Effects of oral administration of anti-inflammatory medications on inhibition of paracentesis-induced blood-aqueous barrier breakdown in clinically normal cats

Amy J. Rankin, DVM, MS; Lionel Sebbag, DMV; Nora M. Bello, VMD, PhD; William R. Crumley, DVM; Rachel A. Allbaugh, DVM, MS

Objective—To assess inhibitory effects of orally administered anti-inflammatory medications on paracentesis-induced intraocular inflammation in clinically normal cats.

Animals—30 clinically normal domestic shorthair cats.

Procedures—Cats were randomly assigned to a control group and 4 treatment groups. Cats in the treatment groups received an anti-inflammatory medication orally once daily at 7 AM (acetylsalicylic acid [40.5 mg/cat], meloxicam [0.1 mg/kg], prednisone [5 mg/cat], or prednisolone [5 mg/cat]) for 5 days beginning 2 days before paracentesis-induced breakdown of the blood-aqueous barrier (BAB) and continuing until 2 days after paracentesis. Paracentesis of the anterior chamber was performed in 1 randomly selected eye of each cat. Fluorophotometry was performed in both eyes of each cat immediately before (time 0) and 6, 24, and 48 hours after paracentesis.

Results—At 24 and 48 hours after paracentesis, fluorescein concentration in the eye subjected to paracentesis in the cats receiving prednisolone was decreased, compared with that in the control cats. At 48 hours, a decrease in the fluorescein concentration was also apparent in the eye subjected to paracentesis in the cats receiving meloxicam, compared with that in the control cats. There was no evidence of treatment effects for acetylsalicylic acid or prednisone. There was no evidence of treatment effects in eyes not subjected to paracentesis.

Conclusions and Clinical Relevance—Orally administered prednisolone and meloxicam significantly decreased intraocular inflammation in clinically normal cats with paracentesis-induced BAB breakdown. Oral administration of prednisolone or meloxicam may be an effective treatment for cats with uveitis. (Am J Vet Res 2013;74:262–267)
Anti-inflammatory treatment includes the use of corticosteroids and NSAIDs. Corticosteroids bind to specific receptors in the cytoplasm of cells in the iris, choroid, sclera, cornea, conjunctiva, and retina and inhibit phospholipase A2 activity on phospholipids, which in turn prevents the biosynthesis of arachidonic acid and subsequent formation of prostacyclin, thromboxane A2, PGs, and leukotrienes. Glucocorticoids can also decrease PG synthesis at the level of the COX pathway, and they may induce local expression of somatostatin, a hormone with anti-inflammatory properties.

Cats appear to be more resistant to the adverse effects of systemically administered glucocorticoids, compared with results in dogs, and reportedly have up to 50% fewer corticosteroid receptors than do dogs. In dogs, there is rapid hepatic conversion of prednisone to the active metabolite, prednisolone, and prednisolone is generally recommended over prednisone in cats.

Nonsteroidal anti-inflammatory drugs inhibit PG synthesis by competing with arachidonate for binding to the COX-active site of PG endoperoxide synthase. Prostaglandin endoperoxide synthase, also known as COX, is the enzyme that converts arachidonic acid to PGs (PGE2, PGD2, PGF2α, and PGL) and thromboxane A2. Two main isoforms of COX (COX-1 and COX-2) have been identified; in general, COX-1 is responsible for production of PGs that are required for tissue homeostasis, such as gastric cytoprotection, regulation of renal blood flow, and platelet function. In contrast, COX-2 is responsible for production of PGs primarily at sites of inflammation by cells that have been stimulated by cytokines and other inflammatory mediators, although COX-2 can be found in low amounts in physiologically normal tissues.

