In vivo effects of carprofen, deracoxib, and etodolac on prostanoid production in blood, gastric mucosa, and synovial fluid in dogs with chronic osteoarthritis

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Objective—To evaluate in vivo activity of carprofen, deracoxib, and etodolac on prostanoid production in several target tissues in dogs with chronic osteoarthritis.

Animals—8 dogs with chronic unilateral osteoarthritis of the stifle joint.

Procedure—Each dog received carprofen, deracoxib, or etodolac for 10 days with a 30- to 60-day washout period between treatments. On days 0, 3, and 10, prostaglandin (PG) E_2 concentrations were measured in lipopolysaccharide-stimulated blood, synovial fluid, and gastric mucosal biopsy specimens; PGE_1 concentrations were measured in gastric mucosal biopsy specimens; and thromboxane B_2 (TXB_2) was evaluated in blood.

Results—Carprofen and deracoxib significantly suppressed PGE_2 concentrations in blood at days 3 and 10, compared with baseline, whereas etodolac did not. None of the drugs significantly suppressed TXB_2 concentrations in blood or gastric PGE_1 synthesis at any time point. All 3 drugs significantly decreased gastric synthesis of PGE_2 at day 3 but not day 10 of each treatment period. All 3 drugs decreased synovial fluid PGE_2 concentrations in the affected and unaffected stifle joints at days 3 and 10.

Conclusions and Clinical Relevance—Results indicate that carprofen and deracoxib act in vivo on target tissues as COX-1–sparing drugs by sparing gastric PGE_1 and PGE_2 synthesis and production of TXB_2 by platelets. Etodolac also appears to be COX-1 sparing but may have variable effects on COX-2 depending on the tissue. In gastric mucosa and synovial fluid, there were no significant differences in PG production between compounds at recommended concentrations. (*Am J Vet Res* 2005;66:812–817)

The use of **nonsteroidal anti-inflammatory drugs (NSAIDs)** for management of acute and chronic pain in dogs is commonplace. Inhibition of **prostaglandin (PG)** synthesis by NSAIDs is thought to be responsible for both the anti-inflammatory therapeutic and toxic effects documented with NSAID use.[1] **Cyclooxygenase (COX)**-2, the inducible isoform of the COX enzyme, is thought to be responsible for the inflammatory activity of PGs. Conversely, COX-1, the constitutive isoform of the COX enzyme, is believed to be responsible for the basal physiologic functions provided by the PGs. These basal functions include gastric cytoprotection, regulation of renal blood flow, and normal platelet activity. Therefore, inhibition of COX-1 by these drugs is thought to result in most of the adverse effects associated with NSAID usage, and inhibition of COX-2 is thought to be responsible for most of the therapeutic effects of NSAID usage.[2] This theory has led to rapid development of numerous COX-1–sparing (COX-2–selective) NSAIDs, with hopes that specific inhibition of the COX-2 isoform (with concurrent sparing of COX-1 activity) would result in less adverse effects. However, the concept that COX-2 is a solely inducible isoform associated with inflammation may be an oversimplified view of the physiologic roles of the COX isoforms.[2]

On the basis of these premises, NSAIDs are now classified according to their ability to preferentially inhibit 1 isoform versus the other. Cyclooxygenase selectivity is typically expressed as a ratio of the concentrations at which a specific drug inhibits each isoenzyme by 50%.[2-3] In the veterinary literature, several studies[4-9] have evaluated the selectivity of various NSAIDs by use of in vitro techniques. However, despite somewhat uniform results among the various NSAIDs tested for their COX selectivity, numerous discrepancies among the studies exist. The greatest discrepancy among studies is typically associated with comparison of the COX selectivity of a particular agent in 1 study versus another. In vitro studies use different methodologies to determine their COX selectivities, thus further complicating the ability to compare the results of the different studies.

