

## 24-Hour Evaluation of the Ocular Distribution of <sup>14</sup>C-Labeled Bromfenac Following Topical Instillation into the Eyes of New Zealand White Rabbits

George A. Baklayan, Hal M. Patterson, Clara K. Song, James A. Gow, and Timothy R. McNamara

### Abstract

**Purpose:** The aim of this study was to determine the distribution and concentrations of bromfenac ophthalmic solution in ocular tissues following topical instillation in New Zealand White (NZW) rabbits.

**Design:** Two animal studies were conducted.

**Methods:** A single 50- $\mu$ L <sup>14</sup>C-bromfenac ophthalmic solution (20–25  $\mu$ Ci or 0.09%) was administered into the right eyes of 14–18 randomly assigned NZW rabbits. At various time points, ocular tissues were collected and analyzed for <sup>14</sup>C-bromfenac contents. Ocular tissues were combusted and the amount of radioactivity was determined by liquid scintillation counting (LSC). Aqueous-humor samples were directly transferred to LSC vials.

**Results:** Peak concentrations of <sup>14</sup>C-bromfenac were observed in the aqueous humor and most ocular tissues at or before 2-hours. The highest concentrations were in the cornea, conjunctiva, and sclera. Similar amounts were detected in the aqueous humor, iris-ciliary body, choroid, and, to a slightly lesser degree, in the retina. Measurable amounts of bromfenac were detected in all samples at the 24-hours time point ( $\geq 0.001$   $\mu$ g equivalent/g).

**Conclusions:** Significant penetration and measurable amounts of <sup>14</sup>C-bromfenac were detected in all ocular tissues over 24 h, including the sclera, choroid, and retina. These results strongly suggest the utility of bromfenac ophthalmic solution 0.09% in treating inflammation of both the anterior and posterior ocular segments.

### Introduction

**B**ROMFENAC OPHTHALMIC SOLUTION 0.09% (Xibrom<sup>TM</sup>; ISTA Pharmaceuticals<sup>®</sup> Inc., Irvine, CA) is a topical non-steroidal anti-inflammatory drug (NSAID) for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone a cataract extraction.\* Bromfenac sodium ophthalmic solution 0.1% was first approved in Japan in 2000 as Bronuck<sup>®</sup> (Senju Pharmaceutical Company Ltd., Osaka, Japan) for the treatment of postoperative inflammation, blepharitis, conjunctivitis, and scleritis.<sup>1</sup> In 2005, the same formulation was approved in the United States as bromfenac sodium ophthalmic solution 0.09% (Xibrom) for the treatment of postoperative inflammation following cataract surgery. In 2006, the Food and Drug Ad-

ministration (FDA) expanded the indication of bromfenac 0.09% to include the reduction of pain following cataract surgery.

For a topical drug to be effective, in addition to potency, the drug should penetrate the affected tissue(s). For example, an ophthalmic topical NSAID would be effective in the prevention or treatment of cystoid macular edema (CME) if it penetrates the ocular tissues to reach the retina. Ocular instillation of various topical NSAIDs provides ocular tissues and aqueous humor with levels adequate to inhibit prostaglandin synthesis and, thus, the anti-inflammatory role. However, the penetration of the various NSAIDs varies considerably among agents, as does the drug potency and efficacy.

In recent years, there have been various models proposed describing the binding of NSAIDs to the cyclo-oxygenase en-

ISTA Pharmaceuticals<sup>®</sup>, Inc., Irvine, CA.

These studies were conducted by ISTA Pharmaceuticals<sup>®</sup>, Inc. (Irvine, CA). The authors are employees and stockholders of ISTA Pharmaceuticals, Inc.

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\*Xibrom Package insert. ISTA Pharmaceuticals, Inc., Irvine, CA 2006.

