REFERENCES

1. Liesegang TJ. Traumatic lens abscess: report of a case. Annals Ophthalmol 1983;15:1151–1154.
2. Fish LA, Ragen MT, Smith RE, Lean J. Propionibacterium acnes lens abscess after traumatic implantation of intralenticular cilia. Am J Ophthalmol 1988;105:423–424.
3. Kaushik S, Ram J, Dogra MR, Narang S, Brar GS, Gupta A. Traumatic lens abscess with chronic endophthalmitis successfully treated with pars plana lensectomy and vitrectomy. Ophthalmic Surg Lasers 2001;32;239–242.
4. Stokes DW, O'Day DM. Iris nodule and intralenticular abscess associated with Propionibacterium acne endophthalmitis. Arch Ophthalmol 1992;110:921–922.
5. Manners RM, Canning CR. Posterior lens abscess due to Propionibacterium acnes and Staphylococcus epidermidis following extracapsular cataract extraction. Br J Ophthalmol. 1991;75:710–712.
6. Zeiter JH, Koch DD, Parke DW II, Font RL. Endogenous endophthalmitis with lenticular abscess caused by Enterobacter agglomerans (Erwinia species). Ophthalmic Surg 1989;20:9–12.
7. Shah GK, Vander J, Eagle RC. Intralenticular Candida species abscess in a premature infant. Am J Ophthalmol 2000;129:390–391.

Prostaglandin E_2 Inhibition and Aqueous Concentration of Ketorolac 0.4% (Acular LS) and Nepafenac 0.1% (Nevanac) in Patients Undergoing Phacoemulsification

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PURPOSE: To determine the prostaglandin E_2 (PGE_2) levels and aqueous concentrations achieved with ketorolac 0.4% (Acular LS; Allergan, Inc, Irvine, California, USA) and nepafenac 0.1% (Nevanac; Alcon Laboratories, Inc, Fort Worth, Texas, USA).

DESIGN: Single-center, randomized, double-masked study.

METHODS: One hundred and thirty-two patients received ketorolac or nepafenac four times daily for two days before cataract extraction. Aqueous samples obtained at surgery were analyzed for PGE_2 levels (competitive enzyme immunoassay) and drug concentrations.

RESULTS: More ketorolac eyes than nepafenac eyes had PGE_2 levels less than the level of detection (<100 pg/ml; 26/42 [61.9%] and 7/40 [17.5%], respectively; $P < .001$). Mean PGE_2 levels in ketorolac eyes were lower than that in nepafenac eyes (159.5 ± 114.66 pg/ml and 322 ± 197.8 pg/ml, respectively; $P < .001$). The mean aqueous level was 1079.1 ± 881.5 ng/ml with ketorolac and 353.4 ± 126.0 ng/ml with amfenac. The nepafenac eyes exhibited 588.4 ± 394.6 ng/ml of the inactive nepafenac molecule ($P < .001$ vs ketorolac).

CONCLUSIONS: Ketorolac 0.4% inhibited PGE_2 and penetrated into aqueous significantly more than nepafenac 0.1%. (Am J Ophthalmol 2007;144:146–147. © 2007 by Elsevier Inc. All rights reserved.)

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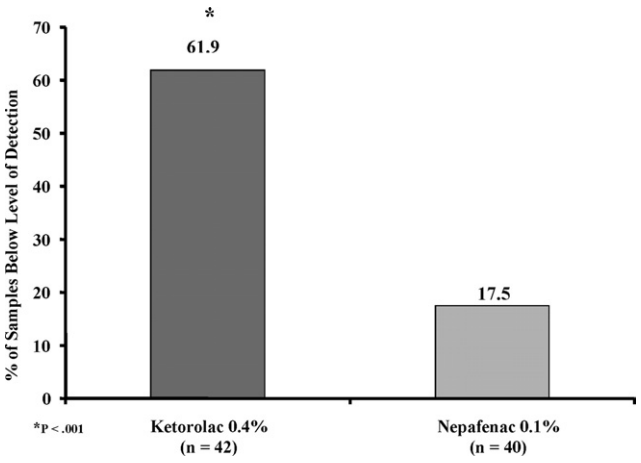

FIGURE 1. Bar graph showing percent of samples treated with ketorolac 0.4% or nepafenac 0.1% that were below the minimum level of detection (100 pg/ml).

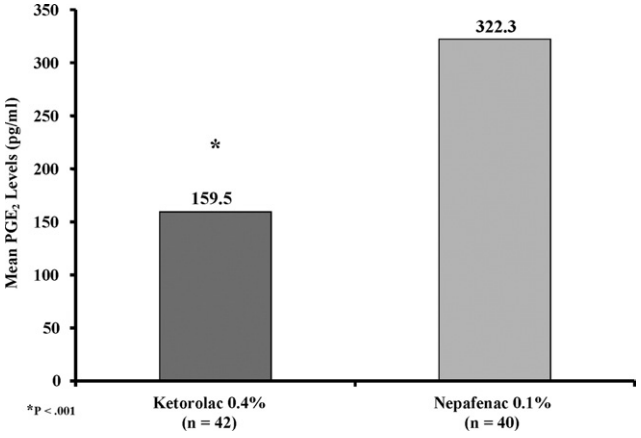

FIGURE 2. Bar graph showing mean prostaglandin E_2 (PGE_2) levels in eyes treated with ketorolac 0.4% and nepafenac 0.1%.

TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) reduce ocular inflammation after ophthalmic surgeries by inhibiting the production of prostaglandins.[1] NSAIDs irreversibly inhibit prostaglandin synthesis by interfering with cyclooxygenases 1 and 2.[2] This study investigated the ocular inhibition of prostaglandin E_2 (PGE_2) and aqueous concentrations achieved by ketorolac

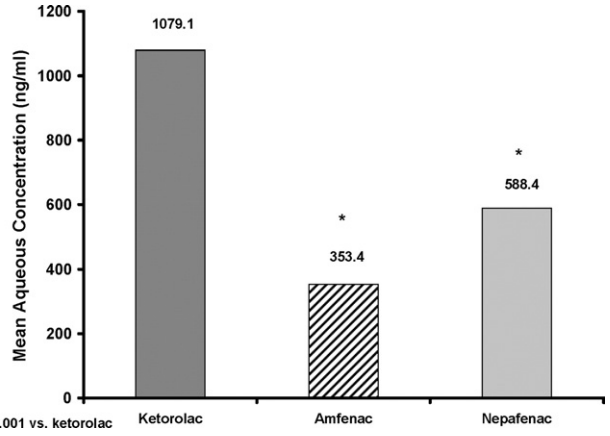

FIGURE 3. Bar graph showing mean aqueous concentration of ketorolac, amfenac, and nepafenac after two days of four times daily treatment followed by dosing four times in the 90 minutes before phacoemulsification.

0.4% and nepafenac 0.1% in eyes of patients undergoing phacoemulsification.

This was a single-center, randomized, double-masked study of 132 patients who received ketorolac or nepafenac four times daily for two days before phacoemulsification. PGE_2 analysis was performed on an initial subset of samples (82/132), and aqueous humor analysis was performed on all 132 samples. The study complied with institutional review board regulations. Patients were excluded if topical NSAID use occurred within one week of study entry or they had undergone prior intraocular surgery.

Patients were randomized to ketorolac or nepafenac four times daily for two days before surgery and an additional four doses in the 90 minutes before phacoemulsification. After creating a paracentesis port, aqueous (0.15 ml) was collected with a 30-gauge needle attached to a tuberculin syringe at the start of the case. For analysis of PGE_2 inhibition, the samples were diluted 1:10 in buffer, assayed in triplicate using a competitive enzyme immunoassay with a monoclonal antibody, and read with a plate reader set at 405 nm. The method of aqueous concentration analysis used 20 μl rabbit aqueous as a surrogate matrix for human aqueous humor for preparation of calibration standards and quality control. Reversed-phase high-performance liquid chromatography was performed using a gradient solvent system at a flow rate of 0.25 ml/minute. Mass spectrometric detection used positive turbo-ion spray ionization and multiple reaction monitoring mode for quantitation.

PGE_2 values were analyzed using two-sample *t* tests with an a priori α level of 0.05. Concentrations were analyzed with an analysis of variance and adjustment for multiple comparisons. StatView Software version 5.0.1 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Ketorolac-treated eyes were significantly more likely to have PGE_2 levels below the level of detection (<100 pg/ml) than nepafenac-treated eyes (26/42 [61.9%] and 7/40 [17.5%]; $P < .001$; Figure 1). Ketorolac eyes exhibited lower PGE_2 levels than nepafenac eyes (159.5 ± 114.66 pg/ml and 322 ± 197.8 pg/ml; $P < .001$; Figure 2). These results assume a value of 99 pg/ml for samples at less than the level of detection. Because significantly more ketorolac-treated samples were at less than the level of detection ($P < .001$), results are likely to favor nepafenac.

Ketorolac was detected at higher levels in the aqueous of ketorolac-treated eyes than amfenac, the active metabolite of nepafenac, in nepafenac-treated eyes ($P < .001$). The mean ketorolac level was 1079.1 ± 881.5 ng/ml, compared with a mean amfenac level of 353.4 ± 126.0 ng/ml. The nepafenac eyes also contained 588.4 ± 394.6 ng/ml of the inactive nepafenac molecule ($P < .001$ vs ketorolac; Figure 3).

Our findings suggest that the prodrug nature of nepafenac does not confer an advantage with regard to ocular penetration and PGE_2 inhibition. Additionally, there was a considerable amount of inactive nepafenac molecule in the aqueous (588.4 ng/ml). Even if this concentration of nepafenac represents a drug that eventually would be hydrolyzed, hydrolysis had not occurred after repeated presurgical dosing, suggesting the nepafenac may not be metabolized to amfenac in time to prevent inflammation resulting from surgery.

It is important to note that dosing for nepafenac in this study was four times daily, exceeding the indicated thrice-daily dosing. This suggests that dosing per label may result in even lower aqueous penetration and PGE_2 inhibition. Finally, we note that visual quality parameters were not measured in this study; therefore, the clinical importance of the difference between the study drugs with regard to visual results is unknown. This clinical study demonstrates that ketorolac 0.4% inhibits PGE_2 synthesis and penetrates into aqueous to a greater extent than nepafenac 0.1% before phacoemulsification.

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REFERENCES

1. McColgin AZ, Heier JS. Control of intraocular inflammation associated with cataract surgery. Curr Opin Ophthalmol 2000;11:3–6.
2. Sciulli MG, Capone ML, Tacconelli S, Patrignani P. The future of traditional nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in the treatment of inflammation and pain. Pharmacol Rep 2005;57:S66–S85.