In veterinary medicine, the use of NSAIDs for treatment of pain is increasing. Once administered primarily to dogs with osteoarthritis to reduce joint pain and decrease synovitis, NSAIDs are now frequently used to control postoperative pain and inflammation. However, these drugs can be associated with adverse effects, most notably gastrointestinal tract ulceration. In dogs, NSAID-associated gastrointestinal tract ulceration most commonly develops in the region of the pylorus and proximal portion of the duodenum.

The principal mechanism of action of NSAIDs is inhibition of COX. However, results of recent studies have indicated that there are multiple isoforms of COX, and the degree to which each NSAID inhibits these COX isoforms varies. The COX enzymes catalyze the conversion of arachidonic acid to PGH₂, which is subsequently metabolized by local prostanoid synthases. Prostanoids, particularly PGE₂, play a role in gastrointestinal tract protection and repair. Cyclooxygenase-1, which is constitutively expressed in the gastrointestinal tract, is thought to exert homeostatic properties that are crucial for gastric physiologic function, including mucosal protection. Cyclooxygenase-2 is inducible in most mammalian tissues in response to proinflammatory stimuli and has been linked to inflammation. However, it is now known that COX-2 is constitutively expressed in certain tissues, such as ovaries and kidney.

Objective—To assess cyclooxygenase (COX) expression and prostanoid concentrations in pyloric and duodenal mucosae of dogs after administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

Animals—8 healthy dogs.

Procedures—Each dog received carprofen (4.4 mg/kg, q 24 h), deracoxib (2 mg/kg, q 24 h), aspirin (10 mg/kg, q 12 h), and placebo (1 dog treat, q 24 h) orally for 3 days (4-week interval between treatments). Before study commencement (baseline) and on day 3 of each treatment, pyloric and duodenal mucosal appearance was assessed endoscopically and biopsy specimens were obtained for histologic examination. Cyclooxygenase-1 and COX-2 protein expressions were assessed via western blotting, and prostanoid concentrations were measured via ELISAs. An ANOVA was used to analyze data.

Results—Treatments had no effect on mucosal appearance and ulceration was not evident histologically. In pyloric and duodenal mucosae, COX-1 expression was unaffected by treatments. Cyclooxygenase-2 expression remained unchanged in pyloric mucosa; in duodenal mucosa, aspirin significantly increased COX-2 expression, compared with effects of deracoxib and carprofen. At baseline, total prostaglandin and thromboxane B₂ concentrations in pyloric mucosa were significantly greater than those in duodenal mucosa. Aspirin significantly decreased both prostanoid concentrations in both mucosal tissues, compared with other treatments. In pyloric mucosa, carprofen administration significantly decreased total prostaglandin and thromboxane B₂ concentrations, compared with deracoxib administration.

Conclusions and Clinical Relevance—In dogs, prostanoid synthesis was greater in pyloric mucosa than it was in duodenal mucosa. Nonselective NSAIDs significantly decreased prostanoid concentrations in these mucosae, compared with the effects of a selective COX-2 NSAID. (Am J Vet Res 2008;69:457–464)
Materials and Methods

This study was approved by the Animal Care and Use Committee at North Carolina State University and was conducted in accordance with the National Institutes of Health and the International Association for the Study of Pain policies on the use of clinical subjects.

Dogs—Eight adult purpose-bred mixed-breed dogs (4 females and 4 males) that weighed 8 to 13 kg were used in the study. All dogs underwent a physical examination to ensure they were healthy prior to inclusion in the study. In addition, a CBC, serum biochemical analysis, and urinalysis were performed immediately prior to study commencement. Also, prior to the start of the study, gastroduodenoscopy was performed on each dog to rule out preexisting gastroduodenal disease.

