Comparison of the effects of IV administration of meloxicam, carprofen, and flunixin meglumine on prostaglandin E₂ concentration in aqueous humor of dogs with aqueocentesis-induced anterior uveitis

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Objective—To compare the effects of meloxicam, carprofen, and flunixin meglumine administered IV on the concentration of prostaglandin E₂ (PGE₂) in the aqueous humor of dogs with aqueocentesis-induced anterior uveitis.

Animals—15 adult dogs with ophthalmically normal eyes.

Procedures—Each dog was assigned to 1 of 4 treatment groups. Treatment groups were saline (0.9% NaCl solution [1 mL, IV], meloxicam (0.2 mg/kg, IV), carprofen (4.4 mg/kg, IV), and flunixin meglumine (0.5 mg/kg, IV). Each dog was anesthetized, treatment was administered, and aqueocentesis was performed on each eye at 30 and 60 minutes after treatment. Aqueous humor samples were frozen at −80°C until assayed for PGE₂ concentration with an enzyme immunoassay kit.

Results—For all 4 treatment groups, PGE₂ concentration was significantly higher in samples obtained 60 minutes after treatment, compared with that in samples obtained 30 minutes after treatment, which indicated aqueocentesis-induced PGE₂ synthesis. For aqueous humor samples obtained 60 minutes after treatment, PGE₂ concentration did not differ significantly among groups treated with saline solution, meloxicam, and carprofen; however, the PGE₂ concentration for the group treated with flunixin meglumine was significantly lower than that for each of the other 3 treatment groups.

Conclusions and Clinical Relevance—Flunixin meglumine was more effective than meloxicam or carprofen for minimizing the PGE₂ concentration in the aqueous humor of dogs with experimentally induced uveitis. Flunixin meglumine may be an appropriate premedication for use prior to intraocular surgery in dogs. (Am J Vet Res 2012;73:698–703)
COX-1 synthesizes prostaglandins required for tissue homeostasis, such as gastric cytoprotection, renal blood flow regulation, and platelet function. In contrast, COX-2 synthesizes prostaglandins primarily at sites of inflammation, although it does have a small role in homeostasis of the CNS, kidneys, reproductive tract, and vascular endothelium, and it is required for the repair of gastric ulcers.\textsuperscript{10,11} Although many studies\textsuperscript{12-14} have been conducted to investigate the selective or preferential inhibition of COX isoenzymes, results have varied depending on the species and method of testing used.

In dogs, the use of selective or preferential COX-2 inhibitors is thought to help prevent adverse effects on the kidneys and gastrointestinal tract that have been associated with COX-1 inhibitors. The NSAIDs currently approved for parenteral use in dogs are carprofen (selective COX-2 inhibitor) and meloxicam (preferential COX-2 inhibitor). Carprofen is approved for SC administration but is commonly administered IV in clinical practice. In the study reported here, carprofen was administered IV to maintain consistency in the treatment protocol and to mimic common presurgical use. Flunixin meglumine (preferential COX-1 inhibitor) is not approved for use in dogs but has been used in an extra-label manner for years for its anti-inflammatory and analgesic effects, including prior to intraocular surgery to minimize subsequent inflammation.\textsuperscript{7,8,17} The purpose of this study was to compare the effects of 3 NSAIDs (carprofen, meloxicam, and flunixin meglumine) administered IV on the concentration of PGE\textsubscript{2} in the aqueous humor of dogs with aqueocentesis-induced anterior uveitis.

**Materials and Methods**

**Animals**—Fifteen adult dogs that weighed between 8 and 31 kg were used in the present study. Eight were sexually intact male Beagles (university-owned research dogs). Seven were mixed-breed shelter-owned dogs (3 sexually intact females, 1 spayed female, and 3 sexually intact males); informed consent for each dog was obtained from authorized shelter personnel. All dogs underwent an ophthalmic examination that included biomicroscopy, indirect ophthalmoscopy, rebound tonometry, and fluorescein staining the day before inclusion in the study. The study protocol was approved by the Oklahoma State University Institutional Animal Care and Use Committee.

