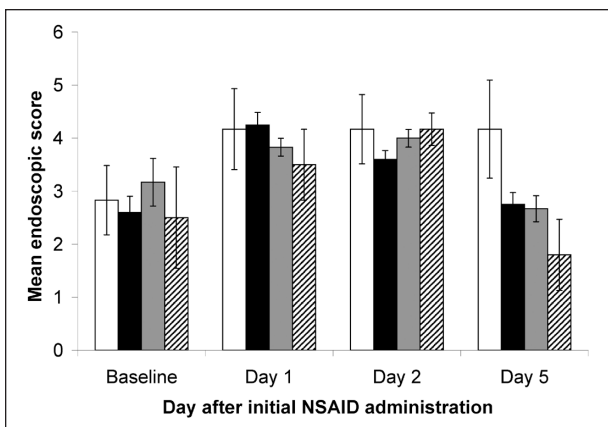


Figure 2—Mean \pm SD lesion scores of the antrum of the stomach determined by use of endoscopy in dogs administered each of 4 NSAID treatments. See Figure 1 for remainder of key.

significant increase from baseline to day 2; however, there was a significant ($P = 0.010$) decrease in lesion scores between day 2 (4.4) and day 5 (2.3). Similarly, scores for treatment 4 increased by day 2 but then decreased by day 5. The score at baseline (3.3) differed significantly ($P = 0.006$) from the score at day 5 (0.8). Similarly, the score at day 2 (3.8) differed significantly ($P = 0.001$) from the score on day 5.

Scores for the gastric regions also differed significantly among treatments on specific days. On day 1 (24 hours after SC injection of the NSAID or saline solution), dogs receiving treatment 2 ($P = 0.010$) or 3 ($P = 0.049$) had a higher lesion score (treatment 2, 4.5; treatment 3, 3.6), compared with the lesion score for dogs receiving treatment 4 (1.5). On day 5 (24 hours after oral administration of the last dose of an NSAID or inert substance), dogs receiving treatments 3 ($P = 0.040$) or 4 ($P = 0.001$) had significantly lower lesions scores (treatment 3, 2.3; treatment 4, 0.8), compared with the lesion score for dogs receiving treatment 1 (4.4).

Time significantly affected lesion scores for the antrum, with mean scores for all treatments increasing significantly ($P = 0.020$) from baseline (3.0) to day 2 (4.0) and decreasing significantly ($P = 0.010$) from day 2 to day 5 (2.9; Figure 2). Overall, treatment ($P = 0.210$) and the treatment-by-time interaction ($P = 0.090$) did not significantly affect lesion scores. Similar to scores for the fundus, scores for the antrum gradually increased in all treatments by day 2 but then significantly decreased by day 5 for all treatments, except for treatment 1. There were some noteworthy treatment differences on day 5. Scores were significantly lower for treatments 2 (2.7; $P = 0.020$), 3 (2.8; $P = 0.020$), and 4 (1.9; $P = 0.001$), compared with the score for treatment 1 (4.2).

Scores for the lesser curvature also had a similar significant ($P < 0.001$) effect of time, with lesion scores increasing, regardless of treatment, through day 2 (2.8) and then decreasing by day 5 (2.2; Figure 3). There was no significant overall effect of treatment ($P = 0.380$) or the treatment-by-time interaction ($P = 0.160$) on scores for the lesser curvature.

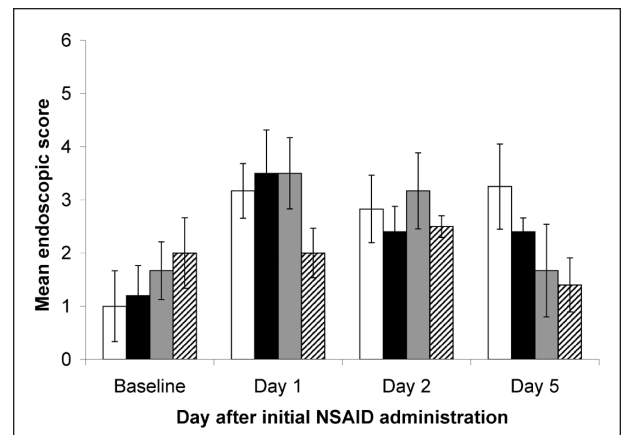


Figure 3—Mean \pm SD lesion scores of the lesser curvature of the stomach determined by use of endoscopy in dogs administered each of 4 NSAID treatments. See Figure 1 for remainder of key.