Experimental protocol—The study was a randomized, placebo-controlled, crossover design. Each dog randomly received carprofen (4.4 mg/kg, q 24 h), deracoxib (2 mg/kg, q 24 h), aspirin (10 mg/kg, q 12 h), or placebo (1 dog treated, q 24 h) orally for 3 days with each drug to attain a theoretical steady state concentration in the plasma and presumably in the tissue of the gastrointestinal tract. Food was withheld from the dogs for 24 hours prior to endoscopy. Anesthesia was induced with propofol (10 to 15 mg/kg according to effect) and maintained with isoflurane vaporized in 100% oxygen to effect following orotracheal intubation. Gastroduodenoscopy and biopsies were performed by 1 investigator (SLM) with a flexible videogastroscope, and the procedures were recorded electronically. All endoscopic procedures were performed at the same time each morning (10:00 AM) to avoid diurnal and feeding-associated effects. Within a region, biopsy locations were at least 2 cm from one another. Mucosal biopsy specimens obtained from the pylorus and duodenum were immediately (within 6 to 8 seconds) snap frozen in liquid nitrogen, stored at –80°C, and subsequently used for western blot analysis of COX-1 and COX-2 expression and measurement of total PG and TXB, concentrations. Care was taken to ensure that each biopsy sample was treated identically. In addition, other mucosal biopsy specimens were immediately placed in neutral-buffered 10% formalin for histologic evaluation.

Western blot analysis—One biopsy sample from the pylorus and 1 biopsy sample from the duodenum of each dog was each added to 200 µL of modified radioimmunoprecipitation buffer including the protease inhibitors aprotinin, phenylmethylsulfonyl fluoride, and sodium orthovanadate. The samples were homogenized on ice, and the supernatants were extracted via centrifugation. Protein analysis of extracted samples was performed, and equal concentrations of protein from each sample were mixed and boiled with sample buffer. The lysates were then loaded into wells of precast gels and protein electrophoresis was performed according to standard protocols.

After the protein was transferred to a polyvinylidene fluoride membrane and blocked in 5% milk with 0.05% Tween-20, washed membranes were incubated overnight (approx 18 hours) in a 1:300 solution of either polyclonal anti–COX-1 or anti–COX-2 primary antibody. The membranes were then incubated in a horseradish-peroxidase–conjugated secondary antibody and developed by addition of enhanced chemiluminescence reagents. β-Actin expression was used as an internal verification that the same amount of protein had been loaded into each well. Recombinant COX protein was used as a positive control sample, and a molecular weight indicator (protein standard) was used to ensure that the canine COX protein bands corresponded to the appropriate measurement (in kilodaltons) for COX. Negative control samples were occasionally used. This approach is similar to that used in a previous study in horses when a specific antibody was not available. For each dog, samples from the pylorus and duodenum for all 4 treatments were processed on a single gel; this allowed comparison of the levels of COX expression following each treatment within each dog. By use of the densitometry values, COX protein concentrations following each treatment were expressed as a percentage of the baseline value for each region (pylorus and duodenum) in each dog. To compare the overall levels of mucosal biopsy specimens were obtained. On day 3, endoscopy took place 2 hours after treatment administration. Food was withheld from the dogs for 24 hours prior to endoscopy. Anesthesia was induced with propofol (10 to 15 mg/kg according to effect) and maintained with isoflurane vaporized in 100% oxygen to effect following orotracheal intubation. Gastroduodenoscopy and biopsies were performed by 1 investigator (SLM) with a flexible videogastroscope, and the procedures were recorded electronically. All endoscopic procedures were performed at the same time each morning (10:00 AM) to avoid diurnal and feeding-associated effects. Within a region, biopsy locations were at least 2 cm from one another. Mucosal biopsy specimens obtained from the pylorus and duodenum were immediately (within 6 to 8 seconds) snap frozen in liquid nitrogen, stored at –80°C, and subsequently used for western blot analysis of COX-1 and COX-2 expression and measurement of total PG and TXB, concentrations. Care was taken to ensure that each biopsy sample was treated identically. In addition, other mucosal biopsy specimens were immediately placed in neutral-buffered 10% formalin for histologic evaluation.

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COX protein expression in the duodenum and pylorus, the densitometric values for each dog were expressed as a percentage of the baseline value for the pylorus.

**Prostanoid analysis**—Each biopsy sample was added to 200 µL of Tris buffer (50mM Tris-HCl, 150mM NaCl, and 1mM EDTA; pH, 7.4), including aprotinin, phenylmethylsulfonyl fluoride, and sodium orthovanadate. Samples were homogenized on ice and the supernatants were extracted via centrifugation. Protein analysis of extracted samples was performed. Prostaglandin and TXB2 concentrations were measured by use of commercially available ELISA assay kits. Results were expressed as picogram of prostanoid per microgram of protein in the tissue.