Another potential problem with in vitro testing for COX selectivity is the difficulty associated with extrapolating the in vitro results to clinical situations. For example, many NSAIDs are highly protein bound in the circulation, which affects drug distribution and in vivo activity.[2,10] Also, COX selectivity is dependent on drug concentrations in the target tissues, and selectivity could thus be lost at higher drug concentrations.[10] If this COX selectivity is lost in certain tissues that rely on basal PG concentrations for normal function, such as the gastric mucosa and renal vasculature, toxicosis could result at higher drug concentrations. Thus, predicting in vivo efficacy and toxicity for a particular drug is not possible from an in vitro assay.[3] As an example, it would be expected that COX-1–sparing agents in vivo should not change gastric PGE_1 and PGE_2 synthesis or

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platelet production of **thromboxane B_2 (TXB_2)** but should decrease joint PGE_2, but this cannot be assessed in vitro.

With these limitations of in vitro testing of COX selectivity in mind, a model was developed to assess in vivo activity of COX isoenzymes in specific target tissues in dogs.[11] The objective of the study reported here was to determine the in vivo activity of approved recommended doses of carprofen, deracoxib, and etodolac in blood, gastric mucosa, and synovial fluid in dogs with chronic osteoarthritis. Our hypothesis was that all 3 drugs are COX-1 sparing in vivo.

Materials and Methods

Dogs—Eight adult male mixed-breed hound dogs that weighed 25 to 40 kg and had unilateral osteoarthritis of 1 stifle joint were used. The dogs are part of a research colony at the University of Georgia. Osteoarthritis was surgically induced by an injury to the cranial cruciate ligament several years prior to the study. The osteoarthritis was confirmed by radiographs and physical examination and resulted in chronic clinical lameness.[12] The study was reviewed and approved by the University of Georgia Animal Care and Use Committee. All dogs were considered in good health with normal findings, except for the stifle joint lameness associated with osteoarthritis, on physical examination and laboratory results that were within reference range for CBC, serum biochemical analyses, and urinalysis performed immediately prior to study commencement. The dogs were receiving no medical treatment for osteoarthritis prior to inclusion in this study.

Experimental design—Each dog received carprofen[a] (2.2 mg/kg, PO, q 12 h), deracoxib[b] (2 mg/kg, PO, q 24 h), or etodolac[c] (10 to 15 mg/kg, PO, q 24 h) for 10 days in a crossover design with a 30- to 60-day washout period between treatments. On days 0, 3, and 10 of each treatment period, blood was collected for evaluation of TXB_2 and PGE_2 concentrations. In addition, anesthesia was induced with propofol[d] (4 mg/kg) and maintained with isoflurane.[e] Synovial fluid was collected from both stifle joints by use of a standard arthrocentesis technique for evaluation of PGE_2 concentrations. Gastroscopy was performed during each anesthetic episode, and 3 to 6 endoscopic biopsy specimens were collected from the gastric antrum for evaluation of PGE_1 and PGE_2 synthesis. On day 0 for each dog, a gastric biopsy specimen was placed into a *Campylobacter*-like organism test kit[f] and evaluated for up to 24 hours for *Helicobacter* spp. Results were determined to be positive or negative as per manufacturer's instructions. Stained slides (H&E) of gastric biopsy specimens were also evaluated for the presence of underlying inflammation.

Blood TXB_2—Six milliliters of blood was collected by use of venipuncture into an evacuated siliconized glass tube, immediately placed in a 37°C waterbath, and incubated for 1 hour. Indomethacin[g] was subsequently added to a final concentration of 30µM to stop further TXB_2 synthesis. Tubes were centrifuged at room temperature (approx 18°C) for 10 minutes at 2,000 × *g*. Serum was divided into 1-mL aliquots and frozen at –70°C pending analysis. The samples were thawed on ice, and a lipid extraction was performed by passage through an ethyl C_2 minicolumn.[h] Thromboxane B_2 was measured by use of an ELISA[11,h] that used a polyclonal antibody to bind, in a competitive manner, the TXB_2 in the sample or an alkaline phosphatase molecule that had TXB_2 covalently bound to it. After a subsequent incubation for 18 hours at room temperature, the excess reagents were washed away and substrate was added. After a short incubation (60 to 90 minutes), the plate was read on a microplate reader at 405 nm. The intensity of the bound yellow color was inversely proportional to the concentration of TXB_2 in either standards or samples. The measured optical density was used to calculate the concentration of TXB_2.