For the 4 treatment periods, all dogs had a period (ie, treatment week) effect. Lesion scores were significantly higher than the scores during the preceding treatment week for treatment weeks 1 through 3 but then significantly decreased during the last treatment week. This effect of treatment week was evident in the cardia, fundus, lesser curvature, and antrum.

Discussion

Manufacturer recommendations have led to a conservative approach when changing NSAIDs in patients, although such approaches are not explicitly stated in package inserts. In 1 online discussion, specific washout times for various NSAIDs were provided by a representative of a pharmaceutical company,^k but to our knowledge, this information has not been reported in an official publication from the manufacturer or in peer-reviewed journals.

In general, veterinarians are advised to discontinue an NSAID for 24 hours to 7 days before initiating administration of a second NSAID. This is less than ideal for patients that need relief from pain during the intervening 1- to 7-day period. Opioids may be prescribed during the washout period, but some patients probably do not receive pain medications during this time because they do not tolerate opioids or because veterinarians are concerned about prescribing opioids for administration by owners.

Although the safety and efficacy of selective COX inhibitors in dogs have been reported in multiple studies,^{10,11,15,16,19,20} it has been suggested anecdotally and in a report¹⁸ of a series of dogs with perforation of the GIT that the use of multiple NSAIDs in close temporal association carries some risk. In that report,¹⁸ 29 dogs with perforation of the GIT were described, and 17 (59%) had received a corticosteroid or another NSAID prior to or after administration of deracoxib, a selective COX-2 inhibitor. In most of those dogs, deracoxib was administered at dosages higher than those recommended by the manufacturer, and the duration and COX-selectivity of the other NSAIDs administered was variable, which make it difficult to determine the specific factors that were most important in the development of gastroduodenal complications. Although our study did not result in gastroduodenal perforation or even mild clinical signs, it should be emphasized that we did not attempt to replicate the long-term and overlapping use of NSAIDs or approximate the conditions of acute or chronic pain described for dogs of the aforementioned case series.¹⁸

The overall results of the study reported here are consistent with results of studies^{10,11} in which investigators evaluated GIT ulcers by administration of specific COX-2-selective inhibitors, such as carprofen, etodolac, and meloxicam, and detected no increased risk of gastric ulcers, compared with results after administration of an inert substance. Although studies on deracoxib have focused primarily on pain evaluation in dogs with experimentally induced acute synovitis^{16,20} and postoperative management of pain in dogs after cruciate ligament repair,¹⁹ rather than endoscopic investigation of lesions in the GIT, comparison of deracoxib, aspirin, and an inert substance with

respect to endoscopically detectable gastric ulcers in 1 study¹ suggested no difference between deracoxib and the inert substance.

In the study reported here, there were no significant differences in scores for the esophagus, cardia, and duodenum among treatments. Although there were significant differences in scores over time for the fundus, antrum, and lesser curvature (eg, baseline to day 2 or day 2 to day 5), lesion scores by day 5 were not significantly different from baseline values or were significantly decreased from baseline scores. The general pattern in these regions, regardless of treatment, was an initial increase in lesion scores through day 2, followed by a decrease in lesion scores by day 5. Although this pattern has not been observed in other studies^{10,11,21} in which investigators used endoscopy to detect gastroduodenal ulcers after NSAID administration, it is important to mention that in most of those studies, the first endoscopic examination was performed 5 to 7 days after drug administration and would therefore not have detected early ulcerative changes. Because our study did not reveal any clinical repercussions of these early lesions, the overall clinical importance of this finding is unknown.

The convenient paradigm of good COX versus bad COX has been challenged by several investigators in studies that revealed a potential role for COX-2 in other functions, including healing of ulcers. Rats receiving inhibitors of COX-1 or COX-2 (or both) after induction of gastric ulcers had a significant delay in healing, compared with results for rats who did not receive COX inhibitors.²² Similarly, investigators in another study,²³ who used rats with gastric ulcers induced by ischemia-reperfusion, detected an increase in COX-2 mRNA during the recovery phase from gastric ulcers. An *in vitro* study⁴ also revealed COX-2 mRNA in the gastrointestinal mucosa of dogs.

