NSAIDs, CME, and Cataract Surgery

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Each installment of the "Peer Review" column examines an important issue in ophthalmology through key studies from the peer-reviewed literature selected by Section Editor Mitchell C. Shultz, MD.

Pseudophakic cystoid macular edema (CME) is an inflammatory reaction associated with cataract surgery that produces localized swelling of the retina. Physicians previously distinguished between angiographic and clinically significant CME (visual acuity of 20/40 or worse), but studies have shown that even subtle thickening of the macula can lead to suboptimal visual acuity and reduced contrast sensitivity.[1] These adverse outcomes are particularly detrimental to patients who receive presbyopia-correcting IOLs and may contribute to their dissatisfaction with their postoperative vision.[2]

The introduction of optical coherence tomography (OCT) has shown that the incidence of pseudophakic CME is higher than surgeons previously thought. This revelation has prompted the development of strategies for preventing pseudophakic CME. Although ophthalmic formulations of topical nonsteroidal anti-inflammatory drugs (NSAIDs) are officially approved only for the maintenance of mydriasis during cataract surgery and for controlling postoperative pain, surgeons have begun using these agents to prevent CME. Consequently, the off-label use of topical NSAIDs such as Acular (ketorolac 0.5%; Allergan, Inc., Irvine, CA), Xibrom (bromfenac 0.09%; Ista Pharmaceuticals, Irvine, CA), Voltaren (diclofenac 0.1%; Novartis Pharmaceuticals Corporation, East Hanover, NJ), and Nevanac (nepafenac 0.1%; Alcon Laboratories, Inc., Fort Worth, TX) has become the standard of care for patients undergoing cataract surgery.

Recent research has focused on the comparative efficacy of the available topical NSAIDs. Although early investigations did not strongly support the use of these drugs after cataract surgery,[3] additional in vivo and in vitro studies suggest that NSAIDs may help reduce the risk of CME not only in high-risk patients but also in those undergoing routine cataract surgery.

RISK FACTORS FOR CME

An analysis of 1,659 cataract surgeries performed at the Massachusetts Eye and Ear Infirmary in Boston between 2001 and 2006 showed that patients who previously had a retinal vein occlusion ($P<.001$), an epiretinal membrane ($P=.07$), and a history of prostaglandin use ($P=.27$) had an elevated risk of developing CME after cataract surgery. The investigators did not observe a similar relationship between CME and factors such as systemic hypertension ($P=.87$), ischemic heart disease ($P=.77$), previous intraocular surgery ($P=1.00$) or a history of uveitis ($P=1.00$). The rate of recovery among patients who developed CME (n = 39) varied according to treatment regimen (72 ±6.9 days for NSAIDs only, 82.6 ±56.9 days for NSAIDs and steroids,176 ±106.5 days for steroid only). Patients treated with a combination of NSAIDs and steroids had significantly shorter times to resolution than those who did not receive medical intervention (249 ±2.8 days).[4]

The investigators suggested that patients who use prostaglandin analogs, who have a history of epiretinal membrane, or who experienced a previous retinal vein occlusion could be susceptible to CME, because "these conditions represent states in which the integrity of the blood-retinal barrier is compromised."[4] The rationale behind the prophylactic use of NSAIDs, therefore, is to inhibit the production of cyclo-oxygenase and prevent additional insult to blood vessels that are susceptible to inflammation.[4]

A prospective, double-masked study of 50 patients randomized to use diclofenac or the corticosteroid fluorometholone for 5 weeks after cataract surgery supported the idea that NSAIDs reduce the risk of CME by maintaining the integrity of the blood-aqueous and blood-retinal barriers. Two weeks postoperatively, Miyake et al found that the patients who used fluo-

rometholone had reduced choroidal blood flow compared with those who used diclofenac. Based on the hypothesis that the exposure to prostaglandins can diminish choroidal blood flow and the observation that the patients who used the NSAID had less aqueous flare than those who used the steroid, the investigators concluded that diclofenac prevented CME more effectively than fluorometholone in pseudophakic eyes during the early postoperative period.[5]

MEASURING THE EFFICACY OF NSAIDs

Setting Clinical Endpoints

The use of Doppler flowmetry in the aforementioned study[5] is atypical for a clinical investigation of an NSAID. To evaluate the efficacy of these drugs, most trials use subjective criteria (quality-of-life questionnaires, degree of ocular discomfort, time to resolution of pain) and objective criteria (concentration of drug in the aqueous, resolution of inflammation and flare, macular thickness). Nevertheless, it is sometimes difficult to compare the efficacy of different NSAIDs, because investigators do not always choose the same outcome measures.

