Effects of firocoxib, meloxicam, and tepoxalin administration on eicosanoid production in target tissues of healthy cats

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Objective—To evaluate the effects of firocoxib, meloxicam, and tepoxalin administration in healthy cats by measuring the ability of stimulated tissues to synthesize eicosanoids ex vivo.

Animals—8 healthy adult male cats.

Procedures—In a blinded, randomized, crossover study design, cats were treated with firocoxib (1 mg/kg, PO, q 24 h), meloxicam (0.05 mg/kg, PO, q 24 h), tepoxalin (5.0 mg/kg, PO, q 12 h), or a placebo for 8 days. Blood samples and gastric and duodenal mucosal biopsy specimens were collected on days 0 (baseline; immediately before treatment), 3, and 8 of each treatment period. Thromboxane B2 (TXB2) concentrations were measured in serum, and prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) concentrations were measured in plasma. Prostaglandin E1 (PGE1) synthesis, PGE2 synthesis, and LTB4 concentrations were measured in mucosal biopsy specimens. A 21-day minimum washout period was observed between treatments. Repeated-measures analyses were performed.

Results—Firocoxib and meloxicam administration resulted in a lower plasma PGE2 concentration than at baseline on days 3 and 8 of administration, whereas tepoxalin administration did not. Tepoxalin administration resulted in a lower serum TXB2 concentration and pyloric and duodenal PGE1 synthesis on both days, compared with baseline and placebo administration. Neither firocoxib nor meloxicam administration altered pyloric or duodenal PGE1 synthesis on either day, compared with placebo administration. Tepoxalin administration also resulted in lower pyloric mucosal LTB4 concentrations on both days, compared with baseline values.

Conclusions and Clinical Relevance—Firocoxib and meloxicam administration had no effect on cyclooxygenase-1 activity, whereas tepoxalin administration resulted in inhibition of cyclooxygenase-1 and 5-lipoxygenase.(*Am J Vet Res* 2010;71:1067–1073)

The physiologic roles of the COX isoforms as well as the therapeutic and toxic effects of their inhibition have been widely studied in human and veterinary medicine. The COX-1 isoenzyme is constitutively expressed in most tissues and is important in maintaining homeostasis. In contrast, expression of the COX-2 isoenzyme is inducible in many tissues and plays a major role in inflammation and gastrointestinal wound healing. Expression of COX-2 is induced on the edges of gastric ulcers,[1] where it accelerates ulcer healing through prostaglandin-dependent[2] and -independent[3] mechanisms. However, similar to the COX-1 isoenzyme, COX-2 plays a homeostatic role in certain tissues. In dogs, COX-2 is constitutively expressed in the macula densa,[4] which suggests that COX-2 may play a physiologic role in renal autoregulation. Furthermore, although gastrointestinal homeostasis is generally maintained by prostaglandins produced by COX-1, in the absence of this isoenzyme, expression of the COX-2 isoform is upregulated and is responsible for producing prostaglandins, thereby maintaining mucosal homeostasis.[5]

Abbreviations

5-LO	5-Lipoxygenase
COX	Cyclooxygenase
LOQ	Limit of quantification
LTB4	Leukotriene B4
PGE1	Prostaglandin E1
PGE2	Prostaglandin E2
TXB2	Thromboxane B2

Because various NSAIDs preferentially inhibit 1 isoform to a greater extent than the other, the COX-1 or COX-2 selectivity of a specific NSAID has important clinical consequences. The ability of various NSAIDs to inhibit COX isoforms in tissues involved in therapeutic responses or toxic events has been assessed. In human medicine, a whole blood assay system was adopted as the standard method to assess the differential inhibition of the COX isoforms.[6] With this technique, used in some studies involving dogs[7] and cats,[8] production of TXB2 by platelets reflects COX-1 function, whereas

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plasma PGE2 production by lipopolysaccharide-stimulated WBCs is an indicator of COX-2 activity.[9] In dogs, the capacity for gastrointestinal mucosal prostaglandin synthesis can be directly quantified and is reflective of both COX-1 and COX-2 isoform activity.[10,11] The inhibition of both isoenzymes is required to decrease mucosal prostaglandin synthesis for > 12 hours.[5]

In cats, NSAIDs are effective analgesics for several painful procedures such as ovariohysterectomy[12] or onychectomy[13] and for osteoarthritic conditions.[14] Despite the potential use of NSAIDs in cats, little is known of the COX-1 and COX-2 selectivities of various drugs in that species. Studies designed to elucidate COX selectivity profiles in cats could be useful in predicting potential adverse effects of treatment and may influence patient monitoring during drug administration.

