In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac

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PURPOSE: To evaluate the aqueous humor concentrations and cyclooxygenase (COX) inhibitory activities of nepafenac, amfenac, ketorolac, and bromfenac after topical ocular administration of Nevanac (nepafenac 0.1%), Acular LS (ketorolac 0.4%), or Xibrom (bromfenac 0.09%).

SETTING: Five private ophthalmology practices throughout the United States.

METHODS: Patients requiring cataract extraction were randomized to 1 of 3 treatment groups: Nevanac, Acular LS, or Xibrom. Patients were administered 1 drop of the test drug 30, 60, 120, 180, or 240 minutes before cataract surgery. At the time of paracentesis, an aqueous humor sample was collected and later analyzed for drug concentration. In addition, COX-1 (homeostatic) and COX-2 (inducible) inhibitory activities of nepafenac, amfenac, ketorolac, and bromfenac were determined via the in vitro measurement of prostaglandin E_2 (PGE_2) inhibition.

RESULTS: Seventy-five patients participated in the study. The prodrug nepafenac had the shortest time to peak concentration and the greatest peak aqueous humor concentration (C_{max}). The C_{max} of nepafenac was significantly higher than that of the other drugs ($P<.05$), including the higher-concentration ketorolac (0.4%). The area under the curve (AUC) of nepafenac was significantly higher ($P<.05$) than the AUCs of amfenac, ketorolac, and bromfenac. The combined AUCs of nepafenac and amfenac were the highest of all drugs tested ($P<.05$). Ketorolac showed the most potent COX-1 inhibition, whereas amfenac was the most potent COX-2 inhibitor. The PGE_2 aqueous humor levels of each study medication were highly variable; as a result, meaningful interpretation of the data was not possible.

CONCLUSION: Nepafenac showed significantly greater ocular bioavailability and amfenac demonstrated greater potency at COX-2 inhibition than ketorolac or bromfenac.

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Ocular inflammation is a common result of cataract surgery, producing pain and photophobia in many patients and potentially leading to serious complications including increased intraocular pressure (IOP), posterior capsule opacification, cystoid macular edema (CME), and decreased visual acuity. The goals of topical prophylactic nonsteroidal antiinflammatory drug (NSAID) treatment include the prevention of intraoperative miosis,[1] management of postoperative inflammation,[1] prevention or treatment of CME,[2–4] and reduction of ocular pain.[5] Steroidal agents have been the standard treatment for ocular inflammation in the past, while the use of topical NSAIDs has increased over the past 2 decades. Clinical evidence suggests that the combined use of NSAIDs and steroids is synergistic.[6,7] In fact, it has become the standard of care to use a regimen of NSAIDs and steroids before and after cataract surgery.[4]

Four topical ocular NSAIDs are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of postoperative inflammation after cataract surgery. They are Acular (ketorolac 0.5%), Xibrom (bromfenac 0.09%), Voltaren (diclofenac 0.1%), and Nevanac (nepafenac 0.1%). Nepafenac 0.1% is the only prodrug NSAID, having less antiinflammatory activity without conversion to its more active state.[8] Upon topical ocular instillation, the molecule penetrates the cornea, where nepafenac is metabolized into the more potent NSAID amfenac through intraocular enzymatic hydrolysis.[9] Ocular penetration and potency are critically important for the activity of a drug, as suggested in a recent study that measured

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aqueous humor drug concentration and correlated it with effect.[10] Although rates of hydrolysis in the ocular tissues have been published for nepafenac,[9] to date no human clinical studies have examined the intraocular concentrations of nepafenac/amfenac or simultaneously compared the 3 primary market-leading NSAIDs in a head-to-head fashion at multiple time points to determine total NSAID exposure (area under the curve [AUC]) and potency.

The objective of this study was to compare aqueous humor concentrations of nepafenac and its more active metabolite, amfenac, with those of ketorolac and bromfenac after administration of nepafenac ophthalmic suspension 0.1% (Nevanac), ketorolac tromethamine ophthalmic solution 0.4% (Acular LS), or bromfenac ophthalmic solution 0.09% (Xibrom) in patients having cataract surgery. These comparators were chosen based on current use of these NSAIDs by ophthalmologists. The cyclooxygenase-1 (COX-1) and COX-2 inhibitory activity of all 4 molecules was also determined via in vitro measurement of prostaglandin (PG) inhibition to rank order the potency of the molecules.

