Pharmacokinetics and pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac

Walters et al.[1] reported that aqueous nepafenac concentrations were significantly higher than those of ketorolac and bromfenac in patients administered a single drop of the nonsteroidal antiinflammatory drug (NSAID) before cataract surgery. In addition, they noted that prostaglandin E_2 (PGE_2) levels were highly variable and "lacked meaningful interpretation." In a similar study in which the dosing regimen was simulated consistent with our clinical practice, we observed that aqueous ketorolac concentrations were significantly higher than nepafenac and amfenac concentrations.[2] In addition, we found that the mean aqueous PGE_2 levels were 50% lower in patients treated with ketorolac than in those treated with nepafenac (159.5 $\pm$ 114.7 pg/mL versus 322.3 $\pm$ 197.8 pg/mL; $P < .001$).[2] Walters et al. criticized our study for using a nonstandard dosing regimen. However, our regimen (4 times a day for 2 days followed by pulse dosing 4 times during the 90 minutes before surgery) mimicked our clinical practice, which is supported by other studies clearly demonstrating the improved efficacy of a 1-day or 3-day preoperative course of topical NSAIDs in conjunction with a pulse dosing strategy just before surgery.[3]

The Walters et al. study included a number of conclusions that did not appear substantiated by the reported data. Nepafenac levels alone or in combination with amfenac were compared with those of the active study drugs, and it was suggested that nepafenac served as a reservoir for continued amfenac production. However, the data presented by Walters et al. demonstrate that nepafenac did not inhibit cyclooxygenase (COX)-2 activity and the half-maximum inhibitory concentration (IC_{50}) for COX-1 inhibition was approximately 100 times higher than the achievable aqueous concentration. This indicates that nepafenac is a prodrug with no in vivo COX inhibitory activity and, therefore, clinically irrelevant. More important, only a fraction of nepafenac was converted to amfenac, despite a steep decrease in aqueous nepafenac concentration. These findings demonstrate that the rate of nepafenac elimination from aqueous humor was far greater than the rate of its conversion to amfenac. Therefore, the nepafenac levels do not translate to an amfenac reservoir in the aqueous humor.

Walters et al. concluded that the exposure to amfenac and ketorolac was similar and significantly higher than the exposure to bromfenac. This conclusion is invalid because the study design ignored the variability of NSAIDs' pharmacokinetics. Consequently, the overall exposure was determined by including timepoints of concentration assessments that represented each study drug at a different stage in the pharmacokinetic curve.

Based on the pharmacokinetic studies reported by Walters et al., amfenac was stated to have a longer near-maximum concentration than ketorolac; it was suggested that it had a prolonged duration of action relative to other topical drugs in this class. However, the Walters et al. study lacked the data to support this conclusion as amfenac concentration was assessed at only 1 timepoint after the peak concentration was reached. Based on the available data, ketorolac maintained near-maximum concentrations longer than amfenac (3 hours versus 2 hours). Given that the dosing frequency of ketorolac and nepafenac is once every 6 and 8 hours, respectively, ketorolac appears to maintain near-maximum concentrations for one-half the dosing cycle, whereas amfenac maintained near-maximum concentrations for one-quarter of the dosing cycle.

Finally, Walters et al. concluded that patients treated with nepafenac had significantly less ocular discomfort than those treated with ketorolac. Yet, they did not present the details about the number of patients experiencing ocular discomfort, the type and duration of the adversities, and the statistical methods used to analyze between-group differences.

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REFERENCES

1. Walters T, Raizman M, Ernest P, Gayton J, Lehmann R. In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. J Cataract Refract Surg 2007; 33:1539–1545
2. Bucci FA Jr, Waterbury LD, Amico LM. Prostaglandin E_2 inhibition and aqueous concentration of ketorolac 0.4% (Acular LS) and nepafenac 0.1% (Nevanac) in patients undergoing phacoemulsification. Am J Ophthalmol 2007; 144:146–147
3. Donnenfeld ED, Perry HD, Wittpenn JR, Solomon R, Nattis A, Chou T. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. J Cataract Refract Surg 2006; 32:1474–1482

REPLY: We thank Bucci and Waterbury for their interest in our study and take this opportunity to address their concerns. First, they cite differences in relative aqueous NSAID concentrations between this study and their previously published study.[1] The most troubling issue with the Bucci study was the comparison of aqueous ketorolac concentration with that of amfenac and nepafenac individually.[2] Since aqueous humor localization of both molecules is a direct result of nepafenac penetration, the concentrations of both must be combined to accurately assess the aqueous penetration of Nevanac.

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