<sup>1</sup>Bronuck package insert. Senju Pharmaceutical Company, Ltd., Osaka, Japan, 2005.

zyme, their role in the inhibition of the enzyme, and, consequently, their potency as anti-inflammatory agents. These pharmacokinetic properties are dependent, to a great degree, on the structure of the molecule itself. Walsh et al.<sup>1</sup> studied the physicochemical properties of amfenac and 19 other derivatives and found that the addition of a substituent to the molecule decreased the anti-inflammatory activity, whereas the addition of a group to the aromatic ring had a pronounced effect on enhancing the anti-inflammatory activity. The researchers reported that the most potent compounds were those with a halogen in the 4'-position (Br ~ I > Cl > F > H). Bromfenac has a chemical structure very similar to that of amfenac (the active form of the prodrug nepafenac), except for the critical addition of a bromine atom in the 4'-position of the benzoyl ring (Figure 1A and 1B).<sup>1</sup> Preclinical data demonstrated that this halogenation of the molecule not only produced greater *in vitro* and *in vivo* potency,<sup>2-5</sup> but also enhanced bromfenac absorption across the cornea and penetration in ocular tissues.<sup>6,7</sup>

The octanol/water (O/W) partition coefficient ( $C_{log P}$ ) and the quantitative structure-activity relationship (QSAR) of a drug is another factor that influences its penetration properties and, consequently, its potency.  $C_{log P}$  estimates the water solubility and the level of lipophilicity of a compound (a key determinant of the pharmacokinetics parameter). It is commonly used in drug-design studies, since this property is related to drug absorption, bioavailability, metabolism, and toxicity. The higher the value, the better the penetration, with a 1.0-unit difference in the coefficient representing a tenfold difference in penetration. Ruiz et al.<sup>6</sup> reported that the  $C_{log P}$  of bromfenac (2.23) is higher than other NSAIDs, such as amfenac (1.23) and ketorolac (1.88). This difference in  $C_{log P}$  explains the higher lipophilicity of bromfenac that provides a more rapid saturation of the epithelium and a minimal lag time before the drug crosses the cornea and, thus, the fast analgesic action.<sup>8</sup>

The aim of this preclinical investigation was to evaluate the penetration of <sup>14</sup>C-bromfenac following a single ocular instillation in New Zealand White (NZW) rabbit eyes.

#### Methods

Two animal studies were conducted at the Biological Test Center (BTC, Irvine, CA) as per-study protocols provided by

ISTA Pharmaceuticals. The protocol, materials, methods, and data analysis were identical for the two studies. The first study had 14 NZW rabbits randomized into seven groups of 2 rabbits each. The second study had 18 NZW rabbits randomized into six groups of 3 rabbits each. The studies complied with the animal welfare policies of BTC and were approved by the Institutional Animal Care and Use Committee. The first study was designed to ensure that enough measurable radiolabeled bromfenac was available. The second study tested commercial-strength bromfenac ophthalmic solution 0.09%.

#### Test article

The <sup>14</sup>C-bromfenac sodium (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan) was analyzed to determine the radioactivity purity prior to its use in the study and was found to be 100% pure (3.11 MBq/mg, 83.97  $\mu$ Ci/mg). Stability testing of the product was not conducted in this study. Stability testing was previously conducted by Senju Pharmaceutical Co., LTD.

#### Dosing-solution preparation and analysis

The dosing solution was prepared by adding either <sup>14</sup>C-bromfenac to bromfenac ophthalmic solution 0.09% to achieve a target concentration of approximately 500  $\mu$ Ci/mL or to target a concentration of 0.09%. Three (3) aliquots (100  $\mu$ L) of the dosing solutions were weighed and brought to a volume of 25 mL with saline. Duplicate aliquots (100  $\mu$ L) of the diluted solutions were quantitated for radioactivity by LSC. The dosing solution was prepared immediately prior to dosing; therefore, no refrigeration was needed. After dosing and prior to high-performance liquid chromatography (HPLC), the solution was refrigerated. The radiochemical purity of the dosing solution was tested again by HPLC following dosing and was found to be 100% pure.

#### Animals

Female NZW rabbits were obtained from The Rabbit Source (Ramona, CA) or Covance (Denver, PA). The animals were at least 12 weeks old and weighed 2.18-3.32 kg at the time of dosing. The animals were housed in individual cages and were identified with ear tags and cage cards.

