Acta Scientiae Veterinariae, 2026. 54: 2002.

RESEARCH ARTICLE
Pub. 2002

ISSN 1679-9216

Experimental Uveitis in Dogs - Comparison of Topical Ketorolac Tromethamine Versus Flurbiprofen

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ABSTRACT

***Background*:** Topical anti-inflammatory medication is the 1st choice to treat anterior uveitis, considered one of the most common eye diseases in dogs. The exacerbated inflammatory process must be controlled because it may cause pain, glaucoma, retinal degeneration and blindness. Flurbiprofen and ketorolac tromethamine are commonly used topical non-steroidal anti-inflammatory drugs in veterinary medicine; however, ketorolac has not been extensively studied in dogs. The aim of this study was to evaluate the effect of 0.5% ketorolac tromethamine versus 0.03% flurbiprofen in dogs with experimentally induced uveitis.

***Materials, Methods and Results*:** The study was a crossover, descriptive and randomized clinical trial. Ten healthy adult (4 ± 3 years old) mongrel dogs (4 neutered male and 6 spayed female) were used and each dog received a double procedure (in the right and left eyes), using 2 different treatments, conducted as a single-blind study. A 0.5% ketorolac tromethamine solution and a 0.03% flurbiprofen solution were administered, respectively, in the right and left eyes. Paracentesis of the anterior chamber was performed to induce uveitis in the right eye. An aliquot of 0.2 mL of the AH was collected at M0 and after 30 min (M1). At this time, one ketorolac drop was instilled, and another aliquot of 0.3 mL of the AH was collected 30 min later (M2). Five days later (washout), the same procedure was carried out in the left eye, followed by treatment with flurbiprofen. Aqueous humor samples were collected to measure the PGE_2 concentration by competitive enzyme immunoassay, and to quantify ketorolac or flurbiprofen by High-performance liquid chromatography (HPLC) method. Ophthalmic examination and Intraocular Pressure (IOP) measurement using Goldmann tonometer were performed 12, 24, 36, 48 and 60 h after M2. All animals were treated with ketorolac and flurbiprofen eye drops (right and left eye respectively), 4 times daily up to 60 h. IOP was not significantly different from the baseline values. Mean levels of PGE_2 decreased in both treated eyes without significant difference. HPLC showed that the concentration of flurbiprofen and ketorolac were also not significantly different.

***Discussion*:** It is believed that IOP measurements of both treated eyes were not different from the basal values because the measurement was performed 8 h after the last paracentesis, when the treatments had already started. The time elapsed associated with the anti-inflammatory effect of both eye drops, therefore, may have been sufficient to restore the pressure after paracentesis and rupture of the blood-aqueous barrier. PGE_2 level in the AH has been used to evaluate the effectiveness of anterior uveitis treatments. PGE_2 decreases in the present study confirm that flurbiprofen and ketorolac were effective to control the inflammatory process induced by paracentesis. The results indicated that 0.5% ketorolac tromethamine had penetration and detectable concentrations in AH of dogs. Topically applied 0.5% ketorolac tromethamine was as effective as flurbiprofen to control ocular inflammation. Further studies are needed to consolidate the information on the pharmacokinetics and pharmacodynamics of this drug in dogs.

Keywords: topical anti-inflammatory drug, blood-aqueous barrier, aqueous humor, eye.

DOI: 10.22456/1679-9216.145940

Received: 21 July 2025 Accepted: 5 December 2025 Published: 27 January 2026

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INTRODUCTION

Topical anti-inflammatory medication is the 1st choice to treat anterior uveitis, considered one of the most common eye disease in dogs. Its pathogenesis involves release of prostaglandins (PG), particularly PGE_2, which increase vascular permeability and influx of cells and proteins into the aqueous humor (AH) and decrease of intraocular pressure (IOP) [5].

The exacerbated inflammatory process must be pharmacologically controlled because it may cause pain, glaucoma, retinal degeneration and, ultimately, blindness [8,12].

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are not indicated as first-line therapy for anterior uveitis due to the greater experience with and efficacy of corticosteroids [8]. However, among the NSAIDs used in veterinary medicine, flurbiprofen and ketorolac tromethamine are highlighted [2,4,11].

The aim of this study was to evaluate the effect of topically applied 0.5% ketorolac tromethamine versus 0.03% flurbiprofen by clinical evaluation and concentration of PGE_2 in the aqueous humor of dogs with experimentally induced blood–aqueous barrier disruption.

MATERIALS AND METHODS

Experimental groups

This study was approved by the institutional animal care committee (CEUA Protocol 109) and adhered to the Association for Research in Vision and Ophthalmology (ARVO) statement for animal use in ophthalmic research.

