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Prostaglandin E₂ 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 E₂ (PGE₂) 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).


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 PGE₂ levels (competitive enzyme immunoassay) and drug concentrations.

RESULTS: More ketorolac eyes than nepafenac eyes had PGE₂ levels less than the level of detection (<100 pg/ml; 26/42 [61.9%] and 7/40 [17.5%], respectively; P < .001). Mean PGE₂ 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 PGE₂ and penetrated into aqueous significantly more than nepafenac 0.1%.

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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 E₂ (PGE₂) levels in eyes treated with ketorolac 0.4% and nepafenac 0.1%.

TOPLIC 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 E₂ (PGE₂) and aqueous concentrations achieved by ketorolac...
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. PGE₂ 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 PGE₂ 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 positive turbo-ion spray ionization and mass spectrometric detection used positive turbo-ion spray ionization and multiple reaction monitoring mode for quantitation.

PGE₂ 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 PGE₂ 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 PGE₂ 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 PGE₂ 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 PGE₂ 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 PGE₂ synthesis and penetrates into aqueous to a greater extent than nepafenac 0.1% before phacoemulsification.

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