**Mucosal lesion scoring and histologic analysis**—After completion of the study, the endoscopy videos were all reviewed by 1 investigator (SLM) who was unaware of the treatment protocols. The pyloric and duodenal mucosae were assessed for lesions, and a score of 0 (apparently normal) to 4 (severely affected) was assigned by use of a subjective scoring system (Appendix). Hematoxylin and eosin-stained slides of pyloric and duodenal biopsy specimens were evaluated for inflammation and ulceration by a board-certified veterinary pathologist (JML) who was not aware of the treatment groups.

**Data analysis**—A 2-way repeated measures ANOVA was used to compare the densitometric data for COX-1 and COX-2 protein concentrations, PG and TXB2 concentrations, and mucosal scores to detect any differences among treatments. A Tukey test was used to identify specific differences among treatments, and significance was set at a value of P < 0.05. An ANOVA on ranks was used when the data were not normally distributed.

**Results**

Prior to commencement of the study, no abnormalities were detected via physical examination for any dog, and clinicopathologic values were within the reference ranges used at the North Carolina State University Veterinary Teaching Hospital clinical pathology laboratory. No clinically important adverse effects were observed after any drug administration.

**Histologic examination** revealed no evidence of ulceration or clinically important inflammation in any biopsy specimen. *Helicobacter* spp were detected in 10 of 32 (31%) histologic samples. These dogs were not omitted from the study on the basis of this finding. No treatment-induced bleeding was observed in the pylorus or duodenum. Some pyloric biopsy samples revealed small lymphoid follicles or mild lymphoplasmacytic enteritis. Mild to moderate abnormalities were evident in 27 of 32 (84%) and 26 of 32 (81%) pyloric antral and duodenal biopsy specimens, respectively. These findings were not related to a specific drug or dog. The mucosal lesion score data were normally distributed; region (P = 0.62) and treatment (P = 0.28) had no effect on the lesion score.

At baseline, densitometric data indicated that the mean amount of COX-1 in the duodenum was 79% of the amount in the pylorus and the mean amount of COX-2 was 81% of the amount in the pylorus, but there was considerable variation from dog to dog. Drug administration had no effect on COX-1 protein expression in the pyloric mucosa or duodenal mucosa and no effect on COX-2 protein expression in the pyloric mucosa. In the duodenal mucosa, aspirin significantly (P < 0.05) increased COX-2 expression, compared with the effects of deracoxib and carprofen (Figures 1 and 2).

At baseline, PG concentration was significantly (P < 0.05) greater in pyloric mucosa, compared with duodenal mucosa (mean ± SEM baseline concentrations, 630 ± 66 pg/µg of protein vs 311 ± 21 pg/µg of protein; Table 1). Aspirin significantly (P < 0.05) decreased PG concentrations in pyloric and duodenal mucosae, compared with effects of all other treatments. In pyloric mucosa, carprofen significantly (P < 0.05) reduced the PG concentration, compared with the effect of deracoxib. At baseline, the mean ± SEM concentration of TXB2 was significantly (P < 0.05) greater in pyloric mucosal tissue (600 ± 105 pg/µg of protein), compared with

![Figure 1](image1.png)

**Figure 1**—Representative western blot of COX-2 protein expression in biopsy specimens of duodenal mucosa obtained endoscopically from 1 dog before baseline; B and after each of 4 treatments. At 4-week intervals, the dog received 3-day treatments with a placebo (P; 1 dog treat, q 24 h), carprofen (C; 4.4 mg/kg, q 24 h), deracoxib (D; 2 mg/kg, q 24 h), or aspirin (A; 10 mg/kg, q 12 h). Notice that compared with baseline, aspirin administration caused an increase in mucosal COX-2 protein expression, whereas administration of carprofen or deracoxib had no effect.