Tepoxalin[a] is a dual COX and 5-LO inhibitor approved for use in dogs to treat osteoarthritic pain. No data have been published regarding the pharmacokinetic or pharmacodynamic properties of this drug in cats. Slightly more is known about the pharmacodynamics and pharmacokinetics of firocoxib[b] and meloxicam.[c] In vitro analyses have shown that firocoxib is COX-2 selective (COX-1 sparing) in cats, with a half maximal inhibitory concentration ratio (ratio of COX-1 to COX-2 activity) of 58,[15] whereas meloxicam is less COX selective, with a ratio of 3.5.[8] The pharmacokinetics of meloxicam and firocoxib are known in cats. Meloxicam administered PO at an initial dose of 0.1 mg/kg followed by a daily maintenance dose of 0.05 mg/kg reaches a maximum blood concentration after 3.17 hours, has an elimination half-life of 28.72 hours, and reaches steady state after 2 days.[d] In a study[15] in which firocoxib was orally administered in 2 cats, the time to maximal plasma concentration was 1 and 4 hours, and the elimination half-life was 8.7 and 12.2 hours.[15]

The purpose of the study reported here was to investigate the effects of firocoxib, meloxicam, and tepoxalin administration in clinically normal cats by measuring the ability of target tissues to synthesize eicosanoids ex vivo. We hypothesized that at the doses administered, firocoxib and meloxicam would have no effect on (ie, would spare) COX-1 activity, whereas tepoxalin would have a nonspecific COX isoform inhibitory effect. In addition, we hypothesized that tepoxalin would inhibit activity of 5-LO.

Materials and Methods

Cats—Eight healthy adult neutered male cats (age range, 1 to 4 years) were subjects in this study. The cats were part of a research colony at the University of Georgia and had no history of gastrointestinal disease. Prior to inclusion in the study, all cats were verified as healthy on the basis of physical examination findings and results of a full plasma biochemical analysis, CBC, and urinalysis. In addition, endoscopic evaluation of the stomach was performed on day 0 (immediately before drug administration) of each treatment period after food was withheld for 12 hours, and all cats included in the study had unremarkable findings. All cats were cared for in accordance with the principles outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the study protocol was reviewed and approved by the Institutional Animal Care and Use Committee of the University of Georgia.

Study design—In this blinded, 4-way crossover study, cats were assigned by use of a randomization table generator to subsequently receive firocoxib (1 mg/kg, PO, q 24 h), meloxicam (0.05 mg/kg, PO, q 24 h), tepoxalin (5.0 mg/kg, PO, q 12 h), or a placebo (1.0 mL of water, PO, q 24 h) for 8 days. All cats received all 4 treatments. On days 3 and 8 of each treatment period, endoscopic evaluation was performed and additional samples were collected by venipuncture and endoscopic biopsy of the gastric and duodenal mucosa. A minimum of 21 days was observed as a washout period between treatments.

The meloxicam dose was based on that used in clinical trials[16,17] involving low-dose, chronically administered meloxicam in cats, whereas the firocoxib dose was based on that used in another study[14] involving cats. Because there are no published reports of the pharmacokinetic or pharmacodynamic properties of tepoxalin in cats, the tepoxalin dose used in our study was selected after consultation with the manufacturer at the time of the trial. Firocoxib and meloxicam were administered in the morning, whereas tepoxalin, dosed twice daily, was administered in the morning and evening.

Sample collection—On day 0, collection of blood, gastric mucosal, and duodenal mucosal samples was performed prior to drug or placebo administration; on days 3 and 8, sample collection was performed within 3 to 4 hours after drug administration. For these procedures, cats were premedicated with butorphanol (0.2 to 0.4 mg/kg, IM) and midazolam (0.2 mg/kg, IM). Anesthesia was induced with isoflurane in 100% oxygen administered by mask and was maintained after endotracheal intubation. Gastrointestinal endoscopy was performed with an 8.9-mm gastroendoscope, and 3 biopsy specimens weighing a minimum of 2.0 mg each were obtained from the gastric fundus and duodenum. Prior to recovery from anesthesia, 8.0 mL of whole blood was obtained from a jugular vein via a 20-gauge, 1-inch needle. Then, 4.0 mL of blood was transferred to an evacuated tube and another 4.0 mL of blood was added to a tube containing sodium heparin. Cats also received lactated Ringer's solution (25 mL/kg, SC) once to ensure adequate hydration, as water had been withheld from the cats during the study day for anesthesia purposes.

Blood samples were submitted for measurement of serum TXB2 concentration and plasma PGE2 and LTB4 stimulation assays. Pyloric and duodenal mucosal biopsy specimens were submitted for PGE1 and PGE2 synthesis assays and measurement of LTB4 concentration.

Serum TXB2 concentration—A siliconized glass tube containing 4 mL of blood was immediately placed into a 37°C water bath and incubated for 1 hour. Indomethacin[e] (final concentration, 30μM) was subsequently added to stop additional TXB2 synthesis. Tubes were centrifuged at 12,000 × *g* for 10 minutes, serum was harvested, and 100 μL of serum was added to 400 μL of methanol. After centrifugation at 12,000 × *g* for an additional 5 minutes, the supernatant was collected

and stored at –80°C until assayed with an ELISA[f] as described elsewhere.[18] The serum interassay variation was < 22%, and the lower LOQ for the assay was 11 pg/mL.

Plasma PGE2 synthesis—For each blood sample, 500 µL of sodium-heparinized blood was transferred to a microcentrifuge tube. Ten microliters of bacterial lipopolysaccharide (*Escherichia coli* serotype O111:B4)[f] was added to each tube to stimulate PGE2 production. Samples were incubated for 24 hours in a 37°C water bath and centrifuged at 12,000 × *g* for 5 minutes, and the plasma was harvested. Solid-phase extraction was performed, and PGE2 was measured by use of an appropriate ELISA[e] as described elsewhere.[18] The serum interassay variations were < 22%, and the lower LOQ for the assay was 36 pg/mL.