Blood PGE_2—Four milliliters of blood was collected into heparinized tubes, and 500 µL of the heparinized blood was placed in a microcentrifuge tube. Fifty micrograms of bacterial **lipopolysaccharide** (**LPS**; *Escherichia coli* serotype 127:B8)[i] was added to each tube, and this combination was incubated at 37°C for 24 hours. After incubation, the tubes were centrifuged at 12,000 × *g* for 5 minutes. Plasma was mixed with 900 µL of methanol and centrifuged again at 12,000 × *g* for 1 minute for extraction of PGs. The sample was stored at –70°C until assayed for PGE_2 with an ELISA.[11,g]

Gastric mucosal PGE_2 synthesis—Biopsy specimens of the gastric mucosa were collected endoscopically from the gastric antrum near the pylorus in each dog. To lessen variability, the same individuals performed collection (JKS) and processing (LRR) of biopsy specimens throughout the study. All specimens were processed within 8 minutes after removal from the stomach. Specimens that weighed < 4 mg were discarded. Prostaglandin synthesis was stimulated via mincing, as described.[11] The sample was divided into 300-µL samples and stored at –70°C until PGE_2 was measured by use of an ELISA.[11,g] Results were reported as milligrams of PGE_2 per kilogram per minute.

Gastric mucosal PGE_1 synthesis—Samples were prepared identically to the aforementioned PGE_2 protocol. The sample was divided into 300-µL samples and stored at –70°C until PGE_1 was measured by use of an ELISA.[11,i] Results were reported as milligrams of PGE_1 per kilogram per minute.

Synovial fluid PGE_2—Synovial fluid was collected from the stifle joints of each dog via a standard arthrocentesis technique. Fifty microliters of sample was mixed with 150 µL of citrate buffer (100mM; pH, 3.0). After extraction through a carbon 18 minicolumn,[h] the PGE_2 concentration was measured by use of an ELISA.[11,g]

Statistical analyses—A repeated-measures ANOVA was used to compare PGE_2 and TXB_2 concentrations over time as well as PGE_1 and PGE_2 gastric synthesis. If significant changes were found, means were compared by use of a least squares difference test. Significance was set at $P < 0.05$.

Results

Histologic evaluation of gastric biopsy specimens revealed mild lymphoplasmacytic inflammation in most dogs. Because dogs did not have any signs associated with gastrointestinal tract disease and mild inflammation is often detected in clinically normal dogs, dogs were not excluded from our study on the basis of this finding. No dog had substantial inflammation. Also, all dogs had some degree of colonization with *Helicobacter* spp histologically, and 7 of 8 dogs yielded positive results via the *Campylobacter*-like organism tests. However, because *Helicobacter* organisms are a common finding in clinically normal dogs,[13] dogs were not excluded from our study on the basis of this finding. All endoscopies were videotaped; however, subsequent review of these videotapes did not reveal any important gastric mucosal lesions associated with the NSAIDs evaluated in this study.

No significant suppression of blood TXB_2 concentrations at either time point (day 3 or 10) was found in any group (**Figure 1**). No significant difference was detected among the drug groups with regard to the degree of change in TXB_2 concentration from baseline to time points after treatment.