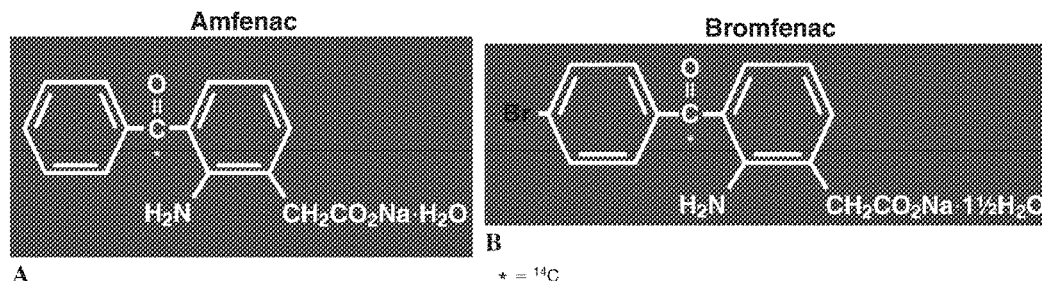


FIG. 1. Chemical structure of newer generation of nonsteroidal anti-inflammatory drugs. (A) amfenac (active form of prodrug nepafenac) and (B) bromfenac.

TABLE 1. THE TISSUE SAMPLING TIME AFTER INSTILLATION AND THE AMOUNT BROMFENAC AND RADIO ACTIVITY IN EACH TREATMENT GROUP

Group	Hours post-dose	Average BF dose (mg)	Average RA dose ( $\mu$ Ci)
A	1 h $\pm$ 5 min	0.276	22.14
B	2 h $\pm$ 15 min	0.284	22.81
C	4 h $\pm$ 15 min	0.253	20.33
D	8 h $\pm$ 15 min	0.306	24.57
E	12 h $\pm$ 15 min	0.236	18.93
F	24 h $\pm$ 1 h	0.282	22.66

BF, bromfenac; RA, radioactivity.

#### Pretreatment examination and dosing procedure

Prior to placement in the study, each animal underwent a thorough pretreatment ophthalmic examination with slit lamp. Acceptance criteria for placement in the study were scores of  $\leq 1$  for conjunctival congestion and swelling and scores of zero for all other observation variables. Prior to dosing, animals were weighed and randomly assigned to six study groups (groups A–F in Table 1) of 2 (study 1) or 3 rabbits each (study 2).

On day 1, 50  $\mu$ L of the freshly prepared dosing solution was administered into the right eye of each animal, using a calibrated pipette, and the time of dose administration was recorded. The actual dose the animals received ranged from 13.3 to 24.6  $\mu$ Ci (study 1) or 0.09% bromfenac (study 2). Actual dosing values in mg and  $\mu$ Ci were used in all subsequent calculations. Animals were observed for mortality and/or morbidity during the course of the study.

#### Samples processing

The animals were euthanized with an intravenous injection of euthanasia solution, and the ocular tissues were collected from the dosed eye at 1-, 2-, 4-, 8-, 12-, and 24-h time points following dosing (Table 1). The 36-h timepoint, group G in study 1, was rendered unusable due to contamination.

The conjunctiva, cornea, lens, iris-ciliary body, sclera, choroid, and retina were weighed into combustion cones and combusted. Combusted samples were trapped in Carbon-14

Cocktail (R. J. Harvey, Hillsdale, NJ) in LSC vials, and the amount of radioactivity was determined by LSC.

Approximately 25- $\mu$ L duplicate aliquots of each aqueous-humor sample were transferred to LSC vials, using Insta-Gel as scintillation fluid, and the amount of radioactivity was determined by LSC. Each vitreous humor sample was homogenized, and duplicate aliquots (100  $\mu$ L each) were transferred to LSC vials, using Insta-Gel (Perkin Elmer Life and Analytical Sciences, Inc., Waltham, MA) as the scintillation fluid, and the amount of radioactivity was determined by LSC.