Plasma LTB4 synthesis—For each blood sample, 1.0 mL of sodium-heparinized blood was transferred into a microcentrifuge tube and challenged with calcium ionophore A23187[f] to stimulate LTB4 production, as described.[18] Briefly, tubes were placed in a 37°C water bath for 15 minutes, followed by an ice bath for 5 minutes. Samples were centrifuged at 12,000 × *g* for 5 minutes, and the plasma was harvested and stored at –80°C until analyzed with an appropriate ELISA.[e] The serum interassay variation was < 26%, and the lower LOQ for the assay was 1.0 pg/mL.

Gastric mucosal PGE1 synthesis—All endoscopic biopsy specimens were processed within 8 minutes after collection from the stomach. Specimens were placed in microtubes containing 1.0 mL of Tris buffer and were weighed. Specimens weighing < 2 mg were discarded. Prostaglandin E1 synthesis was stimulated by mincing of tissue as described elsewhere.[19] After a 3-minute incubation period, samples were centrifuged at 12,000 × *g* for 15 seconds and the supernatant was removed. Then, 1.0 mL of fresh Tris buffer was added, the contents were mixed for 3 minutes by use of a vortex machine and centrifuged at 12,000 × *g* for 15 seconds to pellet the tissue, and the supernatant was harvested and stored at –80°C until analysis with an appropriate ELISA.[g] The mucosal interassay variation was < 24%, and the lower LOQ for the assay was 5.5 pg/mL.

Gastric mucosal PGE2 synthesis—Samples were prepared identically to the aforementioned PGE1 protocol. Samples were stored at –80°C until analysis with an appropriate ELISA.[e] The mucosal interassay variation was < 27%, and the lower LOQ for the assay was 36 pg/mL.

Gastric mucosal LTB4 concentration—Biopsy specimens were placed in 1 mL of Tris buffer, weighed, finely minced for 15 seconds, mixed with a vortex device for 3 minutes, and pelleted. The supernatant was removed and stored at –80°C until LTB4 concentrations were measured by use of an ELISA.[10,e] The mucosal interassay variation was < 35%, and the lower LOQ for the assay was 11 pg/mL.

Statistical analysis—A Kolmogorov-Smirnov test was used to test eicosanoid data for normality of distribution for each treatment and time separately for data expressed as actual change from baseline values, percentage change from baseline values, and actual numbers (raw data). Histograms of eicosanoid data were also examined for severe departures from normality. For the change-from-baseline data, 85% of the distributions tested did not fail the normality test, whereas for the relative-change-from-baseline data, 72% of the distributions tested did not fail the normality test. For the raw data, 80% of the distributions tested did not fail the normality test. Therefore, for this study, change-from-baseline data were used for the various analyses. A repeated-measures model[h] that recognized multiple observations as belonging to the same cat was used to

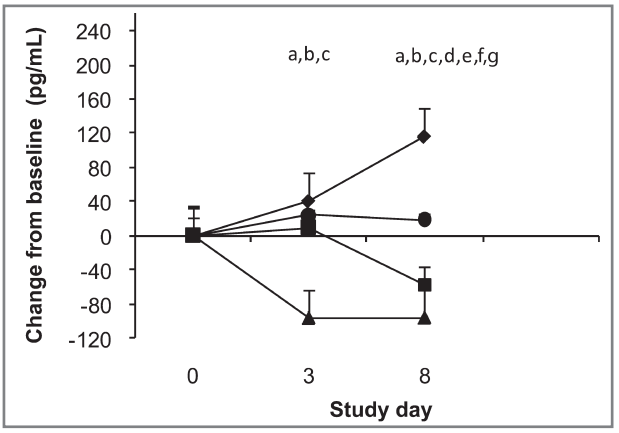

Figure 1—Mean ± SE change from baseline serum TXB2 concentrations in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). [a]Value for firocoxib differs significantly ($P \leq 0.05$) from the corresponding tepoxalin value. [b]Value for tepoxalin differs significantly from the corresponding placebo value. [c]Value for tepoxalin differs significantly from the corresponding baseline value. [d]Value for meloxicam differs significantly from the corresponding baseline value. [e]Value for the placebo differs significantly from the corresponding baseline value. [f]Value for meloxicam differs significantly from the corresponding placebo value. [g]Value for firocoxib differs significantly from the corresponding meloxicam value.