The study was a crossover, descriptive and randomized clinical trial. Ten healthy adult (4 ± 3 years old) mongrel dogs (4 neutered male and 6 spayed female) were used. Each dog received a double procedure (in the right and left eye), using 2 different treatments. Only one of the researchers, excluded from the treatment, was aware of the eye drops used and he identified the drops different bands for 0.5% ketorolac tromethamine[1] [Cetrolac®] and 0.03% flurbiprofen[2] [Ocufen®], respectively.

Experimental procedures

Paracentesis of the anterior chamber was performed to induce uveitis in the right eye (Figure 1) [5,6,9]. An aliquot of 0.2 mL of the AH was collected at M0 and after 30 min (M1). At this time, 1 ketorolac drop was instilled, and 1 aliquot of 0.3 mL of the AH was collected 30 min later (M2). Five days later (washout), the same procedure was carried out in the left eye, followed by treatment with flurbiprofen.

Immediately after collection, AH samples were stored at -80ºC and used to determine the PGE_2 levels by competitive enzyme immunoassay[3]. The M2 samples were also used to determine the levels of ketorolac and flurbiprofen in the right and left eyes, respectively, by HPLC [4].

Ophthalmic examination and IOP measurement using Goldmann tonometer were performed 12, 24, 36, 48 and 60 h after M2.

All animals were treated with ketorolac and flurbiprofen eye drops (right and left eye respectively), 4 times daily up to 60 h.

Statistical analysis

Intraocular pressure and concentrations of the drugs (HPLC) were evaluated by one-way repeated measures analysis of variance (one-way ANOVA) and Tukey's Test for multiple comparison. PGE_2 levels were analyzed using analysis of variance (one-way ANOVA) and Holm-Sidak for multiple comparisons. A significance level of $P < 0.05$ was adopted. Analyses were performed using the Graphpad 5 software.

RESULTS

Intraocular pressure, measured over the evaluation period, was not significantly different from the baseline values (Figure 1).

Means PGE_2 levels in the aqueous humor increased from 65.07 pg/mL at M0 to 9308.68 pg/mL at M1 ($P < 0.001$). At M2, after ketorolac (right eye) and flurbiprofen (left eye) treatment, PGE_2 decreased to 174.81 and 189.3 pg/mL ($P < 0.001$), respectively and these values did not show significant difference compared to M0 ($P = 0.999$ and 0.995) [Figure 2].

No significant difference was observed between treatments ($P = 0.965$). Concentration of ketorolac and flurbiprofen obtained by HPLC (mean ± standard error of the mean) were, respectively, 27.04 ± 14.348 ng/mL and 25.41 ± 16.93 ng/mL ($P > 0.05$) [Figure 3].

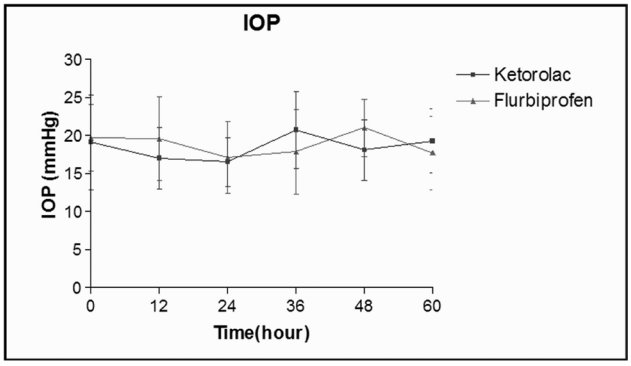

Figure 1. Mean of intraocular pressures measured over time using as basal the mean IOP measured before the experiment (time 0).

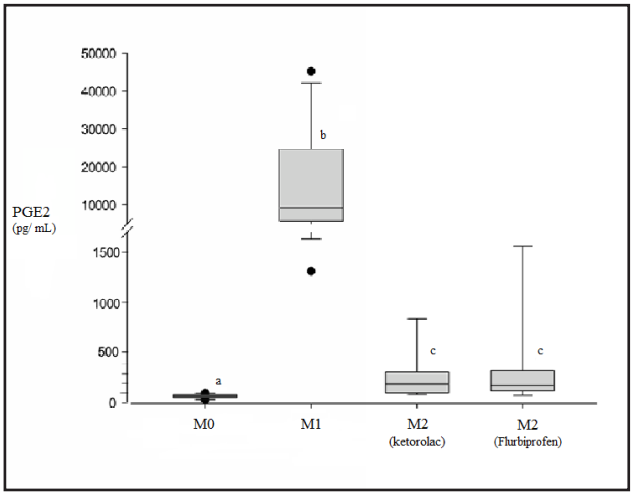

Figure 2. PGE_2 (pg/mL) concentrations in the aqueous humor of dogs submitted to paracentesis at M0, M1 (after 30 min and treatment started) and M2 (30 min after treatment with ketorolac or flurbiprofen). Different letters mean statistically significant results ($P < 0.05$).