![Figure 2](image2.png)

**Figure 2**—Effects of 3-day oral treatments with a placebo (1 dog treat, q 24 h), carprofen (4.4 mg/kg, q 24 h), deracoxib (2 mg/kg, q 24 h), or aspirin (10 mg/kg, q 12 h) on COX-2 protein expression in biopsy samples of duodenal mucosa obtained from 8 dogs in a crossover study. Values are expressed as mean ± SEM percent of baseline level (determined prior to any treatment). Data were analyzed by use of an ANOVA, and post hoc analyses were performed with a Tukey test. *Value was significantly (P < 0.05) increased, compared with values associated with deracoxib and carprofen treatments.
the value in duodenal mucosal tissue (201 ± 50 pg/µg of protein). Aspirin significantly (P < 0.05) decreased TXB₂ concentration in pyloric and duodenal mucosae, compared with effects of all other treatments and baseline values. In pyloric mucosa, carprofen significantly (P < 0.05) reduced the PG concentration, compared with the effect of deracoxib; this effect was not evident in duodenal mucosa.

**Discussion**

In small animal veterinary medicine, deracoxib and carprofen are among the most commonly prescribed NSAIDs for treatment of acute and chronic pain. Carprofen has been described as a COX-1–sparing drug because of its profile of COX-1 and COX-2 inhibition; deracoxib has been described as a selective COX-2 inhibitor.⁵⁻⁸ So, both drugs spare the COX-1 enzyme, thereby potentially improving the safety profile of NSAIDs while retaining efficacy. Efficacy of these NSAIDs is presumed to be associated with COX-2 inhibition. In several in vitro studies,¹⁷⁻²⁰,¹²,¹³,¹⁴ the selectivity of carprofen for COX-2 has varied extensively (almost a 100-fold difference in values), and in 1 investigation,¹³ the COX-2 selectivity of carprofen was high. In another of those in vitro studies,²⁰ the COX selectivity of carprofen and deracoxib was assessed and results indicated that the selectivity of these drugs was 5- to 6-fold and 12-fold as high for COX-2 as for COX-1, respectively. In an in vivo study to compare the effects of carprofen with those of deracoxib by use of platelet function tests, carprofen decreased clot strength and decreased platelet aggregation, whereas deracoxib did not significantly alter platelet function.²⁰ Synthesis of TXA₂, in platelets is a key step in platelet aggregation and is mediated exclusively by COX-1.²¹ From review of the findings of the in vitro and in vivo studies, it is clearly difficult to predict what in vivo effects an NSAID will have on the basis of its theoretical mechanism of action. To our knowledge, the present study is the first to evaluate the in vivo effects of NSAIDs on COX-1 and COX-2 protein expression in both the pyloric and duodenal mucosae of dogs.

The present study was designed to assess the in vivo effects of short-term oral administration of NSAIDs on pyloric and duodenal mucosae, which are tissues at risk for NSAID-induced ulceration.² In our study, no dog developed any clinical signs of gastrointestinal disease, although the duration of each treatment was only 3 days. Ideally, such a study would involve collection of data at several time points over an extended period. One limitation of such an approach is the effect that one endoscopic episode would have on a subsequent endoscopic episode, even several days later. Therefore, as a starting point, the present study was designed to evaluate the effect of initial administration of NSAIDs within a short period. We chose a 3-day treatment period partly because assessments had been made at a 3-day time point in another study,²⁴ and findings indicated that gastric PGE₂ concentration was significantly decreased by all of the drugs evaluated, including deracoxib and carprofen. We wanted to confirm those findings and also to evaluate the response of the duodenal mucosa to oral NSAID administration.

In the pyloric and duodenal mucosal tissue samples collected from the dogs in our study, histologic findings were unremarkable regardless of treatment. Examination of some pyloric biopsy specimens revealed small lymphoid follicles or mild lymphoplasmacytic enteritis, but these findings were not related to a specific drug or dog. Inflammation is often detected in clinically normal dogs, and histologic findings of a previous endoscopic study²⁵ were similar. In that study,²⁵ all of the dogs had *Helicobacter* spp present in histologic samples. Among the biopsy specimens collected from the dogs of the present study, there was also some histologic evidence of *Helicobacter* spp. The species of *Helicobacter* was not determined, and the clinical relevance of *Helicobacter* spp in the gastrointestinal tract of dogs is unclear. *Helicobacter* organisms are commonly found in clinically normal dogs,²⁶ and in a study²⁷ of 31 healthy laboratory dogs, all had various *Helicobacter* spp without any evidence of gastrointestinal disease. Compared with the latter finding, the number of *Helicobacter*-positive dogs in the present study was low. There was no correlation between the mucosal lesion scores and the histologic findings in the present study.