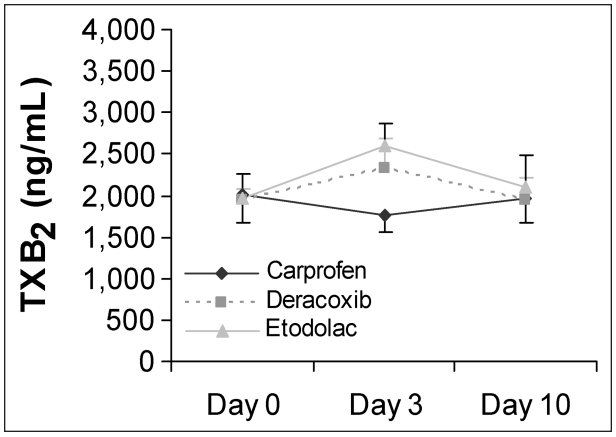


Figure 1—Mean ± SD blood thromboxane B_2 (TXB_2) concentrations in 8 dogs that received carprofen, deracoxib, or etodolac from day 1 to day 10 in a crossover design.

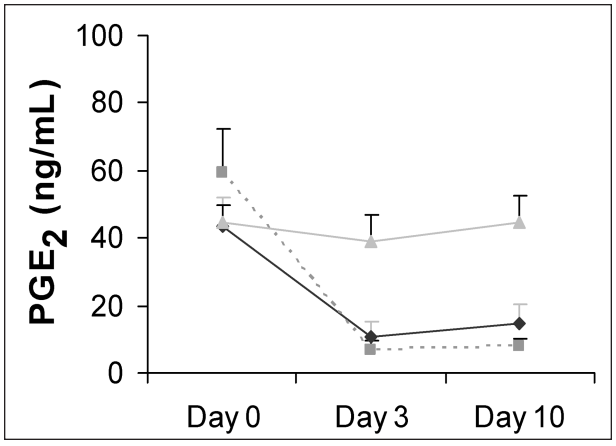


Figure 2—Mean ± SD blood prostaglandin (PG) E_2 concentrations in 8 dogs that received carprofen, deracoxib, or etodolac from day 1 to day 10 in a crossover design. *See* Figure 1 for key.

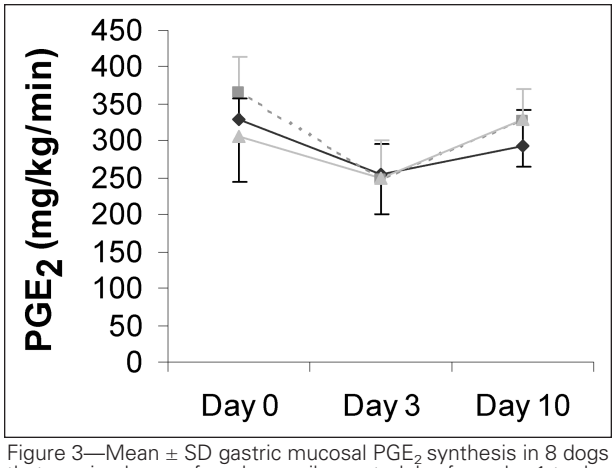


Figure 3—Mean ± SD gastric mucosal PGE_2 synthesis in 8 dogs that received carprofen, deracoxib, or etodolac from day 1 to day 10 in a crossover design. *See* Figure 1 for key.

On days 3 and 10 of treatment, significantly decreased PGE_2 concentration in blood was found in the carprofen and deracoxib treatment groups. However, etodolac did not cause a significant decrease in blood PGE_2 at either time point (**Figure 2**). Among treatment groups, a significant difference was found between the carprofen and deracoxib groups, compared with the etodolac group, on days 3 and 10.

