Next-Generation NSAID Therapy

Acuvail receives FDA approval.

BY ERIC D. DONNENFELD, MD

The latest news in advanced therapeutic for cataract and refractive surgery is the FDA's approval of Acuvail (ketorolac 0.45%; Allergan, Inc., Irvine, CA) on July 23, 2009. This preservative-free nonsteroidal anti-inflammatory drug (NSAID) is indicated for the treatment and elimination of pain and inflammation following cataract surgery. The advanced formulation is optimized for efficacy, tolerability, and patient compliance. The new drug provides enhanced ketorolac bioavailability because it is formulated at a pH of 6.8, which enables deionized drug delivery, and it contains carboxymethylcellulose, which promotes the adherence of ketorolac to the ocular surface. Acuvail is a very different product than the previous formulation, and the new drug achieves therapeutic levels with twice-a-day therapy that could not be accomplished with the older version.

Because patients undergoing cataract surgery today have high postoperative expectations, ophthalmologists need to provide them with optimal comfort and safety in addition to an effective procedure. Topical NSAIDs significantly reduce the incidence of cystoid macular edema after cataract surgery, reduce patients' discomfort, increase pupillary size while preventing miosis during surgery, and reduce the incidence of surgical complications.[1] This article discusses how Acuvail can achieve the aforementioned goals.

FDA TRIAL

Efficacy and Safety

In the FDA trial, the efficacy and safety of ketorolac 0.45% was investigated in two identically designed, multicenter, double-masked prospective trials enrolling more than 500 patients. According to this trials' unpublished data, subjects were randomized 2:1 to twice-daily treatment with ketorolac 0.45% or vehicle control for 16 days. All patients were instructed to begin administering their assigned study agent on the day before surgery.

> "Acuvail is a preservative-free NSAID indicated for the treatment and elimination of pain and inflammation following cataract surgery."

Resolution of inflammation at postoperative day 14 was evaluated as the primary efficacy endpoint and showed the statistically significantly superior efficacy of ketorolac 0.45% versus the vehicle. Fifty-two percent of ketorolac patients and only 26% of controls achieved a summed ocular inflammation score of zero cell and flare ($P < .001$). The efficacy of ketorolac 0.45% b.i.d. was actually documented much earlier. By postoperative day 7, 32% of ketorolac-treated patients had already achieved complete elimination of inflammation, as evidenced by no cells in the anterior chamber compared with only 17% of controls. The benefit of ketorolac was statistically significant and clinically impressive.

Pain relief was assessed as a secondary outcome measure, and the FDA data showed that ketorolac was also highly effective in controlling pain. On the first day after surgery, nearly three-quarters of ketorolac patients (72%) were completely free of pain compared with only 40% of patients in the control group ($P < .001$).

NSAIDs reduce the pain and inflammation associated with cataract surgery by inhibiting the production of prostaglandins by cyclooxygenase (COX), which has two isoforms: COX-1, the constitutive enzyme, and COX-2, the inducible form. The results of previous unpublished studies and others indicate that inhibiting both isoforms is important for preventing prostaglandin release after the trauma induced by ocular surgery.[1] The efficacy of Acuvail can be attributed to its intrinsic properties as a potent inhibitor of both COX-1 and COX-2 along with the enhanced bioavailability characteristics of this new formulation of ketorolac.

Data on adverse events from the pivotal trials showed that only 1.5% (5/330) of ketorolac patients reported burning/stinging. That low rate can be attributed to multiple features of the formulation, including the deionized form of the active ingredient, the carboxymethylcellulose in the formulation, the lack of preservative, and the pH.

Acuvail is expected to be available to patients and physicians later this month. The use of a potent NSAID has been found to dramatically improve surgical results with cataract extraction.[1]

With its potent anti-inflammatory effect and twice-a-day dosing, which should increase patients' compliance, Acuvail is a welcome addition to the cataract surgery armamentarium. ■

Eric D. Donnenfeld, MD, is a trustee of Dartmouth Medical School in Hanover, New Hampshire, and he is a partner in Ophthalmic Consultants of Long Island in Rockville Centre, New York. He is a consultant to Allergan, Inc. Dr. Donnenfeld may be reached at (516) 766-2519; eddoph@aol.com.

1. Donnenfeld ED, Perry HD, Wittpenn JR, et al. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. J Cataract Refract Surg. 2006;2(9):1474-1482.