The toxic effects of NSAIDs are thought to result primarily from inhibition of COX-1. Cyclooxygenase selectivity is typically expressed as a ratio of the concentrations at which a specific drug inhibits each isoenzyme by 50%. Nonsteroidal anti-inflammatory drugs have been classified on the basis of their selectivity for COX-1 and COX-2 on the assumption that greater selectivity for COX-2 would result in fewer adverse effects but still provide anti-inflammatory and analgesic effects. In general, acetylsalicylic acid is considered to be a nonselective COX inhibitor, indicating that it inhibits both COX-1 and COX-2, whereas meloxicam is classified as a selective COX-2 inhibitor. Cats have a reduced ability for glucuronide conjugation that results in prolonged action of many drugs, including most NSAIDs. Therefore, cats may have an increased risk of complications associated with the use of systemically administered NSAIDs, particularly given that little is known about COX selectivity of various NSAIDs in cats.

Although several ophthalmic studies have been conducted to evaluate the efficacy of orally administered anti-inflammatory agents in dogs, the authors are not aware of any such reports for cats. Because of species differences in stability of the BAB and differences in the metabolism of drugs, it is clinically relevant to evaluate the efficacy of anti-inflammatory medications in each species. The purpose of the study reported here was to assess the inhibitory effects of 4 orally administered anti-inflammatory medications on paracentesis-induced intraocular inflammation in clinically normal cats via fluorophotometry.

Materials and Methods

Animals—Thirty domestic shorthair cats (14 neutered males and 16 sexually intact females) weighing between 2.5 and 5.4 kg were used in the study. The cats were 8 to 20 months old (mean ± SD, 11.9 ± 3.2 months). The cats were part of a research colony at the Kansas State University Department of Diagnostic Medicine/Pathobiology; following completion of the study, cats were returned to the colony for subsequent adoption. The study was approved by the Institutional Animal Care and Use Committee at Kansas State University.

An ophthalmic examination, including slit-lamp biomicroscopy, fluorescein staining of the cornea, rebound tonometry, and indirect ophthalmoscopy, was performed on each cat prior to the study. Inclusion criteria for the study required cats to have no abnormal findings for ophthalmic and physical examinations. The cats were housed in a temperature-controlled environment and exposed to 12 hours of light and 12 hours of darkness (light phase from 7 AM to 7 PM).

Anti-inflammatory medications—Cats were assigned via a randomization procedure (randomization was achieved by use of a table of random numbers) to a control group and 4 treatment groups (acetylsalicylic acid, meloxicam, prednisone, and prednisolone); there were 6 cats in each group. Cats in the control group received no medication. Cats in each respective treatment group received an anti-inflammatory medication orally once daily at 7 AM (acetylsalicylic acid [40.5 mg/cat; mean ± SD, 12.8 ± 2.4 mg/kg], meloxicam [0.1 mg/kg], prednisone [5 mg/cat; mean ± SD, 1.6 ± 0.3 mg/kg], or prednisolone [5 mg/cat; mean ± SD, 1.4 ± 0.3 mg/kg]) beginning 2 days before paracentesis (ie, breakdown of the BAB) and continuing until 2 days after paracentesis (total of 3 doses). The cats received 3 doses of the anti-inflammatory medication prior to paracentesis. Investigators performing the fluorophotometry (AJR and WRC) were not aware of the group assignment of each cat.

Paracentesis of the anterior chamber—In each cat, paracentesis of the anterior chamber was performed in 1 eye (selected via flipping of a coin) to induce disruption of the BAB. Cats were sedated with medetomidine (0.03 mg/kg, IV) and ketamine hydrochloride (5 mg/kg, IV). Paracentesis of the anterior chamber was performed with a 30-gauge needle attached to a 1-mL syringe. The needle was introduced into the cornea at a point 1 to 2 mm anterior to the limbus. The needle was advanced into the center of the anterior chamber, and 100 µL of aqueous humor was slowly aspirated during a period of 3 to 5 seconds. Investigators were careful to ensure the iris and lens were not traumatized during paracentesis. The cats were monitored after paracen-
For both modeling strategies, the Kenward-Roger procedure was used to estimate the degrees of freedom and to make the corresponding adjustments in estimated SEs. Models were fitted with statistical software via the Newton-Raphson technique with ridging and the optimization technique. Model assumptions were considered to be appropriately met on the basis of diagnostic testing conducted on Studentized residuals. Estimated least squares means and corresponding SEs were reported. Relevant pairwise comparisons were conducted with Bonferroni adjustments to avoid inflation of the type I error rate attributable to multiple comparisons.