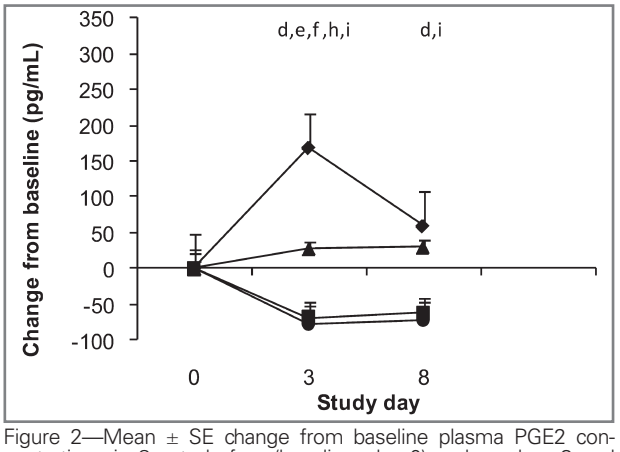

Figure 2—Mean ± SE change from baseline plasma PGE2 concentrations in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). [h]Value for firocoxib differs significantly ($P \leq 0.05$) from the corresponding placebo value. [i]value for firocoxib differs significantly from the corresponding baseline value. *See* Figure 1 for remainder of key.

test for differences between assay change-from-baseline data among treatments and between days of collection (3 and 8). The full model included factors for treatment, study day, and the interaction between the 2. Multiple comparisons were adjusted for by use of the Tukey test. An unstructured covariance structure was used in all repeated-measures models. All hypothesis tests were 2-sided. A value of $P \leq 0.05$ was used to indicate significance in all analyses.

Results

Cats—All cats completed the entire study without complication or adverse events.

Serum TXB2 concentration—Serum TXB2 concentrations on days 3 and 8 during firocoxib administration did not differ significantly from baseline or respective placebo values (**Figure 1**). On the other hand, the TXB2 concentration on day 8 was significantly lower during meloxicam administration than the baseline value ($P = 0.04$) and the placebo ($P < 0.001$) and firocoxib ($P = 0.035$) values on day 8. The TXB2 concentration during tepoxalin administration was significantly lower than the baseline value on days 3 ($P < 0.001$) and 8 ($P < 0.001$). It was also lower on days 3 and 8 than the corresponding placebo values ($P = 0.02$ and $P < 0.001$, respectively) and firocoxib values ($P < 0.001$ and $P = 0.002$, respectively).

Plasma PGE2 synthesis—Plasma PGE2 concentrations during firocoxib administration and meloxicam administration were significantly lower than the baseline value on days 3 ($P = 0.008$ and $P = 0.001$, respectively) and 8 ($P = 0.006$ and $P = 0.001$, respectively) and the placebo value on day 3 ($P = 0.02$ and $P = 0.004$, respectively; **Figure 2**). Plasma PGE2 concentrations on days 3 and 8 during tepoxalin administration did not differ significantly from baseline or respective placebo values.

Plasma LTB4 concentrations—No significant decrease was noted in plasma LTB4 concentrations in cats administered placebo, firocoxib, meloxicam, or tepoxalin at any time in this study (**Figure 3**).

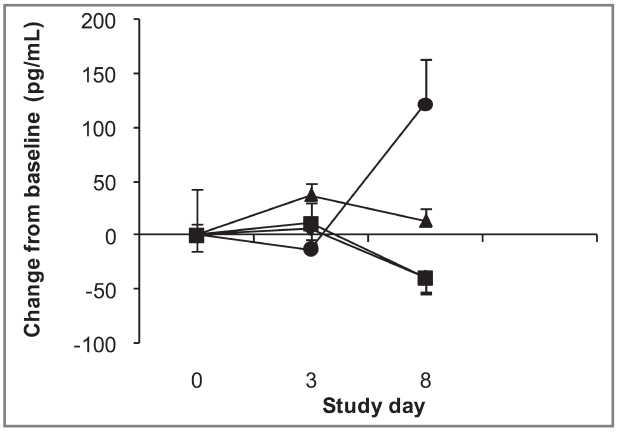

Figure 3—Mean ± SE change from baseline plasma LTB4 concentrations in 8 cats before (baseline; day 0) and on days 3 and 8 during administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles).

Pyloric mucosal PGE1 synthesis—Firocoxib administration resulted in significantly ($P = 0.014$) less pyloric mucosal PGE1 synthesis on day 8 than at baseline; however, its effect was no different from that of the placebo on days 3 and 8 (**Figure 4**). Values on days 3 and 8 during meloxicam administration were similar to those at baseline or during placebo administration. Pyloric mucosal PGE1 synthesis increased from the baseline value on days 3 ($P = 0.005$) and 8 ($P = 0.003$) but did not differ significantly from corresponding placebo values. Furthermore, the placebo value was significantly ($P = 0.045$) lower than the baseline value on day 8.

Duodenal mucosal PGE1 synthesis—Tepoxalin was unable to be measured in duodenum samples at day 8 because concentrations were lower than the detectable limit of the assay when samples were tested without dilution. No significant decrease from baseline

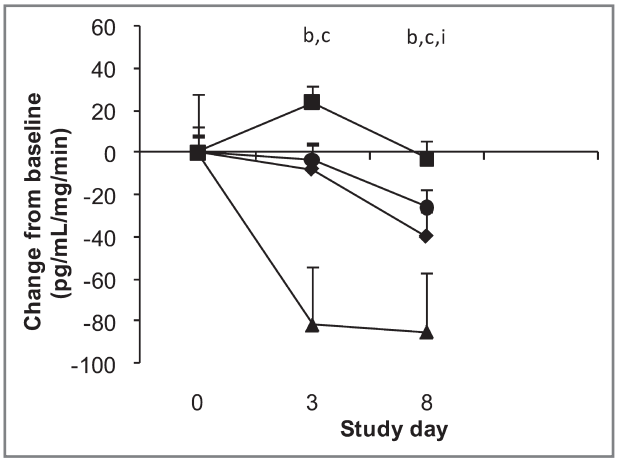

Figure 4—Mean ± SE change from baseline pyloric mucosal PGE1 synthesis in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). *See* Figures 1 and 2 for remainder of key.