Analysis of the results of these studies suggests that inhibition of COX-2 may be deleterious to the healing process when gastric ulcers already exist. This role of COX-2 in healing may have accounted for the acute worsening of the lesions (ie, increase in lesion scores) during the first few days of treatment, especially because the mean endoscopic scores at baseline indicated that some dogs had lesions before administration of any treatments. Ultimately, the endoscopic scores, regardless of treatment group, returned to or below baseline values by day 5. In contrast, in the aforementioned study,²² rats treated with COX-2 had delayed healing at 14 days after induction of ulcers.

One possible explanation for the initial increase in lesion scores, followed by a decrease in lesion scores by day 5, can be found in the human literature on gastric adaptation. A study²⁴ in humans revealed a gastric adaptation effect with use of NSAIDs whereby gastric lesions appear to heal rapidly after the initial lesion despite continued use of the NSAID. By the end of 1 week in healthy human volunteers receiving aspirin, many lesions had resolved, despite the fact aspirin administration was continued. Although there are anecdotal reports of natural resolution of gastric lesions in dogs, studies^{10,11} in which dogs received NSAIDs for up to 28 days have not revealed this effect.

Studies conducted specifically to evaluate gastric adaptation have not been performed in dogs.

In rats, gastric adaptation is a prostaglandin-dependent event related to constitutive prostaglandin production by COX-1.²⁵ Because carprofen and deracoxib are putative COX-1-sparing NSAIDs, the improvement in lesions could be accounted for by the continued production of homeostatic prostaglandins by COX-1. On the other hand, as mentioned previously, COX-2 may also play a role in healing of ulcers, and theoretically, inhibition of COX-2 by carprofen and deracoxib in the study reported here should have interfered with the healing process.

The fact the study reported here was conducted as a crossover design necessitated analysis of the effect of treatment period on endoscopic scores and clinicopathologic data. There was a significant increase in the lesion scores each treatment week for weeks 1 through 3, which was followed by a significant decrease in scores during the final treatment week. Gastric adaptation is an unlikely explanation for the eventual improvement in scores by treatment week 4 because adaptation is generally a phenomenon seen within the first 2 weeks of continuous administration of NSAIDs.^{24,25}

With respect to the increasing lesion scores for treatment weeks 1 through 3, it is possible that despite the 16-day washout period between successive treatments, there were unexpected carryover effects that could not have been predicted by use of the drug half-lives for carprofen or deracoxib.^{16,17} One finding in particular that suggests a carryover effect was the variable scores on day 1 for dogs receiving SC injections of carprofen (3.6 and 1.5 for treatments 3 and 4, respectively). Theoretically, these scores should have been similar because both treatments provided carprofen on day 1. Furthermore, mean baseline scores (ie, before NSAID administration) for the fundus, antrum, and lesser curvature for all treatments ranged from 1.0 to 3.0. Because this was a crossover design, some dogs in each group had already been exposed to other treatments in preceding weeks of the study, which suggests that sequential NSAID administration may exert longer-term effects.

Although 1 pharmacokinetic study¹⁶ of carprofen over prolonged periods did not reveal evidence of accumulation or tolerance, the results of the study reported here were unexpected and suggest that residual drug effects when combining NSAIDs should be evaluated further. Despite the significant differences in lesions scores, none resulted in corresponding clinical or laboratory abnormalities. Similar to other studies in which investigators found GIT lesions without clinical consequences, it is unclear as to the importance of these lesions. In general, because of the short duration of NSAID administration (5 days) and the lack of painful stimulus during anesthesia to approximate a surgical scenario of acute pain, we cannot extrapolate these findings to a clinical setting in which patients typically undergo a painful surgical procedure and receive NSAIDs for several weeks after the procedure. In such circumstances, GIT lesions may be exacerbated and result in clinical consequences.

In 1 study,²¹ investigators evaluated additive effects of an NSAID used in combination with another anti-inflammatory drug. In that study, use of meloxicam in combination with dexamethasone was evaluated in healthy dogs receiving a painful stimulus while the dogs were anesthetized. Analysis of results indicated that although meloxicam alone did not cause gastroduodenal endoscopic scores to differ significantly from those for the group of dogs that received saline solution, the concurrent administration of meloxicam and dexamethasone resulted in a significant increase in endoscopic scores. In the aforementioned case series,¹⁸ 17 dogs receiving a combination of drugs accounted for 59% of the 29 dogs with perforation.