**Procedures**—The Beagles were sequentially assigned to each group in the order of their identification numbers, and the shelter dogs were sequentially assigned to each group in the order they were received at the shelter service for study enrollment. Dogs were allocated into 4 groups: control group (n = 3), meloxicam–treated group (4), carprofen–treated group (4), and flunixin meglumine–treated group (4). Each dog was premedicated with morphine (0.5 mg/kg, IM) and glycopyrrolate (0.01 mg/kg, IM). For each dog, anesthesia was induced with propofol (6 to 8 mg/kg, IV to effect) and maintained with isoflurane, and an isotonic, balanced electrolyte solution\textsuperscript{1} was administered (10 mL/kg/h, IV) for the duration of anesthesia. Dogs were positioned in sternal recumbency. Once anesthetized, each dog received saline (0.9% NaCl) solution (1 mL; control group), meloxicam (0.2 mg/kg), carprofen (4.4 mg/kg), or flunixin meglumine (0.5 mg/kg) IV in accordance with its treatment group allocation. Thirty minutes after treatment administration, controlled aqueocentesis was performed on each eye. A 27-gauge needle was inserted at the limbus and directed 1 mm through the corneal stroma into the anterior chamber to a depth of 1 mm. Aqueous humor (0.15 mL) was slowly aspirated into a 1-mL syringe over a period of 30 seconds. Anesthesia was maintained, and aqueocentesis was repeated on all eyes 60 minutes after treatment administration. Each controlled aqueocentesis was performed by the same investigator (MAG). Immediately following aqueocentesis at 60 minutes after treatment, all dogs were allowed to recover from anesthesia. Dogs in the control group were administered carprofen (4.4 mg/kg, SC) during the period between discontinuation of the isoflurane and extubation, and all dogs received 1% atropine sulfate solution and 1% prednisolone acetate solution topically in each eye. Administration of 1% prednisolone acetate was continued every 12 hours for 24 to 48 hours. All dogs were monitored for 48 hours for signs of pain (blepharospasm and epiphora) and signs of active uveitis (aqueous flare, miosis, and hypopyon).

**Measurement of PGE\textsubscript{2} concentration**—The aqueocentesis performed 30 minutes after treatment administration was used to obtain samples of aqueous humor for baseline measurement of PGE\textsubscript{2} concentrations and to induce uveitis. The aqueocentesis performed 60 minutes after treatment administration was used to obtain samples of aqueous humor for determining changes in PGE\textsubscript{2} concentrations. Samples of aqueous humor were frozen and stored at –80°C until assayed. Samples were thawed, and the PGE\textsubscript{2} concentration was immediately measured with a commercial PGE\textsubscript{2} monoclonal enzyme immunoassay kit.\textsuperscript{3} All samples were measured in triplicate with no dilution. Because of the limited volume of each sample, it was not possible to assay samples at multiple dilutions. One assay plate containing samples from 3 dogs (1 each from the meloxicam-, carprofen-, and flunixin meglumine–treated groups) did not develop properly, which affected the absorbance values obtained from the plate reader for that plate. Data from these 3 dogs were discarded, which resulted in data from 3 dogs/treatment group (6 eyes) for analyses. The upper detection limit of the assay was 1,000 pg/mL; therefore, when necessary, the PGE\textsubscript{2} concentration of the samples was truncated at 1,000 pg/mL during statistical analyses.

**Data analysis**—All data were analyzed with commercially available software.\textsuperscript{7} Homogeneity of variance was determined with the Levene test. Significant heterogeneity of variance was detected between samples; therefore, a natural logarithmic transformation of PGE\textsubscript{2} concentrations was used to alleviate heterogeneity during analyses. Comparisons of PGE\textsubscript{2} concentrations by treatment group and eye (right vs left) were performed via an ANOVA, with time after treatment administration included as an independent variable in each model. No effect of eye (right vs left) was detected within time after treatment administration; therefore, the
mean PGE₂ concentration was calculated for each dog at each time after treatment administration and used for all subsequent analyses. Protected pairwise t tests were used to compare PGE₂ concentrations between treatment groups. Nonparametric methods (Kruskal-Wallis tests) were used to compare PGE concentration in samples obtained 30 minutes after treatment with that in samples obtained 60 minutes after treatment. Nontransformed means and SEs were reported, and values of P < 0.05 were considered significant for all analyses.

