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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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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Next, Bucci and Waterbury take issue with our conclusion that PGE_2 levels could not be meaningfully interpreted, again citing their own research of aqueous PGE_2 levels.[1] However, as we clearly explained in our letter to the editor regarding their study,[2] we learned that measuring PGE_2 levels at the onset of surgery provides no insight into NSAID antiinflammatory activity because it takes hours after ocular insult to achieve elevated PGE_2 levels.[3,4]

Their criticism of our suggestion that nepafenac serves as a reservoir for continued amfenac production[5] may be a result of 2 fundamental misinterpretations. First, nepafenac, as the sole source of the potent COX-1 and COX-2 inhibitor amfenac, is clearly vital to Nevanac's clinical efficacy. Furthermore, they maintain that only a fraction of aqueous nepafenac was converted to amfenac, when almost 60% was converted within only 4 hours. Their claim that the rate of nepafenac elimination from the aqueous was far greater than the rate of amfenac conversion fails to acknowledge that the majority of this "elimination" was actually caused by its conversion to amfenac.

Bucci and Waterbury also charge that we have ignored the variability of the NSAIDs' pharmacokinetics, when, in fact, we have demonstrated this variability by presenting standard deviations of the mean C_{max} values of each analyte. If they are attempting to point out the limitations of measuring pharmacokinetics over a finite time period, this has also been accounted for in each of our interpretations. For instance, they criticize our suggestion that amfenac is likely to have a prolonged duration of action relative to other topical NSAIDs. However, without considering that nepafenac is a reservoir for subsequent amfenac production, amfenac exposure alone during the 4-hour time period was higher than that of ketorolac. While we cannot determine the concentrations beyond this time period, we would expect, based on these results, that amfenac exposure would exceed that of ketorolac beyond 4 hours.

Finally, the unpublished study mentioned by Bucci and Waterbury as having no details provided has since been published[6] and we invite them to read this manuscript for more information on that study.

Despite the above objections by our colleagues, we confidently maintain that our study provides the most comprehensive pharmacokinetic profiles of the leading topical NSAIDs to date, while simultaneously presenting a valid head-to-head potency comparison.—*Tom Walters, MD*

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Consent for cataract surgery: A patient perspective

We were interested in the consent process for cataract surgery discussed by Borovik et al.[1] and Bhojwani et al.[2] Although we appreciate the argument behind the TAHITI approach suggested by Borovik et al., we believe the approach is too simplistic. There is no mention of written information provided to the patients apart from the discussion involving the TAHITI acronym. Written patient information leaflets have been shown to improve patients' understanding of the procedure.[3] Borovik et al. do not indicate at what stage prior to cataract surgery the discussion occurs. This has an important bearing on the process of valid and informed consent.

We did a prospective audit of the consent process for cataract surgery at our unit (Worthing Hospital, United Kingdom). One hundred fifty consecutive patients having cataract surgery were recruited. All were asked to complete an anonymous questionnaire regarding the consent process and to score their understanding of surgery and information provided on a visual analogue scale of 0 (very poor) to 10 (very well) after the surgery.

At pre-assessment, 2 to 4 weeks preoperatively, 53 patients were seen by the specialist nursing staff, who evaluated them for anesthesia options and performed biometry. The nursing staff also provided patients with more verbal and written information about the procedure. A physician reiterated these findings and then obtained consent from these patients. The remaining 97 attended the same pre-assessment appointments but their consent was obtained on the day of the procedure by a physician.