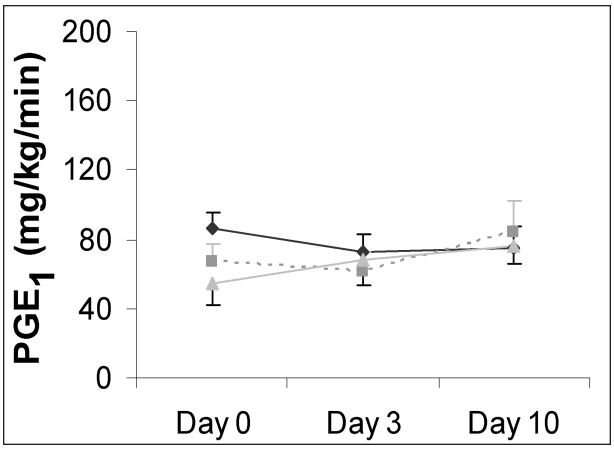
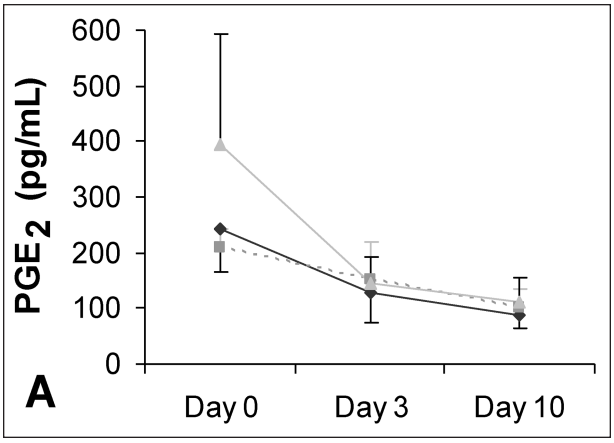


Figure 4—Mean ± SD gastric mucosal PGE_1 synthesis in 8 dogs that received carprofen, deracoxib, or etodolac from day 1 to day 10 in a crossover design. *See* Figure 1 for key.



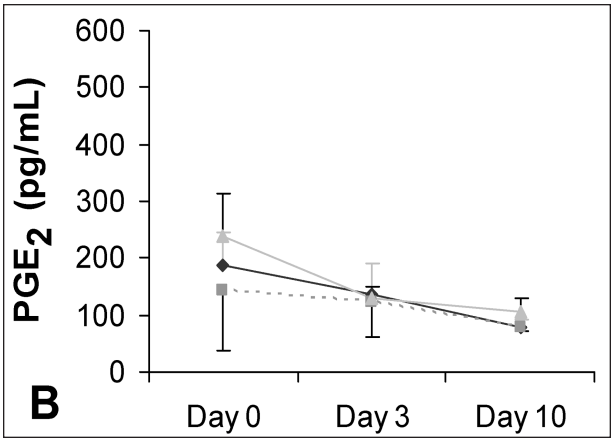


Figure 5—Mean ± SD PGE_2 concentrations in osteoarthritic stifle joints (A) and normal stifle joints (B) in 8 dogs that received carprofen, deracoxib, or etodolac from day 1 to day 10 in a crossover design. *See* Figure 1 for key.

On day 3 of treatment, significantly decreased amounts of gastric PGE_2 synthesis were noted in all 3 treatment groups. However, this suppression was not apparent or significant on day 10 of treatment in any group (**Figure 3**). No significant difference was detected between groups with regard to the degree of change in PGE_2 concentration from baseline to either day 3 or 10 of treatment.

On days 3 and 10 of treatment, no significant differences were detected among groups in gastric PGE_1 synthesis (**Figure 4**). Likewise, no significant differences were detected among groups with regard to the degree of change in PGE_1 concentration from baseline to either day 3 or 10 of treatment.

On days 3 and 10 of treatment for all groups, significantly decreased synovial fluid PGE_2 concentration in the affected and unaffected stifle joints was noted (**Figure 5**). No significance was detected among groups with regard to the degree of change in PGE_2 concentration from baseline to either day 3 or 10 of treatment.