#### Radioactivity measurements

Radioactivity measurements were performed by using a Beckman Liquid Scintillation Spectrometer (Beckman Coulter Inc., Fullerton, CA). Counting time was to a statistical accuracy of  $\pm 2\%$  or a maximum of 10 min, whichever came first. Background noise, approximately 100 disintegrations per minute (dpm), was subtracted automatically. In addition, the spectrometer was programmed to automatically convert counts per minute (cpm) to dpm.

#### Calculations and statistical analysis

The following are the formulas used in this study. For the specific activity (dpm/ $\mu$ g) of  $^{14}$ C-bromfenac:

Specific activity =

$$\frac{\text{dpm/g of dosing solution}}{\text{Concentration of dosing solution (mg/g)} \times 1000 \mu\text{g/mg}}$$

For the ppm ( $\mu$ g/g) of dosed  $^{14}$ C-bromfenac:

$$\text{ppm} = \frac{\text{dpm/g of sample}}{\text{Specific activity of dosing solution (dpm/\mu g)}}$$

For the percent of dose:

$$\% \text{ of dose} = \frac{\text{Radioactivity in sample (dpm)}}{\text{Total radioactivity administered (dpm)}} \times 100$$

When applicable, the mean and standard deviation were used to characterize the data.

TABLE 2.  $^{14}$ C-BROMFENAC RESIDUES IN OCULAR TISSUE AT DIFFERENT TIME-POINTS FOLLOWING A SINGLE TOPICAL INSTILLATION INTO THE RIGHT EYE OF NEW ZEALAND

Sample	Group A (1 h) mean ppm $\pm$ SD	Group B (2 h) mean ppm $\pm$ SD	Group C (4 h) mean ppm $\pm$ SD	Group D (8 h) mean ppm $\pm$ SD	Group E (12 h) mean ppm $\pm$ SD	Group F (24 h) mean ppm $\pm$ SD
Conjunctiva	<b>10.693</b> $\pm$ 0.993	5.632 $\pm$ 0.707	3.889 $\pm$ 1.566	3.024 $\pm$ 3.780	0.911 $\pm$ 0.577	0.835 $\pm$ 0.651
Cornea	9.786 $\pm$ 2.029	<b>11.156</b> $\pm$ 2.180	8.561 $\pm$ 2.327	3.325 $\pm$ 0.723	1.114 $\pm$ 0.088	0.264 $\pm$ 0.138
Lens	0.005 $\pm$ 0.001	0.012 $\pm$ 0.002	<b>0.027</b> $\pm$ 0.004	0.022 $\pm$ 0.004	0.016 $\pm$ 0.007	0.012 $\pm$ 0.001
Iris-ciliary body	0.329 $\pm$ 0.059	<b>0.441</b> $\pm$ 0.123	0.280 $\pm$ 0.026	0.113 $\pm$ 0.025	0.064 $\pm$ 0.002	0.033 $\pm$ 0.013
Aqueous humor	0.304 $\pm$ 0.052	<b>0.495</b> $\pm$ 0.191	0.311 $\pm$ 0.091	0.099 $\pm$ 0.016	0.039 $\pm$ 0.012	0.004 $\pm$ 0.001
Choroid	0.331 $\pm$ 0.094	<b>0.370</b> $\pm$ 0.143	0.272 $\pm$ 0.106	0.131 $\pm$ 0.074	0.074 $\pm$ 0.060	0.019 $\pm$ 0.001
Vitreous humor	0.004 $\pm$ 0.000	<b>0.007</b> $\pm$ 0.008	0.002 $\pm$ 0.000	0.001 $\pm$ 0.000	0.004 $\pm$ 0.005	0.000 $\pm$ 0.000
Retina	0.081 $\pm$ 0.015	<b>0.118</b> $\pm$ 0.072	0.096 $\pm$ 0.044	0.080 $\pm$ 0.082	0.038 $\pm$ 0.028	0.009 $\pm$ 0.003
Sclera	4.511 $\pm$ 0.301	<b>6.212</b> $\pm$ 0.382	2.500 $\pm$ 1.037	1.223 $\pm$ 0.421	1.595 $\pm$ 1.316	0.443 $\pm$ 0.095

ppm, parts per million; SD, standard deviation; Boldface, peak tissue concentration.