**Results**

**Animals**—No clinically relevant abnormalities were found in any of the dogs during the ophthalmic examinations performed prior to study enrollment. One dog had multiple hyperreflective scars in the tapetum fundus of the right eye. After the aqueocenteses were performed, no signs of pain were observed in any

Table 1—Mean ± SE (range) PGE₂ concentration as determined with an enzyme immunoassay in samples of aqueous humor obtained via aqueocentesis from both eyes of 12 anesthetized dogs 30 (baseline) and 60 minutes after administration of saline (0.9% NaCl) solution (1 mL, IV; [n = 3]; control), meloxicam (0.2 mg/kg, IV; [3]), carprofen (4.4 mg/kg, IV; [3]), or flunixin meglumine (0.5 mg/kg, IV; [3]).

<table>
<thead>
<tr>
<th>Group</th>
<th>PGE₂ concentration (pg/mL)</th>
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<tbody>
<tr>
<td></td>
<td>30 minutes after treatment</td>
</tr>
<tr>
<td>Control</td>
<td>5.45 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>(4.42–6.35)</td>
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<tr>
<td>Meloxicam</td>
<td>4.90 ± 0.47</td>
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<td></td>
<td>(3.57–6.11)</td>
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<tr>
<td>Carprofen</td>
<td>4.46 ± 0.46</td>
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<td></td>
<td>(3.36–5.91)</td>
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<tr>
<td>Flunixin meglumine</td>
<td>6.73 ± 1.24</td>
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<tr>
<td></td>
<td>(3.69–10.50)</td>
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*Within a column, value differs significantly (P < 0.05) from the value for each of the other 3 treatments.

In the study reported here, IV administration of flunixin meglumine was more effective than IV administration of carprofen or meloxicam for minimizing the synthesis of PGE₂, in dogs with experimentally induced anterior uveitis, and these results may have clinical relevance for dogs that require intraocular surgery. Aqueocentesis has been used to experimentally induce uveitis by the disruption of the blood-aqueous barrier in several species, including dogs.1,3,5,6,18–26 When the cornea is perforated, there is an acute decrease in intraocular pressure that initiates the release of prostaglandins from cells of the anterior uvea. This has been confirmed directly by the measurement of prostaglandin concentrations in the aqueous humor and indirectly by the measurement of protein concentrations in the aqueous humor, which increase as a result of PGE₂-mediated breakdown of the blood-aqueous barrier.1,3,5,6,8,9,19 Therefore, the aqueocentesis-induction method of anterior uveitis is appropriate for assessing the effects of drugs administered prior to intraocular surgery on the synthesis of PGE₂ by cells of the anterior uvea. In the present study, the increase in PGE₂ concentration in samples of aqueous humor obtained 60
minutes after treatment, compared with that in samples of aqueous humor obtained 30 minutes after treatment, for the control (saline solution–treated) group indicated that aqueocentesis was an effective method for the induction of PGE₂ in aqueous humor.

Concentrations of PGE₂ varied substantially in the aqueous humor samples obtained 60 minutes after treatment for all treatment groups, except for the flunixin meglumine–treated group. For example, the mean PGE₂ concentration in the aqueous humor for 1 dog in the carprofen–treated group was 44.43 pg/mL, whereas the PGE₂ concentrations for the other 2 dogs in that group were 686 and > 1,000 pg/mL. This difference may have been caused by the variable effects of carprofen and meloxicam between dogs or a lack of precision in the measurement of higher concentrations of PGE₂. The enzyme immunoassay used in the present study has the ability to accurately and precisely detect low PGE₂ concentrations, but it becomes less precise as the PGE₂ concentration increases. Although the flunixin meglumine–treated group had the highest baseline PGE₂ concentration, the PGE₂ concentrations detected in samples obtained 60 minutes after treatment were relatively low and consistent (range, 10 to 18 pg/mL) in all 6 eyes from the 3 dogs, which was in contrast to the much higher PGE₂ concentrations and larger ranges detected in the other 3 treatment groups 60 minutes after treatment.

To our knowledge, few studies have been conducted to evaluate the effect of parenterally administered carprofen on the concentration of PGE₂ in aqueous humor, and no studies have been conducted to evaluate the effect of IV administration of meloxicam on the concentration of PGE₂ in aqueous humor. In 1 study, following IV administration of a single dose of carprofen, investigators measured the PGE₂ concentration in aqueous humor samples obtained before and after cataract surgery in dogs with and without uveitis and found no significant difference between carprofen–treated and untreated control dogs. Investigators in another study evaluated the effect of SC administration of carprofen in dogs with aqueocentesis–induced uveitis and found no significant difference between the PGE₂ concentrations in aqueous humor samples obtained from treated and control dogs.