Discussion

Carprofen, deracoxib, and etodolac were chosen for this study because they are among the most commonly prescribed NSAIDs in veterinary medicine for treatment of acute and chronic orthopedic pain. Their clinical efficacies have been evaluated in the recent literature.[14-17,j] In previous in vitro studies,[4-9] carprofen inhibited COX-2, although the degree of COX-1 sparing (COX-2 selectivity) varied widely among the studies. In 2 of the in vitro studies[4,7] of etodolac, this drug was COX-2 sparing (COX-1 selective). However, in a recent study[8] that evaluated COX isoenzyme selectivity, etodolac inhibited COX-2 more than 5 times as much as COX-1. A fourth in vitro study[9] also found that etodolac selectively inhibited COX-2, although carprofen inhibited COX-2 approximately 19 times as effectively as etodolac. That study also found deracoxib to be a potent COX-1–sparing agent with the ability to selectively inhibit COX-2 approximately 20 times as much as carprofen and 375 times as much as etodolac. To our knowledge, ours is the only published in vivo study that has evaluated the COX selectivity of deracoxib.

Prostaglandin production in a grossly normal stomach is a function of COX-1.[18,19] Likewise, platelets produce COX-1, which makes TXB_2 production a function of this isoform.[20,21] Therefore, measurement of PG and TXB_2 production by gastric mucosa and platelets, respectively, should correlate with COX-1 activity. Results of our study indicated that all 3 drugs appear to spare COX-1 activity in vivo because they had no significant effect on TXB_2 production in platelets at day 3 or 10 of treatment or on PG production by gastric mucosa by day 10. Measurement of gastric PGE_1 concentration confirmed this assertion because that concentration was not significantly altered during administration of any of the 3 drugs. We could not explain the cause of the transient yet significant decrease in gastric PGE_2 production on day 3 by all drugs. A possible cause of the decrease may be a contribution of COX-2 to basal PG production by the gastric mucosa that is suppressed immediately after administration of nonselective COX or COX-2–selective agents. The subsequent increase of PGE_2 production to baseline concentrations may be caused by a compensatory upregulation of COX-1 expression. Future temporal studies that use expression and tissue distribution of the COX isoenzymes by measurement of mRNA and protein expression may answer this unsolved question.

The role of COX-2 in gastric mucosal repair, defense, and integrity has been studied extensively in murine models.[22-24] However, the contribution of COX-2 to basal PG production by the gastric mucosa is debatable because studies[25] of normal human gastrointestinal tracts have revealed little to no COX-2 protein or activity in the stomach or duodenum. This finding is supported by a recent canine study[9] that found no COX-2 protein expression in gastrointestinal tissues, regardless of whether they contained COX-2 mRNA detectable via northern blot analysis. The clinical importance of the transient PGE_2 decrease seen on treatment day 3 in the gastric mucosa in the dogs of our study appeared to be negligible because no substantial gross lesions of the mucosa were noted at either day 3 or 10 of treatment with any of the 3 study drugs. This finding is consistent with studies[26,27,k] that evaluated the gastric mucosa endoscopically after various treatment periods with multiple NSAIDs, including carprofen, deracoxib, and etodolac.

Although COX-1 and -2 are involved in the inflammatory response, PGE_2 production by WBCs in blood, incubated with bacterial LPS for 24 hours, is a function of COX-2 induction.[20] Although no specific data exist for dogs, induction of COX-2 is the major contributor to PG production in inflamed joints.[28] Therefore, PGE_2 concentrations in synovial fluid of inflamed joints are most likely the result of increased COX-2 activity. In our study, PGE_2 concentrations in synovial fluid from affected and unaffected stifle joints as well as blood incubated with bacterial LPS were measured. All 3 drugs suppressed PG production in affected and unaffected stifle joints after 3 and 10 days of drug administration, indicating appropriate activity against COX-2 in vivo at this target site. The decreased PGE_2 concentrations in the unaffected stifle joints presumably were associated with suppression of basal PG production by COX-2 in the healthy joints. Carprofen and deracoxib also significantly decreased PGE_2 production from LPS-stimulated WBCs at days 3 and 10. These data were consistent with the COX selectivity in vivo of these 2 drugs. However, etodolac did not significantly suppress PGE_2 production in the LPS-stimulated WBCs at either time point, which was unexplained. Perhaps the concentrations attained in blood at the doses given were unable to suppress PGE_2 production from the LPS-stimulated WBCs. These findings pose an interesting question. As stated, etodolac was COX-1 selective in 2 in vitro studies[4,7] that used ratios of COX activity. One of those studies[7] used a similar LPS-stimulated blood assay. Nevertheless, in our study, significant suppression of COX-2 by etodolac