TABLE 3. <sup>14</sup>C-BROMFENAC 0.09% RESIDUES IN OCULAR TISSUES AT DIFFERENT TIME-POINTS FOLLOWING A SINGLE TOPICAL INSTILLATION INTO THE RIGHT EYE OF NZW RABBITS

Sample	Group A (1 h) mean ppm ± SD	Group B (2 h) mean ppm ± SD	Group C (4 h) mean ppm ± SD	Group D (8 h) mean ppm ± SD	Group E (12 h) mean ppm ± SD	Group F (24 h) mean ppm ± SD
Conjunctiva	0.437 ± 0.133	0.612 ± 0.202	0.484 ± 0.451	0.126 ± 0.085	0.226 ± 0.338	0.397 ± 0.132
Cornea	1.069 ± 0.053	0.715 ± 0.207	0.887 ± 0.102	0.269 ± 0.076	0.121 ± 0.057	0.046 ± 0.042
Lens	0.001 ± 0.001	0.006 ± 0.008	0.002 ± 0.000	0.001 ± 0.000	0.001 ± 0.000	0.002 ± 0.002
Iris-ciliary body	0.087 ± 0.029	0.044 ± 0.005	0.057 ± 0.001	0.027 ± 0.006	0.022 ± 0.004	0.013 ± 0.007
Aqueous humor	0.030 ± 0.008	0.026 ± 0.007	0.039 ± 0.012	0.010 ± 0.005	0.008 ± 0.007	0.003 ± 0.003
Choroid	0.040 ± 0.013	0.039 ± 0.003	0.048 ± 0.018	0.013 ± 0.002	0.005 ± 0.002	0.003 ± 0.005
Vitreous humor	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Retina	0.008 ± 0.003	0.011 ± 0.005	0.007 ± 0.005	0.002 ± 0.001	0.001 ± 0.001	0.003 ± 0.003
Sclera	0.238 ± 0.070	0.186 ± 0.015	0.267 ± 0.197	0.031 ± 0.012	0.038 ± 0.041	0.394 ± 0.526

ppm, parts per million; SD, standard deviation.

**Results**

*Dosing and sample handling*

The radioactivity present in the conjunctiva of 2 dosed eyes in group G (first study) varied greatly, indicating a possible contamination. Consequently, the samples were excluded. Excessive tearing occurred in 1 animal in group E, of the same study, following dosing. Excessive tearing was absorbed with absorbent eye wipe(s). For each eye-wipe sample, the sample was placed in a vial, 15 mL of distilled water was added to it, and each vial was put on a wrist-action shaker for approximately 1 hour. Duplicate aliquots (25 µL) of each sample were analyzed by LSC. The radioactivity present in each wipe was considered as radioactivity lost during dosing, and actual administered doses were calculated accordingly.

*Data analysis*

After the administration of a single 50-µL dose of <sup>14</sup>C-bromfenac ophthalmic solution to achieve a target dose of 20–25 µCi into the right eye of randomly assigned NZW rabbits, measurable amounts of radioactivity were detected in all tissues but the vitreous humor. Peak concentrations of radiolabeled bromfenac were observed in all ocular tissues in the first study at 2 h, with the exception of the conjunctiva, which showed peak tissue concentration at 1 h, and the lens, which showed peak tissue concentration at 3 h (Table 2). In the second study, peak concentrations of radiolabeled bromfenac were observed in all ocular tissues at 1–2 h, with the exception of the lens and vitreous humor (Table 3). The bromfenac concentrations were highest in the cornea. Similar amounts of radiolabeled bromfenac were measured in the aqueous humor, iris-ciliary body, choroid, and, to a slightly lesser degree, the retina. Further, radiolabeled bromfenac was detected in all samples 24 h following topical administration in the first and second studies, with the exception of the vitreous humor. Although the clinical significance of these animal studies is unknown, the data suggest that the extensive penetration profile and the sustained ocular-tissue concentration of bromfenac in the anterior and posterior segments of the eye may support the use of bromfenac in treating inflammatory disorders in other ocular tissues, such as CME (Fig. 2).