Bromfenac

According to Donnenfeld et al, bromfenac 0.09% was the first ophthalmic NSAID approved by the FDA for the reduction of inflammation in the anterior chamber after cataract surgery.[6] This drug was cleared for clinical use based on the results of two phase 3, multicenter, double-masked, placebo-controlled trials in which 527 patients were randomized to use bromfenac (n = 256) or a placebo (n = 171) b.i.d. for 14 days after cataract surgery. Because the investigators did not observe any adverse systemic events or hepatic toxicity among the patients treated with bromfenac, they concluded that the drug had an "excellent safety profile."[7]

Another analysis of the same studies showed that 64% (228 of 356) of the patients who used bromfenac after cataract surgery had a complete resolution of postoperative inflammation after 15 days versus only 43.3% of patients who instilled a placebo according to the same dosing schedule. Bromfenac was also associated with a shorter mean time to the resolution of postoperative pain (2 vs 5 days for placebo).[6]

Ketorolac

Several clinical studies have examined the efficacy and safety of ketorolac. In a prospective, double-masked trial, Sandoval et al found that ketorolac 0.4% and ketorolac 0.5% were similarly efficacious at reducing postoperative inflammation after cataract surgery. The investigators did note, however, that a significantly higher percentage of patients who used ketorolac 0.5% experienced ocular discomfort when they instilled the eye drops on the first postoperative day compared with the patients who used ketorolac 0.4% (70% vs 40%; P=.001).[8]

In a randomized study designed to determine the optimal dosing schedule of ketorolac, 100 patients instilled the drug in their eyes q.i.d. for 3 days (n = 25), q.i.d. for 1 day (n = 25), or three times every 15 minutes during the hour before cataract surgery (n = 25). Patients in a fourth study group (n = 25) administered a placebo every 15 minutes during the hour before surgery.

The investigators found that the patients who followed the 3- and 1-day dosing regimens had significantly less anterior chamber inflammation, a lower incidence of CME, less intra- and postoperative discomfort, and shorter mean surgical and ultrasound times than those who used the placebo or ketorolac only in the hour before surgery. Based on these results, the researchers stated, "patients should be given a 3-day dosing regimen of ketorolac before phacoemulsification to optimize surgical outcomes." [9] If this is not possible, they added, "even 1 day of ketorolac therapy can provide substantial patient benefit."[9]

Wittpenn et al found that none of the patients (n = 268) who used a combination of ketorolac 0.4% and prednisolone acetate 1% q.i.d. for approximately 4 weeks after cataract surgery developed clinically apparent CME. In contrast, the investigators observed this condition among 1.8% (five of 278) of patients who used prednisolone only. OCT also showed a statistically significant difference in mean retinal thickening between the ketorolac-plus-steroid group and the steroid-only group (3.9 vs 9.6 µm; P=.003). The researchers concluded that "adding perioperative ketorolac to postoperative prednisolone significantly reduces the incidence of CME and macular thickening in cataract surgery patients already at low risk for this condition."[10]

Almeida et al also found that patients who used a combination of ketorolac and prednisolone (n = 53) had 45.8% less macular swelling (0.2392 mm^3 of accumulated fluid) than those who used only prednisolone (n = 53; 0.4420 mm^3 of accumulated fluid; P=.009) for 29 days after cataract surgery. The investigators therefore concluded that "total macular volume, a direct measure of macular swelling with low interobserver variability and a surrogate of CME pathogenesis, was significantly lower in the ketorolac group than in the control group."[11]

Nepafenac

Nepafenac differs from other ocular NSAIDs, because its prodrug formulation is converted to amfenac inside the eye. This process reportedly prevents the drug from accumulating in the cornea and increases its therapeutic duration inside the eye.[12] Several studies have evaluated nepafenac's efficacy for inhibiting prostaglandin synthesis and stabilizing the blood/retina barrier after cataract surgery.

In a randomized, double-blind, vehicle-controlled trial of 476 patients at 21 ophthalmologic clinics in the United States, Lane et al found that t.i.d. dosing with nepafenac after cataract surgery was associated with "lower mean aqueous cells, flare, and cells plus flare scores at all visits" compared with a placebo ($P<.0001$). By postoperative day 14, 62.6% (152 of 243) of patients in the nepafenac group were cured (aqueous cells score + aqueous flare score = 0) versus 17.2% (40 of 233) of patients in the placebo group. The study also suggested that nepafenac controlled postoperative pain better than the placebo, because almost twice as many patients who used the prodrug NSAID reported being free of pain at all visits (83.1% to 93% vs 41.6% to 46.4%, respectively).[13]