PATIENTS AND METHODS

Test Articles

All products were supplied in identical opaque, sealed 4 mL bottles filled with 3 mL test article.

Study Design

In this multicenter double-masked single-dose investigative study, patients were randomized in a 1:1:1 ratio to the treatment groups (Nevanac, Acular LS, Xibrom) and then to 1 of 5 time points (30 ± 2 minutes, 60 ± 2 minutes, 120 ± 4 minutes, 180 ± 4 minutes, or 240 ± 4 minutes) in each drug group. Patients were administered 1 drop of the test article by the surgical staff at the assigned time before cataract surgery so that 1 sample per patient was taken (ie, sparse-sampling methodology). The collection of samples at discrete time points from distinct patients permits an estimation of pharmacokinetics of each analyte to be made. The study was approved by the IntegReview Institutional Review Board.

Inclusion and Exclusion Criteria

Patients 18 years or older who were in need of cataract surgery, regardless of sex or race, were eligible for this study if they met all informed consent requirements. Women of childbearing potential were eligible for participation if they were not pregnant or lactating and agreed to use adequate birth control methods during the study. Exclusion criteria included known or suspected hypersensitivity to any component of the study medication; history of invasive ocular surgery in the study eye within 4 months; use of any study medication or other NSAIDs within 7 days; contact lens wear beginning 2 days before surgery; history of ocular trauma, ocular infection, or nasolacrimal drainage system malfunction within 3 months; history of uveitis within 12 months; presence of external ocular disease, infection, or inflammation at the screening visit; corneal abnormality that would prevent reliable assessment of visual acuity; concurrent corneal disease; current use of punctal plugs; bleeding tendencies; a visually nonfunctioning fellow eye or a fellow eye enrolled or previously enrolled in the study; history of hepatitis A, B, or C or human immunodeficiency virus; or recent history of alcohol abuse.

Postoperative Examinations

All patients had a postoperative visit within 2 days after surgery. Visual acuity assessment, slitlamp evaluation, and IOP assessment were conducted at each examination. Adverse events were recorded throughout the study.

Pharmacokinetic Analysis

At the time of paracentesis, the aqueous humor sample (approximately 0.15 mL) was collected from the operated eye. Each sample was divided into 2 approximately equal aliquots and frozen (−70°C) no later than immediately after the surgery. The first aliquot was analyzed for drug concentration and the second for prostaglandin E_2 (PGE_2) concentration. Drug concentrations in the human aqueous humor sample were determined using a high-performance liquid chromatography–tandem mass spectrometry method by an independent lab (ALTA Analytical Laboratories). The method was validated for accuracy, precision, and stability in accordance with guidelines.

In Vitro Cyclooxygenase Inhibition Assay

Nepafenac, amfenac, ketorolac, and bromfenac were products of AMCIS, Alcon, QUIMICA, and Wyeth-Ayerst, respectively. The COX-1 and COX-2 inhibition assays conducted on masked samples were performed according to manufacturer's protocol by an independent lab (Cayman Chemical). The COX-1 enzyme (ovine) and the COX-2 enzyme (human recombinant) were tested separately. Each COX enzyme was incubated with each drug (nepafenac, amfenac, ketorolac, or bromfenac, each dissolved in dimethyl sulfoxide) for 10 minutes at 37°C. Arachidonic acid (100 µmol/L) was added to initiate reaction and incubated for 2 minutes at 37°C. After the reaction was stopped with

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hydrochloric acid, stannous chloride was added. (Stannous chloride reduction of COX-derived prostaglandin H_2 produces $PGF_{2\alpha}$, PGE_2, PGE_1, and $PGF_{1\alpha}$.) All 4 PG species were assessed by enzyme immunoassay via a detection antibody that recognizes all major PG products equally as part of the manufacturer's standard methodology for measuring COX inhibition. Tests were run with 13 concentrations of each drug to construct a dose-response curve and determine the concentration causing a half-maximum inhibition relative to control values (IC_{50}). Each series of concentrations was run in triplicate for each drug.

Prostaglandin E_2 Analysis

The PGE_2 concentration was measured according to kit instructions using a competitive microtiter-based immunoassay method in which the PGE_2 within the sample or the standard competes for binding to a PGE_2-specific monoclonal antibody with an alkaline phosphatase conjugate of PGE_2. After incubation and washing, substrate was added and a color reaction was read at 405 nm. Reagents for the immunoassay were obtained from Assay Designs, Inc.