**Results**

**Animals**—Paracentesis and fluorophotometry procedures were tolerated well by all cats in the study. Results of the ophthalmic examinations at the end of the study were within anticipated limits and did not reveal any abnormalities.

**Fluorescein concentrations**—In the eyes not subjected to paracenteses, there was no evidence of significant ($P > 0.900$) treatment effects during the study. At time 0, there were no significant ($P < 0.900$) treatment effects in the eyes subsequently subjected to paracentesis.

At 24 and 48 hours after paracentesis, the concentration of fluorescein in the eyes subjected to paracentesis in the prednisolone-treated cats was significantly ($P = 0.012$ and 0.041, respectively) decreased, compared with the concentration in those same eyes of the control cats. At 48 hours, a significant ($P = 0.041$) decrease was also apparent in meloxicam-treated cats, compared with the concentration in the control cats. There was no evidence of a treatment effect for acetylsalicylic acid or prednisone on eyes subjected to paracentesis, compared with the concentration in the control cats, at any time point during the study (Figure 1).

In comparing the effectiveness of the drugs, there was a significant ($P = 0.031$) difference at 6 hours after...
paracentesis between the meloxicam-treated and prednisolone-treated cats, with prednisolone-treated cats having lower fluorescein concentrations. Both at 6 and 24 hours after paracentesis, there were significant differences between the prednisolone-treated (P = 0.007) and prednisone-treated (P = 0.005) cats, with prednisolone-treated cats having lower fluorescein concentrations. At 48 hours after paracentesis, there was no significant difference among fluorescein concentrations in cats after treatment with any of the medications.

**Percentage increase in fluorescein concentration**—At time 0, there were no significant (P > 0.900) differences among the treatments for percentage increase in fluorescein concentration. However, at 6 hours after paracentesis, the prednisone-treated cats had a significantly (P = 0.004) greater percentage increase in fluorescein concentration, relative to results for the control cats. At 24 and 48 hours after paracentesis, the prednisolone-treated cats had a significantly (P < 0.001) smaller percentage increase in fluorescein concentration, compared with results for the control cats. The meloxicam-treated cats had a significantly (P = 0.002) smaller percentage increase in fluorescein concentration, compared with results for the control cats, at 24 and 48 hours after paracentesis. The acetylsalicylic acid–treated cats had no significant differences in the percentage increase in fluorescein concentration, compared with results for the control cats, at any time point (Figure 2).

Comparisons among treatments revealed that at 6 hours after paracentesis, the percentage increase in fluorescein concentration was significantly lower in the prednisolone-treated cats, compared with results for the meloxicam-treated (P = 0.046) and prednisone-treated (P < 0.001) cats. Cats treated with prednisone had a significantly higher percentage increase in fluorescein concentration than did cats treated with acetylsalicylic acid (P = 0.002) or meloxicam (P = 0.033). At 24 hours after paracentesis, prednisolone-treated cats had a significantly lower percentage increase in fluorescein concentration than did the acetylsalicylic acid–treated (P = 0.008) or prednisone-treated (P < 0.001) cats, and the meloxicam-treated cats had a significantly (P = 0.043) lower percentage increase in fluorescein concentration than did the prednisone-treated cats. At 48 hours after paracentesis, cats treated with prednisolone or meloxicam had a significantly (P < 0.001) lower percentage increase in fluorescein concentration than did cats treated with prednisone.

**Discussion**

In the study reported here, we used fluorophotometry to evaluate the ability of 4 orally administered anti-inflammatory medications to inhibit paracentesis-induced BAB disruption in clinically normal cats. Paracentesis-induced disruption of the BAB has been used experimentally in several species, including cats.22-23 The ciliary body epithelium in the anterior pars plicata is most likely the site of disruption of the BAB following paracentesis of the anterior chamber.22,24-25 Paracentesis-induced breakdown of the BAB is thought to be mediated primarily by PGs.17,22,26-29 Prostaglandins cause miosis, hypotony, and increased permeability of the anterior uveal vasculature.22,30-32 Inhibition of the breakdown of the BAB by prophylactic treatment with NSAIDs via topical ophthalmic or systemic administration in several studies31-33,37,38,39 supports the role of PGs as mediators of ocular inflammation.