Although our treatments did not result in clinically important lesions, the increase in lesions scores for the first 3 treatment weeks suggested that intermittent, sequential administration of NSAIDs could be problematic. Our study also did not include a painful stimulus, a component that is usually found in clinical settings in which NSAIDs are used and that may exacerbate the development of lesions in the GIT. In a study²⁶ of nonselective COX inhibitors, investigators found that renal perfusion and prostaglandin production in anesthetized dogs receiving a painful stimulus were significantly worse than in anesthetized dogs that did not receive a painful stimulus. Inhibition of COX in a prostaglandin-dependent state induced by pain in dogs subjected to decreased renal perfusion may also apply to the GIT of dogs, but the study reported here did not assess this possibility.

Stress-induced ulcers are a phenomenon in human critical care patients and are believed to be caused, in part, by hypovolemia.^{27,28} Gastric ulcers have also been reported in performance horses²⁹ and Alaskan sled dogs,³⁰ with proposed mechanisms ranging from microscopic bleeding in the GIT to exercise-induced ischemia. It is possible that the stress of repeated anesthetic episodes for endoscopic procedures may have accounted for ulcers at baseline examinations as well as the worsening of lesions during the first 3 treatment weeks. Repeated episodes of anesthesia, with the potential for hypotension and disruption of gastric blood flow, may have resulted in gastric ulcers independent of NSAID administration. Several studies have used ischemia-reperfusion injury to create gastric ulcers in animals.³¹ Although such methods require occlusion of blood flow to the stomach or severe decreases in systemic arterial blood pressure from simulated hemorrhage that were not replicated in our study, the cumulative effect of multiple anesthetic episodes over several weeks on gastric mucosa is unknown. In the future, a large-scale study could include addition of a control group of dogs that are only anesthetized during each of the treatment periods to help rule out an effect of repeated anesthesia on GIT ulcers.

Other sources of stress, such as psychogenic stress that results in animals subjected to water immersion and restraint techniques, can cause various degrees of gastric ulcers.³² The stress of housing in the laboratory environment and repeated restraint for anesthesia, monitoring, and treatments could cause psychogenic

stress. However, there is no evidence within the veterinary literature that the psychologic stress of housing in a laboratory environment alone leads to gastric ulcers. Furthermore, the dogs of the study reported here were allowed to exercise and received social contact daily throughout the study and did not have laboratory-based or clinical signs of stress. Therefore, it is unlikely that the stress of housing in the laboratory environment and conduct of the study resulted in GIT ulcers.

Similar to reports of other studies, certain regions of the stomach appeared more susceptible to lesions. In humans, the most frequently and severely affected site is the gastric antrum.⁵ Although duodenal ulcers are less common than gastric ulcers in humans, complications from gastric ulcers are seen with similar frequency, compared with complications from duodenal ulcers.⁷ In dogs, the duodenum may be less important for the development of major lesions. Two studies^{10,11} of NSAID administration in dogs revealed significantly fewer duodenal lesions, compared with the number of gastric lesions. In the aforementioned case series of dogs with gastroduodenal perforation,¹⁸ 18 of 29 (62%) dogs had gastric or pyloric perforation, although an unusually high number of duodenal perforations (10 of 29 dogs) was reported in that study. It was hypothesized that this slightly higher proportion of duodenal ulcers or perforations may have been attributable to inhibition of COX-2 and its reparative properties in the face of ongoing ulcers.

In another retrospective study,³³ nearly half of 43 dogs with gastroduodenal ulcers had duodenal ulcers. However, many of those dogs had other predisposing factors (hepatic disease, inflammatory bowel disease, or sepsis) that could have accounted for the ulcerative lesions. Although all dogs in the study reported here developed lesions in the duodenum at some point during the study period, the mean endoscopic score for all treatments was ≤ 1.2 . We intentionally did not examine the duodenum on each of the study days because of the risk of increased trauma to the pyloric antrum. Therefore, it is possible that these lesions had a pattern similar to that for other regions of the stomach (ie, increase in scores for the first several days followed by a decrease in lesion scores).

Renal damage was not evident in the dogs reported here, even with consecutive administration of NSAIDs. Acute renal damage is more likely to result from NSAID use in animals with already compromised renal function, as indicated in a study³⁴ in which investigators evaluated carprofen and renal function in healthy dogs. Because dogs of our study had no prior evidence of renal disease and were appropriately hydrated before and during anesthesia, renal compromise was not expected.