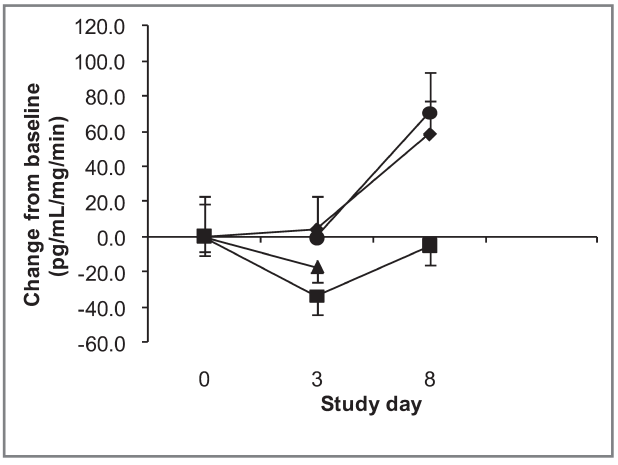

Figure 5—Mean ± SE change from baseline duodenal mucosal PGE1 synthesis in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). *See* Figure 1 for key.

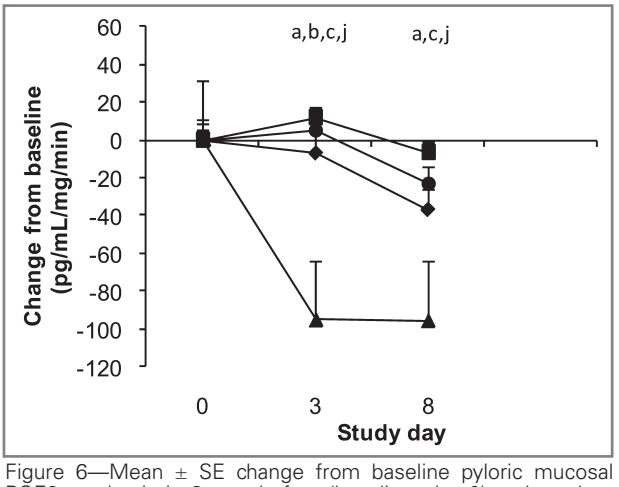

Figure 6—Mean ± SE change from baseline pyloric mucosal PGE2 synthesis in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). [1]Value for meloxicam differs significantly ($P \leq 0.05$) from the corresponding value for tepoxalin. *See* Figure 1 for remainder of key.

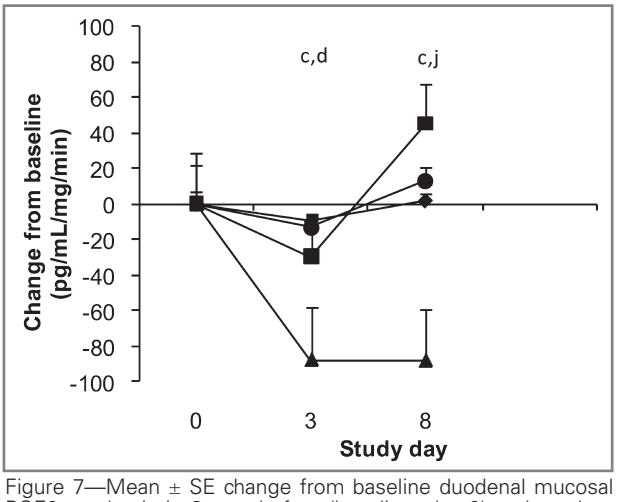

Figure 7—Mean ± SE change from baseline duodenal mucosal PGE2 synthesis in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). *See* Figures 1 and 6 for key.

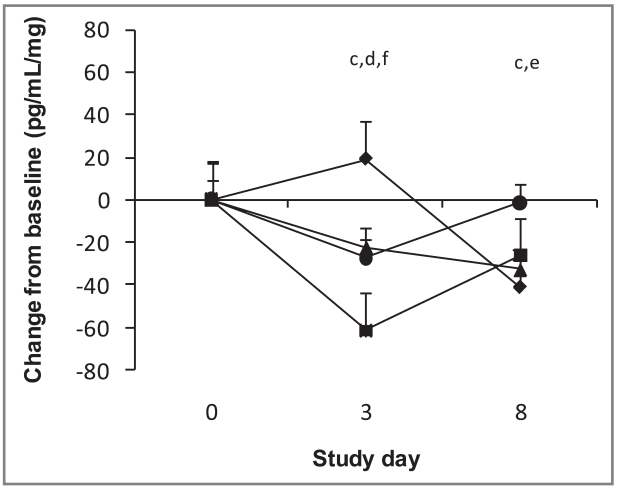

Figure 8—Mean ± SE change from baseline pyloric mucosal LTB4 concentrations in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles). *See* Figure 1 for key.