**Discussion**

In addition to potency, another important criterion of topical anti-inflammatory drugs is the ability to penetrate the tissues to reach their target(s) in a timely manner and appropriate concentration. Thus, the ability to penetrate ocular tissues is an important determinant of the safety and efficacy of ophthalmic NSAIDs. The two animal studies presented in this report demonstrate that a single topical dose of commercial-strength bromfenac ophthalmic solution 0.09% rapidly, within 2 h, achieved measurable levels in all ocular tissues and detectable levels were sustained over 24 h. One unexpected finding revealed that, unlike other ocular tissues, radiolabeled bromfenac was undetectable in the vitreous humor after 1 h (≤0.001 µg equivalent/gm). This was most likely due to the enhanced lipophilicity of bromfenac, which could impart a more

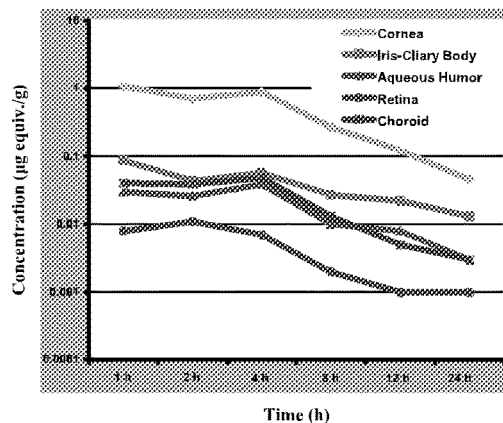


FIG. 2. Radioactive concentrations of <sup>14</sup>C-bromfenac in ocular tissues following a single 0.09% topical dose of commercial-strength bromfenac to the right eye of New Zealand white rabbits. Detectable levels of various ocular tissues were seen through 24 h and beyond.



rapid drug-transit time through tissues and/or the choroidal blood flow to posterior-segment tissues. A separate, but similar, penetration study of  $^{14}\text{C}$ -nepafenac (precursor of amfenac), using three times the commercially available dose, found no significant levels of nepafenac/amfenac in the aqueous humor and choroid after 12 h and in the retina after 6 h following instillation.<sup>3</sup> However, the cornea and iris-ciliary body showed detectable drug levels