Statistical Analysis

Pharmacokinetic measures, including peak aqueous humor concentration (C_{max}), time to peak concentration (T_{max}), and the AUC from time 0 to 4 hours, were estimated on the original scale. The linear trapezoidal method for sparse sampling was used to calculate the AUC and its 95% confidence interval.[11]

Between-group comparisons were conducted using an analysis-of-variance test for numeric variables and Mantel-Haenszel chi-square test, for categorical variables. The confidence level was set to 95% for all tests. Statistical analyses were performed using SAS (version 9.1.2).

RESULTS

Patient Demographics

Seventy-five patients, 39 men and 36 women, were enrolled in the study. The mean age of the patients was 67.5 years (range 43 to 90 years). Sixty-four patients (85.3%) were white, 8 (10.7%) were black, 2 (2.7%) were Hispanic, and 1 (1.3%) was Asian. All 3 groups were statistically equivalent in age, sex, and race (Table 1).

Aqueous Humor Analyte Pharmacokinetics

Table 2 summarizes the pharmacokinetics of each analyte. Nepafenac C_{max} was significantly higher than that of the other drugs over the time course sampled; it was approximately 3- to 3.5-fold higher than that of amfenac ($P = .0395$) or ketorolac ($P = .0161$), and more than 8-fold higher than that of bromfenac ($P = .0162$). The C_{max} of bromfenac was significantly lower than that of amfenac ($P = .0058$), but not of ketorolac ($P = .1250$). The C_{max} values of amfenac and ketorolac were statistically similar.

Pairwise comparisons of drug concentrations were calculated at each time point. Nepafenac concentration was significantly higher than that of the other analytes at 30 minutes and 60 minutes. In addition, bromfenac concentration was significantly lower than that of ketorolac concentration at 60 minutes and of amfenac at 180 minutes.

The AUC for nepafenac (308.9 ng × h/mL) was highest of all analytes tested, followed by that of amfenac (180.7 ng × h/mL), ketorolac (176.9 ng × h/mL), and bromfenac (47.2 ng × h/mL) (Figure 1). The AUC of nepafenac was significantly higher than the AUC of each of the other individual analytes ($P < .05$). During the time period tested, the AUC of both amfenac and ketorolac was significantly higher than that of bromfenac ($P < .05$), although the bromfenac concentration appeared to be increasing at the latest time point measured. The combined AUC of amfenac and nepafenac yielded the highest AUC (471.0 ng × h/mL) of all the products and was significantly higher than the AUC of ketorolac and bromfenac ($P < .05$).

Table 1. Patient Demographics.

Characteristic	Nepafenac 0.1% (n = 25)	Ketorolac 0.4% (n = 25)	Bromfenac 0.09% (n = 25)	*P* Value*
Age (y)				.6360
Mean ± SD	65.9 ± 12.2	68.8 ± 10.7	67.9 ± 9.9	
Range	43.2–88.0	48.7–90.1	50.0–86.8	
Sex, n (%)				1.0000
Male	13 (52.0)	13 (52.0)	13 (52.0)	
Female	12 (48.0)	12 (48.0)	12 (48.0)	
Race, n (%)				.3453
White	21 (84.0)	23 (92.0)	20 (80.0)	
Black	4 (16.0)	1 (4.0)	3 (12.0)	
Hispanic	0	1 (4.0)	1 (4.0)	
Asian	0	0	1 (4.0)	

*Analysis of variance for age comparison between groups; Mantel-Haenszel chi-square test for sex and race comparisons between groups

Table 2. Pharmacokinetic summary.

Drug	Mean AUC (ng × h/mL)	T_{max} (min)	Mean ± SD C_{max} (ng/mL)
Amfenac	180.7	180	70.1 ± 20.1
Nepafenac	308.9	30	205.3 ± 101.7
Ketorolac	176.9	60	57.5 ± 38.8
Bromfenac	47.2	240	25.9 ± 3.9

AUC = area under the curve; C_{max} = peak aqueous humor concentration; T_{max} = time to peak concentration

Figure 2 shows the aqueous humor levels of each analyte over a 4-hour period using a sparse-sampling technique (5 discrete time points). Aqueous humor concentrations of nepafenac were significantly higher than the concentrations of any of the other 3 individual analytes ($P < .05$) and decreased steadily after T_{max} was reached at the first time point of 30 minutes. Ketorolac concentrations peaked at 60 minutes and slowly decreased throughout the remaining 3 hours. Amfenac reached T_{max} at 180 minutes and maintained a statistically similar concentration at 240 minutes. Bromfenac's highest concentration was not reached until the latest time point (240 minutes); thus, it cannot be determined whether this represents bromfenac's T_{max}. Similarly, although bromfenac concentrations were significantly lower than the concentrations of all the other analytes during the 4-hour period tested ($P < .05$), this may not be the case at later time points given that its C_{max} may not have been reached.