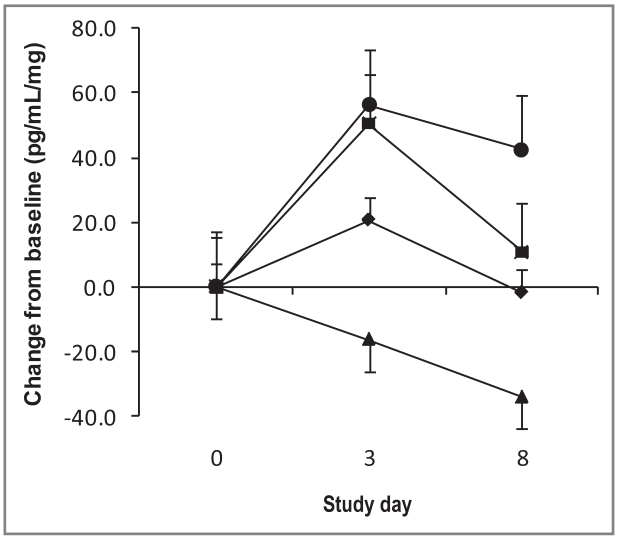

Figure 9—Mean ± SE change from baseline duodenal mucosal LTB4 concentrations in 8 cats before (baseline; day 0) and on days 3 and 8 during PO administration of a placebo (diamonds), firocoxib (1 mg/kg, q 24 h; circles), meloxicam (0.05 mg/kg, q 24 h; squares), or tepoxalin (5.0 mg/kg, q 12 h; triangles).

or corresponding placebo values was evident for duodenal mucosal PGE1 synthesis on days 3 and 8 during meloxicam administration (**Figure 5**). However, there was significantly greater synthesis of PGE1 on day 8 during firocoxib administration, compared with synthesis at baseline. No significant changes from baseline or placebo values were evident on day 3 of tepoxalin administration; data were insufficient to analyze the effect of tepoxalin at day 8.

Pyloric mucosal PGE2 synthesis—Neither firocoxib nor meloxicam administration resulted in lower pyloric mucosal PGE2 synthesis on days 3 and 8, compared with baseline or corresponding placebo values (**Figure 6**). Tepoxalin administration resulted in a significant decrease in PGE2 synthesis relative to the baseline value on days 3 ($P < 0.001$) and 8 ($P < 0.001$); however, the decrease relative to placebo values was evident only on day 3 ($P < 0.002$). Pyloric mucosal PGE2 synthesis was also lower on days 3 and 8 during tepoxalin administration than it was during firocoxib ($P = 0.008$ and $P = 0.008$, respectively) and meloxicam ($P = 0.001$ and $P = 0.02$, respectively) administration.

Duodenal mucosal PGE2 synthesis—Firocoxib administration had no effect on duodenal mucosal PGE2 synthesis on days 3 and 8, compared with baseline or placebo administration (**Figure 7**). Meloxicam administration resulted in a significant ($P = 0.03$) decrease in PGE2 synthesis on day 3, compared with baseline. Tepoxalin administration resulted in lower duodenal mucosal PGE2 synthesis on days 3 ($P = 0.001$) and 8

($P < 0.001$) relative to the baseline value and on day 8 relative to the meloxicam value ($P = 0.05$).

Pyloric and duodenal mucosal LTB4 concentrations—Placebo administration resulted in a significant ($P = 0.002$) decrease from the baseline LTB4 concentration on day 8 in pyloric mucosal tissue (**Figure 8**). Meloxicam administration resulted in lower pyloric mucosal LTB4 concentrations on day 3 than at baseline ($P = 0.002$) or during placebo administration ($P = 0.05$). Tepoxalin administration resulted in lower pyloric mucosal LTB4 concentrations on days 3 ($P = 0.04$) and 8 ($P = 0.02$), compared with the baseline value. None of the treatments resulted in changes in duodenal mucosal LTB4 concentrations (**Figure 9**).

Discussion

The present study was designed to determine the effects of firocoxib, meloxicam, and tepoxalin administration on eicosanoid synthesis in clinically normal cats. Results supported the hypothesis that, at the dose administered, firocoxib would be COX-1 sparing. However, findings were less convincing regarding the hypotheses that, at the doses and frequencies administered, meloxicam would be COX-1 sparing, tepoxalin would have nonspecific COX inhibitory activity, and tepoxalin would have 5-LO inhibitory activity.