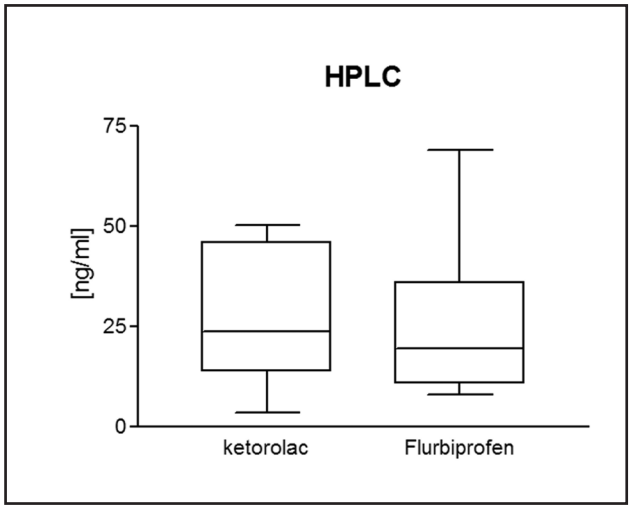

Figure 3. Ketorolac and flurbiprofen concentrations in the aqueous humor of dogs, 30 min after treatment (M2).

DISCUSSION

Ketorolac is available for topical ophthalmic use and its antiinflammatory efficacy has been confirmed by studies in rabbits [1,12,15] and humans [11]. A single study has evaluated ketorolac concentrations in the aqueous humor of dogs undergoing cataract surgery, following preoperative administration, for the prevention of postoperative ocular inflammation [17]. However, to our knowledge, the efficacy of topically administered ketorolac in canine uveitis has not been previously reported. In the present study, ketorolac was administered after uveitis induction, which better reflects clinical practice, since uveitic events cannot usually be predicted to justify prophylactic administration.

In addition, this study also evaluated the anti-inflammatory action of ketorolac when administered topically, unlike other studies that evaluated its effect when administered by anterior subconjuntival injection or intravitreal injection [7,10].

Despite the expected IOP decrease, in the present study, IOP measurements of eyes treated with both ketorolac and flurbiprofen were not different from the basal values. It is noteworthy that the IOP was measured 8 h after the last paracentesis, when treatment had already started. The elapsed time, combined with the anti-inflammatory effects of the eye drops, may have been sufficient to restore the pressure after paracentesis and rupture of the blood-aqueous barrier.

Prostaglandins play an important role in the ocular response to trauma or irritation [16] and PGE_2 level in the AH has been used to evaluate the effectiveness of anterior uveitis treatments [1,5,6,9,16]. Mean PGE_2 level was 65.07 pg/mL at M0, considered basal value for comparison with other times. The AH of normal dogs contained little PGE_2 but these values vary in the literature, from values below the detection limit of the commercial kit (< 15 pg/mL) [5] to 130 pg/mL [9].

In fact, the difference in PGE2 levels in the AH between M0 and M1 confirmed that the technique is effective to induce the rupture of the blood-aqueous barrier and consequent inflammation [5,6,9,16].

One study, that evaluated the effect of carprofen following anterior chamber paracentesis, observed a significant increase in PGE_2 4 h after the 1st paracentesis, which remained almost unchanged up to 8 h in untreated eyes [9]. In the present study, however, PGE_2 level decreased at M2, without significant difference from the basal values (M0), confirming that

flurbiprofen and ketorolac were effective to control the inflammatory process induced by paracentesis.

In our study, ketorolac reached concentrations in the AH to suppress inflammation as in rabbits studies, that evaluated topical ophthalmic use and its antiinflammatory efficacy [1,2,12]. The concentration of ketorolac obtained after 30 min in the present study was consistent with another study that evaluate rabbits subjected to anterior subconjunctival administration of ketorolac [10], and other study that evaluated human patients undergoing cataract surgery, with a peak concentration at 60 min equivalent to 57.5 ng/mL [14].

Additionally, studies in humans and dogs also verified that ketorolac had detectable concentration in AH samples obtained during surgical procedures [4,17]. In a study, evaluating dogs submited to cataract surgery, the prior administration of ketorolac controlled the inflammation induced by the surgical trauma [17].

The anti-inflammatory effect of ketorolac tromethamine was probably attributed to satisfactory penetration in the anterior chamber [3,13], which leads to the reduction of prostaglandins' effects, especially PGE_2 [1,11].

CONCLUSIONS

The results indicated that 0.5% ketorolac tromethamine had penetration and detectable concentrations in AH of dogs. The reduction in prostaglandin levels in the aqueous humor indicates that ketorolac has efficacy comparable to flurbiprofen to control ocular inflammation. Further studies are needed to consolidate the information on the pharmacokinetics and pharmacodynamics of this drug in dogs, specially evaluating their role in uveitis and other inflammatory diseases of the eye.

MANUFACTURERS

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***Ethical approval*.** This study was approved on June 14th of 2013, by the institutional animal care committee (CEUA Protocol 109) and adhered to the Association for Research in Vision and Ophthalmology (ARVO) statement for animal use in ophthalmic research.

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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