It is difficult to compare results of studies in which investigators evaluated the efficacy of orally administered medications for the control of intraocular inflammation because different methods of disrupting the BAB and of assessing the breakdown of the BAB have been used. These differences, along with variation in BAB stability and metabolism of drugs among species, highlight the clinical relevance of evaluating the efficacy of anti-inflammatory medications in each species.

In the present study, orally administered meloxicam significantly decreased the amount of fluorescein that entered the anterior chamber following paracentesis in clinically normal cats, compared with fluorescein concentrations in the control cats. These results are in accordance with those of a recent study4 in dogs that revealed IV administration of meloxicam was effective for the control of aqueocentesis-induced uveitis quantified on the basis of PGE2 concentrations in the aqueous humor. However, in another study,11 PGE2 concentrations in the aqueous humor were not significantly different between control dogs and dogs orally administered meloxicam prior to disruption of the BAB. In cats, meloxicam administered orally at a dose of 0.1 mg/kg followed by a daily dose of 0.05 mg/kg results in a maximum blood concentration 3.17 hours after administration, an elimination half-life of 28.72 hours, and steady-state concentrations after 2 days.9 Meloxicam is licensed for oral use in cats in the United Kingdom and Canada as well as other countries, but it is currently approved only for SC injection in cats in the United States.

In the present study, we detected greater efficacy of prednisolone versus prednisone in cats. The percentage increase in fluorescein concentration for the prednisolone-treated cats was significantly (P < 0.001) lower than that for the prednisone-treated and control cats at both 24 and 48 hours after paracentesis. Prednisone
must be converted to the active metabolite, prednisolone, in the liver by the enzyme 11β-hydroxysteroid dehydrogenase. The bioavailability for orally administered prednisone and prednisolone tablets does not appear to differ significantly between dogs35,36 and humans, and the drugs can be used at the same dosage interchangeably. However, prednisolone is generally preferred over prednisone for use in cats. It is unclear whether the inferior pharmacokinetics of prednisone in cats are the result of decreased gastrointestinal absorption or decreased hepatic conversion of the drug. The poor pharmacokinetics of orally administered prednisone in cats of the present study may be the reason that prednisone did not significantly decrease breakdown of the BAB, compared with results for the control cats.

Although previous studies12,13,15 have confirmed the efficacy of acetylsalicylic acid in controlling or reducing intraocular inflammation in dogs with experimentally induced uveitis, acetylsalicylic acid did not significantly reduce the breakdown of the BAB, compared with results for the control dogs, in a study15 in the cats of the present study. Acetylsalicylic acid was effective in reducing protein concentrations in the aqueous humor of dogs, compared with results for the control group, in the cats of the present study. Acetylsalicylic acid was effective in reducing protein concentrations in the aqueous humor of dogs, compared with results for control dogs, in a study12 in which investigators used aqueocentesis and reverse cyclophlaxis-induced inflammation. In another study13 in dogs, acetylsalicylic acid was found to be moderately effective in stabilizing the BAB after aqueocentesis.

Oral administration of prednisolone and meloxicam appeared to be more effective than oral administration of acetylsalicylic acid or prednisone for reducing the breakdown of the BAB after periocular anesthesia-induced intraocular inflammation in clinically normal cats, as evaluated via fluorophotometry. Orally administered prednisolone or meloxicam may be appropriate choices when treating feline patients with anterior uveitis. Although it was not evaluated in this study, it is possible that there may be greater penetration of orally administered anti-inflammatory medications, and therefore possibly greater efficacy, in cats with naturally occurring intraocular inflammation as a result of an increase in BAB disruption that may accompany severe inflammation.

References


266