It was unexpected to find an effect of NSAIDs on COX protein expression because NSAIDs are thought to

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**Table 1**—Mean ± SEM concentrations of PG and TXB₂ in pyloric and duodenal tissue specimens collected before (baseline) and after 3-day treatments with placebo (1 dog treat, PO, q 24 h), carprofen (4.4 mg/kg, PO, q 24 h), deracoxib (2 mg/kg, PO, q 24 h), and aspirin (10 mg/kg, PO, q 12 h) in 8 dogs in a crossover study (4-week intervals between treatments). Data were analyzed by use of an ANOVA to compare treatment groups within a region and also to compare baseline values between regions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pyloric mucosa</th>
<th>Duodenal mucosa</th>
<th>Pyloric mucosa</th>
<th>Duodenal mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>630 ± 66</td>
<td>311 ± 21</td>
<td>600 ± 105</td>
<td>201 ± 50</td>
</tr>
<tr>
<td>Placebo</td>
<td>640 ± 62</td>
<td>302 ± 37</td>
<td>694 ± 86</td>
<td>160 ± 51</td>
</tr>
<tr>
<td>Carprofen</td>
<td>410 ± 77</td>
<td>359 ± 33</td>
<td>448 ± 70</td>
<td>248 ± 53</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>707 ± 41</td>
<td>284 ± 12</td>
<td>783 ± 49</td>
<td>290 ± 41</td>
</tr>
<tr>
<td>Aspirin</td>
<td>147 ± 52</td>
<td>119 ± 22</td>
<td>48 ± 20</td>
<td>34 ± 10</td>
</tr>
</tbody>
</table>

*Baseline PG concentrations in the pyloric mucosa were significantly higher than findings in the duodenal mucosa.*

*Carprofen administration significantly (P < 0.05) reduced PG concentration, compared with the effect of deracoxib administration and baseline values.*

*Administration of aspirin significantly (P < 0.05) reduced PG and TXB₂ concentrations in pyloric and duodenal mucosa, compared with effects of all other treatments.*

*Baseline TXB₂ concentrations in pyloric mucosa were significantly higher than findings in the duodenal mucosa.*

*Carprofen administration significantly (P < 0.05) reduced TXB₂ concentration, compared with the effect of deracoxib administration.*
inhibit COX enzyme action but not alter the expression of the COX enzymes. However, there is some evidence that suggests NSAIDs may alter (decrease) expression of the COX mRNA or enzyme.\textsuperscript{30-33} Such an effect has also been identified in equine intestinal mucosa by our group.\textsuperscript{33} During the present study, drug administration did not affect the expression of COX-1 protein in the pyloric or duodenal mucosal tissue in dogs; in addition, there was no detectable effect on COX-2 protein expression in the pyloric mucosa. However, in the duodenal mucosa, aspirin significantly increased COX-2 expression, compared with the effects of deracoxib and carprofen. The mechanism and relevance of this finding will require further investigation. One limitation of our study was the fact that tissue concentrations of each NSAID were not measured; thus, we could not relate our findings to tissue concentrations of the drugs.

In the present study, the finding of constitutive expression of COX-2 protein in canine gastrointestinal mucosa was novel. Historically, in most species, COX-2 has been regarded as inducible in the gastrointestinal tract; our findings are in contrast to those of another study\textsuperscript{37} in which no COX-2 protein expression was detected in gastrointestinal tissues in dogs that had not received any NSAIDs. In humans and rodents, COX-2 expression is upregulated in inflamed gastrointestinal tissue, consistent with its role as an inducible enzyme under conditions of inflammation.\textsuperscript{35,37} Results of other investigations\textsuperscript{36,37} have indicated that COX-2 expression is upregulated in the margins of healing gastric ulcers. In addition, research has determined that selective inhibition of COX-1 alone may not cause ulcers, but simultaneous blockade of both COX isoforms induces lesions, suggesting a possible housekeeping role of COX-2 in the gastrointestinal tract.\textsuperscript{38,39} The finding in our study of constitutive expression of COX-2 protein in pyloric and duodenal mucosae of dogs both prior to and after being treated with NSAIDs supports the suggestion that COX-2 has some housekeeping role in the proximal portion of the gastrointestinal tract. Nevertheless, its exact role remains to be determined.