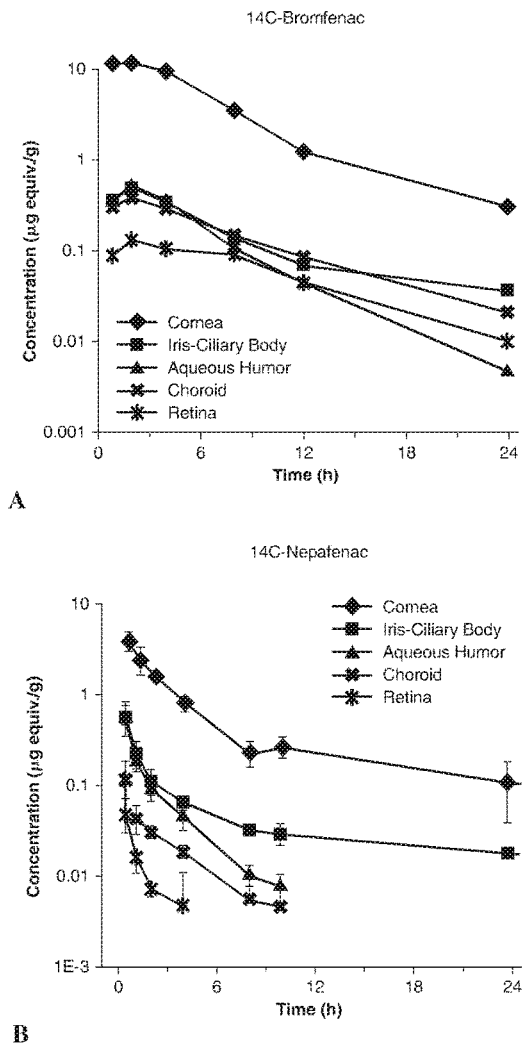


FIG. 3. Comparison of ocular-tissue concentrations of  $^{14}\text{C}$ -bromfenac (A) or  $^{14}\text{C}$ -nepafenac (B) following the administration of a single topical dose, three times the commercial strength, to rabbits. (A) Detectable levels in all ocular tissues through the 24-h time-point. (B) Retina not detectable at 6 h and aqueous humor and choroid not detectable at 12 h.

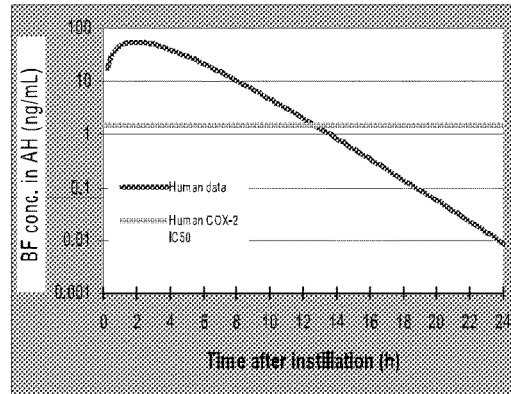


FIG. 4. Comparison of the estimated aqueous-humor concentration after the instillation of Bronuck<sup>®</sup> (bromfenac sodium 0.1% ophthalmic solution; Senju Pharmaceutical Company, Ltd., Osaka, Japan) to the human eye with the  $\text{IC}_{50}$  value of recombinant human cyclo-oxygenase-2.

of nepafenac/amfenac at 24 h following the topical administration of  $^{14}\text{C}$ -nepafenac<sup>9</sup> (Fig. 3B).

The anti-inflammatory and analgesic effects of all NSAIDs are due to their inhibitory activity on cyclo-oxygenase enzymes, mainly cyclo-oxygenase-2 (COX-2). However, the relative potency of NSAIDs against COX-2 varies among the different NSAID molecules. The unique chemical structure of bromfenac, with a bromine atom at the 4'-position of the aromatic ring, has demonstrated its pronounced effects on bromfenac's potency, absorption across the cornea, and penetration into ocular tissues where it maintained detectable levels for up to 24 h following topical administration, making it the most potent ophthalmic NSAID in inhibiting the COX-2 enzyme.<sup>2-5,10</sup> Kida et al.<sup>5</sup> compared COX-2 inhibitory activities of the four commercially available ophthalmic NSAIDs: amfenac (active metabolite of nepafenac), bromfenac, diclofenac, and ketorolac. Bromfenac was approximately three to four times more potent than the other three NSAID molecules in inhibiting the COX-2 enzyme. This potency may explain why bromfenac ophthalmic solution 0.09% is the first and only ophthalmic NSAID approved for twice-daily dosage.<sup>1</sup> Further, Ogawa et al.<sup>11</sup> evaluated the pharmacokinetic profile of bromfenac sodium 0.1% in 54 subjects undergoing cataract surgery. One (1) drop was administered at various time points 30–345 min prior to surgery. The concentration of bromfenac in a 100- $\mu\text{L}$  sample of the aqueous humor was determined by using HPLC. The peak aqueous-humor concentration of bromfenac was achieved 2.5–3.0 h following topical instillation. Bromfenac remained at a therapeutic concentration above the  $\text{IC}_{50}$  value for COX-2 for 12 h. In addition, a computer simulation projected a measurable concentration at or beyond 24 h (Fig. 4).

Currently, the four principal roles ophthalmic NSAIDs play in ophthalmic surgery are the prevention of miosis during cataract surgery, management of postoperative pain and inflammation following cataract and refractive surgery, and the prevention and treatment of CME after cataract sur-

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