Cyclooxygenase Inhibition

Table 3 and Figure 3 show the COX IC_{50} values of each analyte. Ketorolac had the most potent COX-1 inhibition followed by bromfenac, amfenac, and nepafenac. The COX-2 inhibition was greatest with amfenac, followed by bromfenac and ketorolac. Nepafenac showed no measurable COX-2 inhibition under the assay conditions.

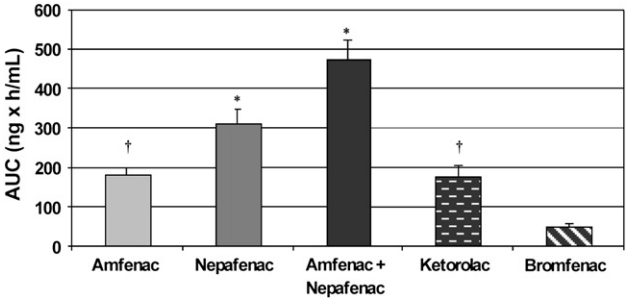

Figure 1. Aqueous humor AUC.

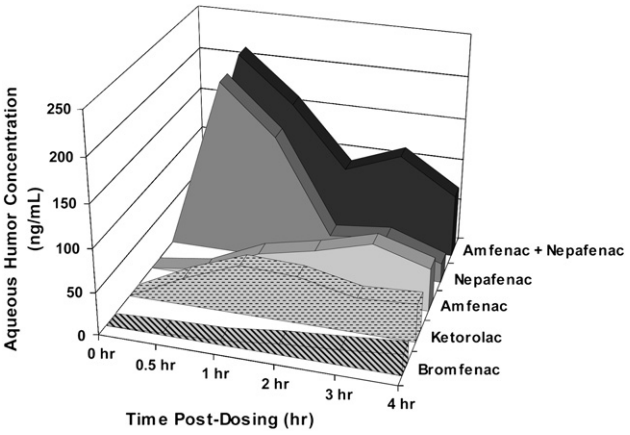

Figure 2. Aqueous humor drug concentration over time.

Safety

One drug-related adverse event was reported. The IOP in 67-year-old man in the Xibrom group was elevated by 8 mm Hg in the operated eye 1 day postoperatively. The adverse event resolved with ß-blocker treatment. No other unexpected changes in visual acuity or IOP over baseline or assessed by slitlamp examination were noted postoperatively in any patient.

DISCUSSION

This is the first study to compare the pharmacokinetics of nepafenac/amfenac, ketorolac, and bromfenac in humans. In addition, this study maintains the design features (ie, randomized, parallel, double-masked, multicenter, active-controlled) required for valid results while simultaneously comparing the market-leading products in a head-to-head fashion. The starting concentrations of the study medications were not identical, ranging from 0.09% (Xibrom) to 0.4% (Acular LS); however, this was designed intentionally to evaluate the actual pharmacokinetics of these FDA-approved agents under actual clinical conditions.

Because nepafenac is a neutral (noncharged) molecule, it has been hypothesized to have greater corneal permeability than other NSAIDs, which have acidic structures.[12] In an in vitro study of rabbit tissue,

Table 3. In vitro pharmacodynamic summary.