In the present study, there was no significant difference in PGE₂ concentrations among dogs treated with meloxicam, carprofen, or saline solution (control). These results are similar to results of another study in which investigators evaluated orally administered tepoxalin, carprofen, and meloxicam for the control of aqueoucentesis–induced intraocular inflammation. In that study, orally administered tepoxalin inhibited PGE₂ synthesis significantly more than did meloxicam or carprofen. Tepoxalin is a COX-1 preferential inhibitor and also inhibits 5-lipoxygenase, which is required for leukotriene synthesis but does not affect prostaglandin synthesis. In the present study, flunixin meglumine, which is also a COX-1 inhibitor, inhibited PGE₂ synthesis significantly more than did meloxicam or carprofen. Results of these 2 studies indicate that COX-1 may have a more important role in anterior uveitis than has been assumed previously, and NSAIDs that inhibit COX-1 may be most appropriate for the premedication of patients prior to intraocular surgery.

In dogs, the use of a COX-1 inhibitor may raise concerns about renal function and the integrity of the gastrointestinal tract. Flunixin meglumine can cause gastrointestinal ulceration and perforation in dogs; however, these were associated with chronic oral administration or for a long duration. Dogs of the latter study were additionally compromised by dehydration or concurrent use of dexamethasone sodium phosphate. Investigators in 2 studies detected a significant reduction in PGE₂ synthesis in dogs treated with flunixin meglumine IV prior to experimental induction of uveitis. Both studies included the use of a higher dose of flunixin meglumine (1.1 and 2.2 mg/kg) than was used in the present study, and no significant difference in PGE₂ concentration was found between dogs receiving 1.1 and 2.2 mg/kg doses. The 0.5 mg/kg dose of flunixin meglumine was selected for the present study because it is the dose most commonly used prior to intraocular surgery. On the basis of our clinical experience and long-term observations, flunixin meglumine administered IV at a dose of 0.5 mg/kg and appropriate IV administration of fluids during anesthesia resulted in minimal adverse effects on renal function and the gastrointestinal tract. However, it is still prudent to consider the use of an NSAID that is a COX-2 inhibitor for the treatment of geriatric patients, patients with renal or gastrointestinal compromise, and patients currently receiving a COX-2–inhibitor NSAID. Although NSAIDs that are COX-2 inhibitors are considered to have a wide margin of safety, clinicians should be cognizant that their use has the potential for adverse effects such as signs of nausea, diarrhea, gastrointestinal ulcers with or without hemorrhage, nephrotoxicosis, platelet dysfunction, and idiosyncratic hepatotoxicosis. The most common adverse effect associated with preoperative, parenteral administration of an NSAID is nephrotoxicosis, whereas adverse effects on the gastrointestinal tract are more common with long-term, oral administration of NSAIDs. The risk of nephrotoxicosis during anesthesia can be reduced by monitoring blood pressure and appropriate IV administration of fluids.

The inability to accurately measure PGE₂ concentrations > 1,000 pg/mL was a limitation of the present study. Determination of the actual PGE₂ concentrations may have revealed even greater differences among treatment groups. For most of the samples, there was insufficient aqueous humor for serial dilutions to be performed in triplicate. In another study in which a few sample dilutions were performed for comparison, PGE₂ concentrations determined for diluted samples differed substantially from PGE₂ concentrations determined for undiluted samples. This may have been attributable to the loss of PGE₂ in the samples as a result of repeated freezing and thawing. In the present study, the loss of data for 3 dogs (6 eyes) limited the number of samples, and a larger sample size would have strengthened the validity of the results. However, even with the reduced sample size in the study reported here, the lower concentration of PGE₂ in aqueous humor samples obtained...
from dogs treated with flunixin meglumine, compared with the PGE$_2$ concentration in aqueous humor samples obtained from dogs treated with carprofen or meloxicam, would appear to be clinically meaningful. Also, the lower PGE$_2$ concentration in aqueous humor detected following administration of flunixin meglumine in the present study was similar to that detected following administration of tepoxalin, another preferential COX-1 inhibitor, in a previous study.

Flunixin meglumine administered IV was more effective than IV administration of carprofen or meloxicam for minimizing the concentration of PGE$_2$ in the aqueous humor of dogs with experimentally induced uveitis. The effects of carprofen and meloxicam on PGE$_2$ concentration did not differ from that of saline solution. Therefore, flunixin meglumine may be an appropriate choice for the premedication of dogs prior to intraocular surgery.

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