Although the PCV and concentration of total solids decreased significantly from baseline to day 5 in all except 1 treatment (ie, treatment 2), all of these values were within reference ranges established by the laboratory. None of the fecal occult blood tests during the study yielded positive results, and there were no concurrent clinical signs suggestive of GIT bleeding. It is possible that this mild decrease was attributable to IV administration of fluids during the multiple anes-

thesia procedures for each treatment week. During the 16-day washout period, PCVs returned to the preceding values by the subsequent treatment week.

The importance of the fact the dogs of our report had positive results when tested to determine their *Helicobacter* status is unknown. *Helicobacter* spp reportedly can be found in a substantial number of healthy animals. In 1 report,³⁵ 100% of healthy laboratory dogs and 67% of client-owned animals had positive results for various *Helicobacter* spp without evidence of gastric disease. Although some cats and dogs that are treated for *Helicobacter* infections will transiently yield negative results when tested (with or without resolution of clinical signs), they often yield positive results when tested after cessation of treatment. It is unclear whether this represents complete lack of clearance or reinfection. The positive status of all dogs in our study precludes analysis of severity of lesions relative to *Helicobacter* status.

The dogs in the study reported here had no clinically apparent adverse effects throughout the study, nor did they develop any laboratory-based evidence of renal compromise or GIT hemorrhage. Although it is possible that the short duration of administration prevented development of more serious adverse effects, these findings are consistent with other studies^{5,6} of COX-2-selective NSAIDs in which investigators found no significant differences among treatment groups, compared with results for an inert substance, over longer treatment periods. Analysis of our results suggests that sequential administration of NSAIDs during a short-term (5 days) period may not result in clinically important ulcers in healthy dogs that do not have acute or chronic pain. However, the finding that the baseline scores did not return to 0 after a 16-day washout period between treatments was not expected and suggests that there may be a residual effect of sequential NSAIDs on the GIT.

Should a crossover design be used in future studies, it would seem prudent to provide a washout period of > 16 days. For studies conducted in accordance with a noncrossover design, a lengthy follow-up period would be necessary to determine whether sequential NSAID administration results in chronic gastric ulcers. A large-scale study investigating the effect of administering sequential NSAIDs in animals with acute or chronic pain, and over longer treatment durations, is essential to further characterize our findings and is necessary before clinicians can make recommendations regarding overlapping administration of NSAIDs in clinical settings.

- a. 21% lab dog diet, Harlan Tekland, Madison, Wis.
- b. Rimadyl sterile injectable solution, Pfizer Animal Health, Paxton, Pa.
- c. Allergy Free Doggie Bites, Veterinarians Best Inc, Santa Barbara, Calif.
- d. Deramaxx, Novartis Animal Health, Greensboro, NC.
- e. Rimadyl chewable tablets, Pfizer Animal Health, Paxton, Pa.
- f. Hemoccult fecal occult blood test, Beckman Coulter Inc, Fullerton, Calif.
- g. BBL urease agar slant, Becton-Dickinson Co, Sparks, Md.
- h. *Clostridium perfringens* ELISA test, TechLab, Blacksburg, Va.
- i. Olympus Evis gastrointestinal videoscope (GIF-XQ140), Olympus America Inc, Melville, NY.

- j. Proc Mix, SAS, version 9.1, SAS Institute Inc, Cary, NC.
- k. Weiner R. Veterinary Information Network Web site: Public message board post, Aug 5, 2003. Available at: www.vin.com. Accessed May 8, 2005.
- l. Senello K. Comparison of the effects of deracoxib, buffered aspirin, and placebo on the gastric mucosa of healthy dogs (abstr), in *Proceedings. 22nd Annu Am Coll Vet Intern Med Forum 2004*;77.

Appendix

Grading system used to score lesions detected during endoscopic examination of the stomach and proximal portion of the duodenum.¹⁰

Grade	Lesion description
0	No visible erosions, hemorrhage, or ulcers
1	1 to 5 punctate erosions or hemorrhage*
2	6 to 15 punctate erosions or hemorrhage
3	16 to 25 punctate erosions or hemorrhage
4	≥ 25 punctate erosions or hemorrhage or 1 to 5 invasive erosions†
5	≥ 5 invasive erosions
6	Ulcer of any size‡

*Punctate erosions were defined as pinhead-size or smaller discontinuations of the mucosal epithelium. †Invasive erosions were defined as erosions with evidence of invasion (indicated by detectable breadth or depth substantially greater than the size of a pinhead) or extensive hemorrhage. ‡Ulcers were defined as lesions resulting in wide discontinuation of the mucosa that had a craterlike center.

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