did occur in the joint with significant suppression of synovial PGE_2 production that was not significantly different from that induced by carprofen and deracoxib. More recent in vivo data[29] differs from previous in vitro data obtained by use of a different method of assessing COX isoenzyme inhibition ratios.

In the study reported here, it was interesting to note that no drug altered target tissue PG concentrations greater than any other drug. This strongly contradicts the classic COX-2 preferential and selective classification scheme, which is often used to imply that the larger the COX-1:COX-2 ratio attained in vitro, the greater the potential for more selective activity in vivo. Our data highlight the inherent problems with extrapolating in vitro results to in vivo situations. For example, the in vitro COX-1:COX-2 ratios for carprofen have been reported to be 129.0,[4] 65.0,[8] 16.8,[7] 6.5,[6] and 1.75[5]; thus, each of these values places the drug in the COX-1–sparing group. For etodolac, ratios of 3.4,[9] 0.53,[7] and 0.517[4] have been reported, which are contradictory and may indicate slight COX-1 or -2 inhibition. Deracoxib was reported[9] to have a COX-1:COX-2 ratio of 1,275.0, which also places it in the COX-1–sparing group. If these ratios were used as predictors of selective inhibition, deracoxib would be expected to be superior at altering target tissue PG concentrations, followed sequentially by carprofen and etodolac. However, with the notable exception of the apparent inability of etodolac to suppress PGE_2 production by LPS-stimulated WBCs, the other findings in our study (including sparing of platelet COX-1 activity, lack of significant suppression of gastric PGE_1 and PGE_2 synthesis at day 10 of each treatment period, and suppression of PGE_2 production in inflamed synovium by all 3 drugs) indicated no significant differences among the drugs in vivo with regard to the net effect on PG production. Thus, the applicability of COX-1:COX-2 ratios obtained in vitro must be questioned. Although a drug may be determined to be consistently COX-1 sparing in vitro, we question the importance of the numerical value assigned to its COX-1:COX-2 ratio when assessing the ability to alter blood, gastric mucosal, and synovial fluid PG concentrations. Further in vivo studies of proposed COX-1–sparing agents in different tissues, such as bone, are needed to better solve this pertinent question.

a. Rimadyl, Pfizer Animal Health, New York, NY.
b. Deramaxx, Novartis Animal Health, Greensboro, NC.
c. Etogesic, Fort Dodge Animal Health, Madison, NJ.
d. Rapinovet, Schering-Plough Animal Health, Union City, NJ.
e. Isoflurane, Abbott Laboratories, North Chicago, Ill.
f. CLO (*Campylobacter*-like organism test), Ballard Medical Products, Draper, Utah.
g. TXB_2, PGE_2 ELISAs, Cayman Chemical Co, Ann Arbor, Mich.
h. Ethyl C_2 minicolumns, Amersham Life Science, Little Chalfont, Buckinghamshire, England.
i. PGE_1 ELISA, Assay Designs Inc, Ann Arbor, Mich.
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k. Sennello KA, Lieb MS. Comparison of the effects of deracoxib, buffered aspirin, and placebo on the gastric mucosa of healthy dogs (abstr). *J Vet Intern Med* 2004;18:422.

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