In a small case series, Hariprasad et al found that nepafenac effectively reduced ocular inflammation in patients who had acute (n = 3) or chronic (n = 3) CME. A comparison of OCT scans obtained at baseline and 3 weeks after t.i.d. dosing with nepafenac showed that the NSAID reduced the patients' retinal thickness by a mean of 282.8 µm (range, 531.3 to 248.5 µm). In addition, nepafenac was associated with a mean improvement in visual acuity of 2.5 lines and a "sustained inhibition of prostaglandin synthesis relative to [diclofenac] (6 hours vs 20 minutes.)"[14]

A retrospective review of charts by Wolf et al found a higher incidence of visually significant CME among patients who used prednisolone alone (five of 240) than among those who used a combination of nepafenac and prednisolone (zero of 210) for 1 month after uneventful cataract surgery ($P=.0354$).[15]

Nepafenac Versus Ketorolac

Researchers frequently use the concentration of an NSAID in the aqueous as a surrogate measure of the drug's efficacy. As the following series of articles shows, however, investigators evaluating the same drug often reach contradictory conclusions about its bioavailability and ability to inhibit the production of prostaglandins.

Bucci et al compared the level of prostaglandin E2 (PGE2) in the aqueous of patients who used ketorolac 0.4% or nepafenac 0.1% q.i.d. for 2 days before they underwent cataract surgery. Because the investigators detected higher mean levels of PGE2 in the aqueous of patients who used nepafenac (322 ±197.8 ng/mL vs 1.59.5 ±114.66 ng/mL with ketorolac) and a higher concentration of active ingredient in the aqueous of patients who used ketorolac (1,079.1 ±881.5 ng/mL vs 353.4 ±126.0 ng/mL of amfenac), they concluded that "the prodrug nature of nepafenac does not confer an advantage with regard to ocular penetration and PGE2 inhibition."[16]

In their comparison of aqueous concentrations of nepafenac 0.1%, ketorolac 0.5%, and bromfenac 0.9%, Walters et al concluded that "the prodrug demonstrated greater ocular bioavailability" as measured by peak concentration, time to peak concentration, and the area under the curve, "possibly providing a reservoir within the aqueous humor for continued amfenac production."[17] The investigators also asserted that "the results of the analyses of aqueous PGE2 concentrations were highly variable, which would preclude a meaningful interpretation of the data."[17] This assertion calls into question the methods of comparison used by Bucci et al.[16]

The subsequent exchange between Bucci et al and Walters[18] argues various aspects of each study's design and the investigators' choice of outcome measurements. This debate illustrates how difficult it can be to compare the efficacy of different NSAIDs based on clinical studies.

Duong et al used a combination of subjective and objective outcome measures to compare the efficacy of nepafenac and ketorolac.[19] Although the investigators did not note any statistically significant difference between the drugs' ability to reduce inflammation and improve visual acuity after cataract surgery, they found that patients who used ketorolac q.i.d. (n = 94) consistently reported lower pain scores on a questionnaire than those who used nepafenac t.i.d. (n = 89; $P=.025$) for 3 days preoperatively and 7 days postoperatively. Both treatment regimens included prednisolone and an anti-infective agent. Patients in each study group used a steroid and antibiotic produced by different companies (Pred Forte and Zymar [both from Allergan, Inc.] with ketorolac; Econopred and Vigamox [both from Alcon Laboratories, Inc.] for nepafenac).

In a letter to the editor, James P. McCulley, MD, questioned the results of the prospective trial conducted by Duong et al. He argued that there were flaws in the study's design, including the NSAIDs' different dosing regimens, the pairing of each NSAID with a different steroid and fourth-generation fluoroquinolone, and a failure of the investigators to describe how they graded

posterior capsular opacification.[20] The reply from Duong et al addressed each of McCulley's points separately, but it did not offer additional information about the outcome of their study. They pointed out, however, that "the study was conducted at a single-center private practice and no party involved had any financial proprietary gains."[20]

IS PROPHYLAXIS NECESSARY?

While investigators continue to compare how quickly various NSAIDs reach therapeutic concentrations in the anterior chamber and whether one drug prevents postoperative CME more effectively than the others, Kim and Stark have asked if it is necessary to use these drugs for low-risk patients undergoing routine cataract surgery. They argue that most cases of subclinical CME (as detected with OCT) resolve spontaneously by 6 weeks postoperatively. Kim and Stark added that, after 3 months, the prophylactic use of NSAIDs does not produce a statistically significant difference in measures of visual acuity. "If vision is our primary concern," they asked, "how much do 'low-risk' patients benefit from prophylaxis with NSAID therapy?"[21] Kim and Stark instead advocate reserving topical NSAIDs for high-risk patients, and they encouraged investigators to designate visual function (vs measuring aqueous concentration or macular thickness) as the primary endpoint of studies evaluating the prevention and treatment of CME.[21] ■