Gastric mucosal injury induced by NSAIDs is thought to be attributable to inhibition of the synthesis of PGs.\textsuperscript{40} Synthesis of PGs is a normal function of COX-1 in the stomach, and the PGs provide protection to the gastrointestinal mucosa.\textsuperscript{38,41} The protective effects of PGs include stimulation of epithelial proliferation, regulation of mucosal blood flow, and stimulation of mucous-bicarbonate secretion.\textsuperscript{38,41} It is postulated that PGs generated by COX-2 also participate in gastrointestinal tract protection, but the exact role of the enzyme is not known, and the conditions under which such activity might occur are not understood.\textsuperscript{42} In the present study, total PG concentrations were measured. With current techniques, it is not possible to determine which COX isoform induces each prostanoid in tissues other than whole blood. In our study, measurement of total PG synthesis allowed the investigation of synthesis of all PGs by both COX enzymes, and the actual tissue concentrations of PG (and TXB\textsubscript{2}) at the time of biopsy were assessed. Other investigators have measured the total amount of prostanoids that can be generated when tissue biopsy specimens are subsequently stimulated ex vivo.\textsuperscript{34} This latter approach is probably a good indicator of total COX enzyme activity in tissue but it does not reflect the prostanoid level in that tissue at the time of biopsy specimen collection. We consider the protocol used in our study more clinically relevant because it reflects the effect of a drug treatment on the actual tissue concentrations of prostanoids and not the effect of a drug treatment on the total possible synthesis of prostanoids by a tissue. The 2 approaches have not been directly compared. Moreover, results obtained from a study to evaluate the concentrations of PGE\textsubscript{2}, at different regions of the rat gastrointestinal tract by use of these 2 approaches indicate that the 2 techniques may not be comparable.\textsuperscript{43} In the dogs of our study, baseline PG concentrations in the pyloric mucosa were significantly higher than those in the duodenal mucosa, which may be explained by differences in COX expression in those 2 areas of the gastrointestinal tract. Baseline COX-1 expression was higher in the pyloric mucosa, compared with findings in the duodenal mucosa. This finding in our study is similar to the results of a study of 4 dogs by Kargman et al.,\textsuperscript{14} although no statistical evaluation was performed on their data. In that investigation,\textsuperscript{14} PGE\textsubscript{2} synthesis in human duodenal tissues was higher than that in gastric tissues, but the converse was true for rat and rhesus monkey tissues; PGE\textsubscript{2} concentrations in tissues from dogs were not examined. Those investigators concluded that, in general, higher PGE\textsubscript{2} concentrations correlated with greater concentrations of COX-1 protein.\textsuperscript{14} In the present study, carprofen and aspirin decreased the total concentration of PGs in gastric mucosa, whereas PG concentrations were not altered by deracoxib. In another study\textsuperscript{30} in which an assay method involving stimulation of PG synthesis was used, both carprofen and deracoxib decreased gastric PGE\textsubscript{2}, concentration, but not PGE\textsubscript{2} concentration, after 3 days of oral administration. In our study, it appeared that inhibition of PG synthesis was only detected after administration of drugs that were considered to inhibit COX-1 activity. This suggests that the PG concentrations measured in our study were more reflective of COX-1 activity, despite the fact that COX-2 protein was also detected in the mucosa. The decrease in pyloric mucosal PG concentration in association with aspirin administration in dogs has been reported previously.\textsuperscript{44} To further assess the effect of drug administration of 3 days’ duration on COX-1 and COX-2, an ex vivo investigation of blood samples could have been conducted as part of the present study. However, it is unknown how the results of such an ex vivo investigation of a different tissue type (ie, blood) would relate to NSAID-induced COX inhibition in the gastrointestinal mucosa.