Drug	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)
Amfenac	0.138	0.00177
Nepafenac	82.3	>1000
Ketorolac	0.0139	0.0911
Bromfenac	0.0864	0.0112

COX = cyclooxygenase; IC_{50} = half-maximum inhibition relative to control values

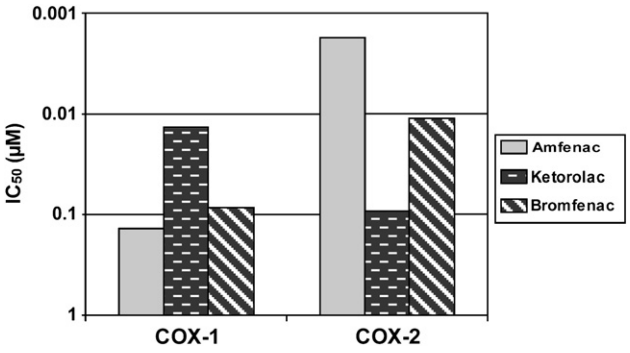

Figure 3. The COX IC_{50} values for each analyte.

nepafenac had 6-fold greater corneal penetration than diclofenac as well as a faster rate of penetration.[9] Similarly, in the current study, nepafenac aqueous humor C_{max} values were 3.6-fold higher than those of ketorolac despite having a starting concentration 4-fold lower (0.1% versus 0.4%). Nepafenac C_{max} values were more than 8-fold higher than those of bromfenac, despite having similar starting concentrations (0.1% versus 0.09%). Furthermore, nepafenac had the shortest T_{max} of all analytes. Therefore, the results in this human study support the conclusions in published preclinical studies indicating that the prodrug nepafenac has a faster corneal penetration rate than other conventional NSAIDs.

Ke et al.[9] report that nepafenac is rapidly converted to its more active metabolite amfenac upon its absorption through the cornea. Conversion occurs predominantly in the intraocular vascular tissues; thus, little amfenac is produced in the cornea.[9] In the current study, nepafenac concentrations in the aqueous humor peaked at the first time point (30 minutes) and declined steadily thereafter. In contrast, amfenac concentration was low at 30 minutes and did not peak until 180 minutes. These observations are consistent with the hypothesis that nepafenac concentrations decline as the prodrug is converted to amfenac, whose levels subsequently increase.

Intraocular drug concentrations are expected to correspond with the antiinflammatory efficacy of a drug. Based on this study, near-maximum concentrations of amfenac appear to be maintained longer than those of ketorolac, suggesting that Nevanac may have a prolonged duration of action relative to other topical products in this class. This may be due to nepafenac's prodrug structure, which allows it to rapidly traverse the cornea, reaching C_{max} in the aqueous humor within 30 minutes. In contrast, amfenac aqueous humor concentrations increase slowly over the course of several hours, which is consistent with the hypothesis that the prodrug nepafenac serves as a reservoir for continued amfenac production. A prolonged COX-inhibitory activity by Nevanac is supported in the literature. Ex vivo inhibition of PG synthesis by nepafenac/amfenac in the iris/ciliary body and the retina/choroid was significantly greater and of longer duration than that of another NSAID.[8]

Because PGE_2 is a known mediator of ocular inflammation, PGE_2 levels are frequently assayed to quantify the amount of inflammation under specific study conditions.[13,14,15] In particular, the study by Bucci et al.[5] reports the aqueous humor PGE_2 levels after ketorolac and nepafenac application. However, the study had several design limitations. First, in the single-center study, a nonstandard preoperative dosing (4 times daily for 2 days) and pulse NSAID dosing (4 drops 90 minutes prior to surgery) were used. No detail on product masking was provided. Finally, PGE_2 analysis was performed on an undefined subset of patients (82 of 132 patients). Accounting for these shortcomings and the highly variable results, the current study was designed to provide the most valid results possible.

In the current study, the results of the analyses of aqueous PGE_2 concentrations were highly variable, which precludes meaningful interpretation of the data. A thorough search of the literature produced a likely explanation for this variability: Production of PGE_2 does not increase immediately after the induction of an inflammatory response; therefore, we measured PGE_2 levels at a time when no inferences of therapeutic activity are possible. In preclinical animal studies, PGE_2 levels did not rise the first 1 to 2 hours after induction; rather, most studies reported a significant increase above baseline levels at 6 hours, with a maximum concentration reached at 14 to 24 hours.[16–19] Given this information, it is likely that the intraoperative aqueous humor PGE_2 levels measured in this study and by Bucci et al. are baseline values.

A noteworthy factor in a drug's anti inflammatory potential is its ability to inhibit COX enzymes. As expected from previously published results and its known status as a prodrug,[8] nepafenac showed less COX-1 and no measurable COX-2 inhibitory activity compared with the other analytes. Although amfenac and ketorolac had similar AUCs, their COX-inhibitory profiles were markedly different. Under the experimental conditions in the current study, ketorolac demonstrated greater COX-1 inhibition and amfenac demonstrated greater COX-2 inhibition. Furthermore, amfenac had the greatest COX-2/COX-1 inhibitory ratio of all other analytes tested in this assay. Bromfenac had intermediate COX-inhibitory activity but the lowest AUC of all analytes.