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1. Wittpenn J, Silverstein SM, Hunkeler JD, et al. Subclinical cystoid macular edema reduces contrast sensitivity and final visual acuity in low-risk cataract patients. Poster presented at: The Annual Meeting of the Association for Research In Vision and Ophthalmology; May 10, 2007; Fort Lauderdale, FL.
2. Donnenfeld E, Solomon K. The effect of a topical NSAID on quality of vision with a multifocal IOL. Paper presented at: The 2006 ASCRS Symposium on Cataract, IOL, and Refractive Surgery; March 19, 2006; San Francisco, CA.
3. Sivaprasad S, Bunce C, Wormald R. Non-steroidal anti-inflammatory oedema following cataract surgery: a systematic review. *Br J Ophthalmol*. 2005;89:1420-1422.
4. Henderson BA, Kim JY, Ament CS, et al. Clinical pseudophakic cystoid macular edema. Risk factors for development and duration after treatment. *J Cataract Refract Surg*. 2007;33:1550-1558.
5. Miyake K, Nishimura K, Harino S, et al. The effect of topical diclofenac on choroidal blood flow in early postoperative pseudophakias with regard to cystoid macular edema formation. *Invest Ophthal Vis Sci*. 2007;48(12)5647-5652.
6. Donnenfeld ED, Holland EJ, Stewart RH, et al. Bromfenac ophthalmic solution 0.09% (Xibrom) for postoperative ocular pain and inflammation. *Ophthalmology*. 2007;114:1653-1662.
7. Stewart RH, Grillone LR, Shiffman M, et al. The systemic safety of bromfenac ophthalmic solution 0.09%. *J Ocular Pharm Ther*. 2007;23:601-612.
8. Sandoval HP, Fernandez de Castro LE, Vroman DT, Solomon KD. Evaluation of 0.4% ketorolac tromethamine ophthalmic solution versus 0.5% ketorolac tromethamine ophthalmic solution after phacoemulsification and intraocular lens implantation. *J Ocular Pharmacol Ther*. 2006;22:251-257.
**9. Donnenfeld ED, Perry HD, Wittpenn JR, et al. Preoperative ketorolac tromethamine 0.4% in phacoemulsification outcomes: pharmacokinetic-response curve. *J Cataract Refract Surg*. 2005;32:1474-1482.
**10. Wittpen JR, Silverstein S, Heier J, et al. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am J Ophthalmol*. 2008;146(4):554-560.
11. Almeida DRP, Johnson D, Hollands H, et al. Effect of prophylactic nonsteroidal anti-inflammatory drugs on cystoid macular edema assessed using optical coherence tomography quantification of total macular volume after cataract surgery. *J Cataract Refract Surg*. 2008;34:64-69.
*12. Lindstrom R, Kim T. Ocular permeation and inhibition of retinal inflammation: an examination of data and expert opinion on the clinical utility of nepafenac. *Curr Med Res Opin*. 2006;22(2):397-404.
*13. Lane SS, Modi SS, Lehmann RP, Holland EJ. Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg*. 2007;33:53-58.
14. Hariprasad SM, Callanan D, Gainey S, et al. Cystoid and diabetic macular edema treated with nepafenac 0.1%. *J Ocular Pharm Ther*. 2007;23:585-589.
15. Wolf EJ, Braunstein A, Shih C, et al. Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac. *J Cataract Refract Surg*. 2007;33:1546-1549.
16. Bucci FA Jr, Waterbury D, Amico L. Prostaglandin E2 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.
*17. Walters T, Raizman M, Ernest P, et al. In vivo pharmacokinetics and in vitro pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. *J Cataract Refract Surg*. 2007;33:1539-1545.
18. Bucci FA Jr, Waterbury LD. Pharmacokinetics and pharmacodynamics of nepafenac, amfenac, ketorolac, and bromfenac. *J Cataract Refract Surg*. 2008;34(8):1226; author reply 1226-1227.
19. Duong H-VQ, Westfield K, Chalkney THF. Ketorolac tromethamine LS 0.4% versus nepafenac 0.1% in patients having cataract surgery. Prospective randomized double-masked clinical trial. *J Cataract Refract Surg*. 2007;33:1925-1929.
20. McCulley JP. Ketorolac versus nepafenac in cataract surgery. J *Cataract Refract Surg*. 2008;34:345-346; author reply 346.
21. Kim A, Stark WJ. Are topical NSAIDs needed for routine cataract surgery? [editorial]. *Am J Ophthalmol*. 2008;146(4):483-486.

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