To our knowledge, measurements of TXB\textsubscript{2} concentrations in intestinal mucosal samples obtained from dogs following NSAID treatments have not been previously reported. In the dogs of the present study, TXB\textsubscript{2} concentrations were significantly higher in the pyloric mucosa, compared with findings in the duodenal mucosa, which appeared to reflect higher concentrations of COX protein expression in the region of the pylorus. Thromboxane is indicative of COX-1 activity in the gastrointestinal tract in pigs.\textsuperscript{33} However, it is not known
whether TXB$_2$ can be linked to COX-1 activity in the gastrointestinal tract of dogs. Nevertheless, the drug with the least COX-1–sparing activity (aspirin) significantly reduced TXB$_2$ concentration in pyloric mucosa, compared with effects of all other treatments. Carprofen also significantly decreased TXB$_2$ concentrations, compared with the effect of deracoxib; this suggested that carprofen also inhibits COX-1 activity in the gastric mucosa of dogs, whereas deracoxib has no effect on that activity. In the duodenal mucosa, the only significant decrease in TXB$_2$ concentrations was detected in dogs treated with aspirin. The differences between the effects of carprofen and deracoxib on total PG and TXB$_2$ concentrations in the pyloric and duodenal mucosa may reflect a degree of activity–dependent inhibition by carprofen. If true, such a phenomenon has not been reported previously. In the pyloric mucosa, which had greater tissue concentrations of PGs and TXB$_2$, (and presumably greater COX-1 activity) than the duodenal mucosa, treatment with carprofen affected prostanooid synthesis to greater extent than deracoxib. The yet greater ability of aspirin to inhibit prostanooid synthesis may explain results from several studies$^{46,47}$ in which almost all dogs that were administered aspirin developed gastric lesions. However, the clinical relevance of those lesions is debatable.$^{48}$

The findings of the present study suggest that different NSAIDs reduce prostanooid synthesis to a different degree in the pylorus and duodenum of dogs, and this appears to relate to the drugs’ COX selectivity. Apart from a few studies$^{17–19,21,25}$ that have examined the effect of NSAIDs on gastric mucosal production of prostanooids, COX selectivity has largely been determined by use of in vitro assays, and assumptions about the gastrointestinal tract effects of NSAIDs have been based on those determinations. Because of the variability in results from such assays$^{17–19,21,25}$ and our lack of understanding of the physiologic actions of COX in the proximal portion of the gastrointestinal tract of dogs, making assumptions about the effects of various NSAIDs on the basis of in vitro experimental results may lead to erroneous conclusions. The purpose of our study was to assess the in vivo action of NSAIDs in the region of the gastrointestinal tract that appears to be at greatest risk for ulceration in dogs. This then leads to the question of why drugs that appear to be highly selective for COX-2 have been associated with perforating ulcers in the pylorus and duodenum in dogs in reports received by the FDA.$^{30}$ It must be remembered, however, that there is no control on the quality of information received by the FDA, and that information does not take account of how the drugs were used, underlying diseases, other drugs administered at the same time, and other non–drug-related possible causes of gastrointestinal ulceration. Despite this, the possibility of gastrointestinal tract erosion and ulceration is also indicated on the drug labels for the selective COX-2 inhibitors deracoxib$^{51}$ and firocoxib.$^{52}$ To date, 2 short clinical studies have assessed the association between selective (deracoxib)$^{53}$ and preferential (meloxicam$^{55}$) COX-2 inhibitors and gastroduodenal perforation. The study$^4$ of deracoxib revealed that for almost all dogs that were receiving the drug and had ulceration, an appropriately high dose of deracoxib was administered, other NSAIDs or corticosteroids were administered concurrently, or treatments were rapidly switched from one NSAID to another. In the present study, there was no significant effect of administration of the selective COX-2 inhibitor deracoxib on gastroduodenal prostanooid production.

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Appendix appears on the next page
Appendix

Scoring system used to subjectively assess pyloric and duodenal mucosal lesions in dogs during review of video recordings of endoscopic procedures.

<table>
<thead>
<tr>
<th>Score</th>
<th>Pyloric mucosa</th>
<th>Duodenal mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Apparently normal appearance</td>
<td>Apparently normal appearance</td>
</tr>
<tr>
<td>1</td>
<td>Erythema</td>
<td>Increased granularity</td>
</tr>
<tr>
<td>2</td>
<td>5 to 10 punctate hemorrhages or 1 to 4 erosions</td>
<td>Increased friability</td>
</tr>
<tr>
<td>3</td>
<td>11 to 20 punctate hemorrhages</td>
<td>Bleeding</td>
</tr>
<tr>
<td>4</td>
<td>Confluent hemorrhage, 10 to 20 erosions, or any ulcer</td>
<td>Erosions or any ulcer</td>
</tr>
</tbody>
</table>