In our study, administration of firocoxib to cats at a dosage of 1.0 mg/kg once daily resulted in COX-2 isoform inhibition as demonstrated by the significant decrease from baseline in plasma PGE2 concentration on days 3 and 8. Firocoxib administration did not result in COX-1 isoform inhibition. Compared with the baseline value or the effect of placebo administration on days 3 and 8, firocoxib had no effect on serum TXB2 concentration or on the duodenal and mucosal synthesis of PGE1 and PGE2. Pyloric mucosal PGE1 synthesis on day 8 was lower than that at baseline but was not significantly different from the corresponding placebo value. This was the only finding that did not support the hypothesis that firocoxib was COX-1 sparing in healthy cats at the dose given. The reason baseline and placebo values were dissimilar was unclear; however, given the preponderance of evidence suggesting a COX-1 sparing effect of firocoxib, we put less importance on this 1 deviance from baseline values. Overall, our data were consistent for those collected similarly in dogs.[20] They were also consistent with in vitro data in cats.[15,i]

In the study reported here, PO meloxicam administration to cats at the dose of 0.05 mg/kg once daily resulted in COX-2 inhibition. The meloxicam data were similar to those of firocoxib, with significant reductions in plasma PGE2 concentrations, compared with values for the placebo at day 3.

With regard to COX-1 sparing effects, meloxicam administration yielded mixed results. Serum TXB2 concentrations were lower on day 8 during meloxicam administration than the baseline and corresponding placebo values. However, no changes in pyloric mucosal PGE1 and PGE2 synthesis were associated with meloxicam; likewise, duodenal PGE1 and PGE2 synthesis was unaffected except on day 3, upon which PGE2 synthesis was lower than at baseline. Thus, most of the evidence reported here suggests that with short-term, low-dose administration, meloxicam has a COX-1 sparing effect. These data are consistent with in vitro findings that meloxicam has COX-1 sparing activity as indicated by a COX-1-to-COX-2 ratio > 1.[8,i] The degree of COX-1 inhibitory activity appears to be dose related. One study[21] involving cats revealed that meloxicam, when administered after IV endotoxin challenge in cats, has significant antipyretic effects, with lower doses of meloxicam resulting in a decreased effect. In that study, a dose of 0.1 mg/kg did not result in as large an antipyretic response as the 0.3 or 0.5 mg/kg dose in cats. The febrile response is postulated to involve prostaglandin production stimulated by COX-1 and COX-2,[22] and therefore, dose differences may have affected COX isoform activity. In addition to COX inhibitory activity, meloxicam transiently decreased the pyloric mucosal LTB4 concentration on day 3, which may suggest some effects on LTB4 as reported in humans and to some degree in dogs.[11,23]

In the study cats, tepoxalin administration at the dose used had no effect on plasma PGE2 concentration, indicating a lack of COX-2 inhibitory activity for tepoxalin. The fact that tepoxalin significantly decreased pyloric and duodenal mucosal synthesis of PGE1 and PGE2 does not suggest that some COX-2 activity was inhibited. However, without confirmation from another target tissue in which the amount of prostaglandin measured can be attributed entirely to COX-2 activity, our study did not yield conclusive evidence that at the dose administered, tepoxalin had a significant COX-2 inhibitory effect. Certainly, the significant decrease in serum TXB2 concentrations and in pyloric and duodenal mucosal synthesis of PGE1 and PGE2 confirm the COX-1 inhibitory actions of tepoxalin. The drug did appear to have some 5-LO inhibitory effect, as suggested by the significant decrease in pyloric mucosal LTB4 concentration on days 3 and 8 of administration.

The inhibitory profile of tepoxalin administration in cats can be compared with that in dogs. In dogs, tepoxalin is a dual inhibitor of COX and 5-LO enzymes, decreasing the production of prostaglandins, thromboxanes, and leukotrienes in target tissues.[11] Although the ability of tepoxalin to inhibit COX-1 and 5-LO in the cats of the present study is similar to that in dogs, the drug did not have similar COX-2 inhibitory activity when compared with the canine data. Yet, a closer look at the canine data revealed that tepoxalin has less of an inhibitory effect on PGE2 synthesis in the plasma when compared with the effects of meloxicam and firocoxib.[11,20] Therefore, the lack of COX-2 inhibition in our study may have been the result of the dose or frequency of tepoxalin administration, duration of administration, or differences in feline and canine drug pharmacodynamics. It is also possible that some COX-2 activity would have been detected in a target tissue different from those evaluated in our study.

The few situations in which agreement was lacking between differences from baseline and placebo values for the drugs evaluated are not easy to explain. They may have been attributable to small sample sizes and the potential for committing a type II error. In those situations, we believe it is appropriate to carefully con-

sider the reported significant differences and interpret them with respect to other results involving the drug. Furthermore, the fact that only male cats were included in the study must be considered when interpreting the results. Overall, we found that firocoxib, meloxicam, and tepoxalin at the doses administered resulted in various amounts of COX-1 and COX-2 isoform inhibition. Findings for meloxicam and tepoxalin administration suggested some ability of these drugs to inhibit 5-LO activity; however, this effect was not consistent throughout the study.

a. Zubrin, Schering-Plough Corp, Kenilworth, NJ.
b. Previcox, Merial, Duluth, Ga.
c. Metacam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
d. Dammgen J. The use of metacam 0.5 mg/mL oral suspension in cats with osteoarthritis, in *Proceedings*. Metacam Symp Arthritic Dis Cats 2007;19–20.
e. Cayman Chemical Co, Ann Arbor, Mich.
f. Sigma Chemical Co, St Louis, Mo.
g. Assay Designs, Ann Arbor, Mich.
h. PROC MIXED, SAS, version 9.1, SAS Institute Inc, Cary, NC.
i. Punke JP, Reynolds LR, Speas AL, et al. In vitro assessment of cyclooxygenase selectivity of several nonsteroidal anti-inflammatory drugs in feline whole blood (abstr). *J Vet Int Med* 2007;21:616.