Although the current study is the first to directly compare the pharmacokinetics and pharmacodynamics of nepafenac/amfenac, ketorolac, and bromfenac, other studies provide some information about

particular analytes and their relationships to one another. Although Gamache et al.[8] report similar inhibitory activity of amfenac against either COX isoform, the current study found that amfenac was more active against COX-2. This highlights an important point when interpreting the literature: Cross-trial interpretations are made difficult because numerous assay variables can significantly affect results. Because many NSAIDs are time-dependent inhibitors, increasing assay incubation times will result in lower (more potent) IC_{50} values. Likewise, variations in other assay conditions (eg, temperature, source of enzymes, measuring oxygen consumption versus PG production) will affect the results. Potential variables between the Gamache study and the current one include incubation times, enzyme purity, and method of measuring enzymatic activity (ie, oxygen consumption versus PG production). These variables make it difficult to directly compare IC_{50} values across trials.

Another study analyzing NSAID COX inhibitory activities was conducted by Waterbury et al.[20] at the same laboratory at which ketorolac and bromfenac were compared (nepafenac and amfenac were not tested). The authors reported that ketorolac inhibited COX-1 more strongly than bromfenac while bromfenac had greater COX-2 inhibitory activity than ketorolac. The same relationship was observed in the current study, providing validation of Waterbury et al.'s results. Although both studies measured COX inhibition by PG production using isolated COX enzymes, there were minor differences in assay conditions, which likely account for the differences in IC_{50} values between studies. This highlights that the rank order of the test compounds in a specific study may be more useful than the IC_{50} values themselves. Because ophthalmologists are often provided COX-inhibition data to compare products, it is critically important to understand the need to compare all products under controlled conditions and within the same study.

The contribution of COX-1 and COX-2 inhibition is key to extrapolating the potential antiinflammatory properties of each drug. Cyclooxygenase-1 is a ubiquitous protein that is important to physiological housekeeping functions such as gastric protection, platelet aggregation, and maintenance of renal function, while COX-2 is an inducible enzyme that is primarily responsible for increased PG production during inflammation in many tissues,[21] including ocular tissues.[22–25] However, in the presence of substrate, both isoforms will convert arachidonic acid into prostanoids.[21] This indicates that NSAIDs with broad cyclooxygenase inhibitory activity could have favorable efficacy profiles.

The greater ocular bioavailability of nepafenac and amfenac, combined with amfenac's broad COX inhibition (COX-1 IC_{50} of 0.138 mM and COX-2 IC_{50} of 0.00177 μmol/L), suggests that Nevanac has a favorable antiinflammatory profile[21–25] and would be expected to perform favorably compared with Acular LS or Xibrom.

Lane et al.[26] recently published the Nevanac pivotal regulatory trial using preoperative 3 times daily dosing for 1 day in all patients who had cataract surgery. These results support Nevanac's safety and efficacy in the control of pain and inflammation associated with cataract surgery. Although the current study suggests advantages based on pharmacokinetic and pharmacodynamic differences, head-to-head studies similar in design to the Lane study are needed. In such studies, the concomitant use of steroids and preoperative NSAID dosing should be standardized. If these variables are not controlled, clinical differentiation between NSAIDs may not be evident. A recent large head-to-head clinical trial using preoperative NSAID dosing in the absence of steroids demonstrated a clinical advantage of nepafenac over ketorolac for pain control 3 days postoperatively and for the prevention of inflammation at day 14 (unpublished data, Alcon Laboratories). Thus, these results support the pharmacokinetic and pharmacodynamic results presented in this report. Finally, nepafenac produced significantly less ocular discomfort than ketorolac.

CONCLUSION

The prodrug nepafenac demonstrated significantly greater ocular bioavailability than any other drug tested, possibly providing a reservoir within the aqueous humor for continued amfenac production. Amfenac was the most potent COX-2 inhibitor compared with ketorolac and bromfenac. This study provides scientific collaboration of preclinical studies and supports the clinical efficacy of Nevanac compared with Acular LS and Xibrom.

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