References

1. Kargman S, Charleson S, Cartwright M, et al. Characterization of prostaglandin G/H synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. *Gastroenterology* 1996;111:445–454.
2. Cheng T, Cao W, Wen R, et al. Prostaglandin E2 induces vascular endothelial growth factor and basic fibroblast growth factor mRNA expression in cultured rat Muller cells. *Invest Ophthalmol Vis Sci* 1998;39:581–591.
3. Hirose M, Miwa H, Kobayashi O, et al. Inhibition of proliferation of gastric epithelial cells by a cyclooxygenase 2 inhibitor, JTE522, is also mediated by a PGE2-independent pathway. *Aliment Pharmacol Ther* 2002;16(suppl 2):83–89.
4. Khan KN, Venturini CM, Bunch RT, et al. Interspecies differences in renal localization of cyclooxygenase isoforms: implications in nonsteroidal antiinflammatory drug-related nephrotoxicity. *Toxicol Pathol* 1998;26:612–620.
5. Tanaka A, Hase S, Miyazawa T, et al. Role of cyclooxygenase (COX)-1 and COX-2 inhibition in nonsteroidal anti-inflammatory drug-induced intestinal damage in rats: relation to various pathogenic events. *J Pharmacol Exp Ther* 2002;303:1248–1254.
6. Brooks P, Emery P, Evans JF, et al. Interpreting the clinical significance of the differential inhibition of cyclooxygenase-1 and cyclooxygenase-2. *Rheumatology (Oxford)* 1999;38:779–788.
7. Streppa HK, Jones CJ, Budsberg SC. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs in canine blood. *Am J Vet Res* 2002;63:91–94.
8. Giraudel JM, Toutain PL, Lees P. Development of in vitro assays for the evaluation of cyclooxygenase inhibitors and predicting selectivity of nonsteroidal anti-inflammatory drugs in cats. *Am J Vet Res* 2005;66:700–709.
9. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:413–421.
10. Sessions JK, Reynolds LR, Budsberg SC. In vivo effects of carprofen, deracoxib, and etodolac on prostanoid production in blood, gastric mucosa, and synovial fluid in dogs with chronic osteoarthritis. *Am J Vet Res* 2005;66:812–817.
11. Agnello KA, Reynolds LR, Budsberg SC. In vivo effects of tepoxalin, an inhibitor of cyclooxygenase and lipoxygenase, on prostanoid and leukotriene production in dogs with chronic osteoarthritis. *Am J Vet Res* 2005;66:966–972.
12. Al-Gizawiy MM, P Rudé E. Comparison of preoperative carprofen and postoperative butorphanol as postsurgical analgesics in cats undergoing ovariohysterectomy. *Vet Anaesth Analg* 2004;31:164–174.
13. Carroll GL, Howe LB, Peterson KD. Analgesic efficacy of preoperative administration of meloxicam or butorphanol in onychectomized cats. *J Am Vet Med Assoc* 2005;226:913–919.
14. Lascelles BD, Hansen BD, Roe S, et al. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *J Vet Intern Med* 2007;21:410–416.
15. McCann ME, Rickes EL, Hora DF, et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. *Am J Vet Res* 2005;66:1278–1284.
16. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study of 28 cases. *J Small Anim Pract* 2006;47:439–445.
17. Gunew MN, Menrath VH, Marshall RD. Long-term safety, efficacy and palatability of oral meloxicam at 0.01–0.03mg/kg for treatment of osteoarthritic pain in cats. *J Feline Med Surg* 2008;10:235–241.
18. Jones CJ, Streppa HK, Harmon BG, et al. In vivo effects of meloxicam and aspirin on blood, gastric mucosal, and synovial fluid prostanoid synthesis in dogs. *Am J Vet Res* 2002;63:1527–1531.
19. Argentieri DC, Ritchie DM, Ferro MP, et al. Tepoxalin: a dual cyclooxygenase/5-lipoxygenase inhibitor of arachidonic acid metabolism with potent anti-inflammatory activity and a favorable gastrointestinal profile. *J Pharmacol Exp Ther* 1994;271:1399–1408.
20. Punke JP, Reynolds LR, Speas AL, et al. Effects of firocoxib, meloxcam, and tepoxalin on prostanoid and leukotriene production on the duodenum, and other tissues of osteoarthritic dogs. *Am J Vet Res* 2008;69:1203–1209.
21. Justus C, Quirke JF. Dose-response relationship for the antipyretic effect of meloxicam in an endotoxin model in cats. *Vet Res Commun* 1995;19:321–330.
22. Blatteis CM. The onset of fever: new insights into its mechanism. *Prog Brain Res* 2007;162:3–14.
23. Chang DM, Young TH, Hsu C, et al. Endoscopic comparison of the gastroduodenal safety and the effects on arachidonic acid products between meloxicam and piroxicam in the treatment of osteoarthritis. *Clin Rheumatol* 2001;20:104–113.