# Nonsteroidal Anti-inflammatory Drugs and Cataract Surgery

PROSTAGLANDINS ARE 20-carbon metabolites of arachidonic acid that are biosynthesized by ocular tissues and are involved in human intraocular inflammation.[1] They are released in response to ocular trauma, including surgery.[2] When released in large concentrations following trauma, intraocular surgery, or in association with uveitis, they may contribute to the disruption of the blood-aqueous barrier, miosis, and cystoid macular edema (CME). By inhibiting the cyclooxygenase pathway of prostaglandin biosynthesis, a major metabolic pathway of arachidonic acid, nonsteroidal anti-inflammatory drugs (NSAIDs) may be useful in patients undergoing cataract surgery.[3] Inhibitors of the lipoxygenase pathway, another major pathway of arachidonic acid metabolism, also are being evaluated.

The US Food and Drug Administration (FDA) has approved several topical NSAIDs, each primarily a cyclooxygenase inhibitor, for clinical use in ophthalmology, but these approvals have been limited solely to specific indications. For example, flurbiprofen sodium (Ocufen) and suprofen (Profenal) are only approved for the prophylaxis of surgical miosis. Ketorolac tromethamine (Acular) has recently been approved for the relief of itching due to occasional allergic conjunctivitis, and diclofenac sodium (Voltaren) has been approved for the treatment of postcataract inflammation.

Although there are only a few approved indications for marketed topical NSAIDs, it is likely that there are other valid clinical uses for these agents. These limited approved indications may solely represent an expedient strategy by the manufacturer to obtain approval from the FDA to market a drug and do not necessarily reflect any judgment concerning whether an agent is best suited for one indication or another.

The FDA oversees manufacturer labeling (package insert), advertising, and promotion; it does not approve or disapprove of how a legally marketed drug is used by a practitioner. Hence, many valid uses of drugs are recognized before they are included, if ever, in product labels. Often there is no financial incentive for a manufacturer to pursue approval for either a common or uncommon need. For many other reasons, valid uses of marketed drugs may never be added to existing labeling. These comments are particularly relevant to patients undergoing cataract surgery as there has been recent attention directed at the adjunctive use of NSAIDs in this setting.[3]

Potential uses of NSAIDs with cataract surgery include preventing the disruption or facilitating the reformation of the blood-aqueous barrier, decreasing flare and cells in the eye, and prophylaxis of or therapy for CME. Since CME is the most frequent cause of visual loss following modern-day cataract surgery, any method of preventing it or treating it would be of great benefit.[4-8] However, to date, no available topical NSAID has been approved for treating CME. How can a clinician determine whether a marketed topical NSAID should be used for an indication that is not on the product label (eg, treatment of CME)? In large part, the decision should depend on the availability of well-designed, appropriate clinical trials. This article will review what has been published to date on this topic and provide a rational basis for future clinical trials.

## MIOSIS

Several studies have suggested that the use of topical NSAIDs may decrease intraoperative miosis and that this effect facilitates planned extracapsular surgery or phacoemulsification.[9-11] It has been suggested that the miosis that may occur during cataract surgery is partly mediated by prostaglandins, although not all investigators agree with this.[12-14] There is considerable variation in the degree of miosis reported by different investigators and the apparent effect of NSAIDs.[2,12,13] Although widely used by cataract surgeons, the effect on miosis of these drugs, especially when compared with the effect of epinephrine in the infusion fluid and the use of anticholinergic drugs,[12] is small. It is likely that other mediators, not inhibited by NSAIDs or parasympatholytic drugs, play some role in the residual miosis that is seen despite the use of NSAIDs and anticholinergic agents.[1,2,15]

## POSTCATARACT SURGERY INFLAMMATION

Disruption of the blood-aqueous barrier and cellular infiltration with consequent inflammation are undesirable results of intraocular manipulation seen following cataract surgery. Intraocular inflammation can cause increased intraocular pressure; adhesions of the iris to the

angle, lens implant, lens capsule or vitreous; deposits on the implant; opacification of the posterior capsule; and in severe cases can result in substantial visual impairment. From studies conducted to date,[3,16-20] there is some evidence that topical NSAIDs may be of benefit when used for the prophylaxis and treatment of postoperative inflammation following cataract surgery.

To study the efficacy of NSAIDs and other anti-inflammatory drugs, several techniques have been applied in cataract patients to provide an objective measurement of inflammation after cataract surgery. A flare-cell meter (Kowa FC-1000, Kowa Company Ltd, Japan) is available that quantitates the amount of aqueous flare and the number of cells in the aqueous humor. Breakdown of the blood-aqueous barrier can also be quantitated by the measurement of fluorescein dye levels in the aqueous humor following intravenous injection of fluorescein (anterior segment fluorophotometry). It should be recognized that the increased leakage of fluorescein following surgical manipulation may not be measuring the same phenomenon as the measurement of flare and cells. Nonsteroidal anti-inflammatory drugs, including flurbiprofen, diclofenac, and ketorolac, reduce the breakdown of the blood-aqueous barrier as measured by aqueous fluorophotometry.[16-20]

To prevent or treat postoperative inflammation, many surgeons use a one-time injection of corticosteroid subconjunctivally or under Tenon's capsule at the end of surgery and a regimen of postoperative topical corticosteroids. To our knowledge, there are no well-conceived studies demonstrating the benefit of the injected corticosteroids. In the postoperative period, possible regimens include topical corticosteroids, topical NSAIDs, combinations of these agents, or no medication at all. Although postoperative eyes usually have only mild signs of anterior segment inflammation, most cataract surgeons at present utilize anti-inflammatory therapy in an attempt to ameliorate it and to prevent occasional, more severe inflammation. While topical corticosteroids have been the mainstay of therapy for many years, results from recent studies mentioned above[16-20] have suggested that topical NSAIDs (flurbiprofen, diclofenac, and ketorolac) are at least as effective and perhaps more effective than corticosteroids in preventing disruption of or reestablishing the blood-aqueous barrier following cataract surgery (as measured by flurophotometry).

## CME FOLLOWING CATARACT SURGERY

The occurrence of the Irvine-Gass syndrome following cataract surgery is defined by the presence of cystic spaces in the fovea on clinical examination and by leakage of fluorescein dye in a cystoid pattern in the macula.[6] Angiographic CME is much more common than visually significant CME, being present in about 20% of eyes undergoing planned extracapsular lens extraction or phacoemulsification.[6] Chronic, visually significant macular edema, namely, sustained macular edema severe enough to affect visual acuity, occurs in perhaps 1% to 2% of patients. Many trials have demonstrated that prophylactic topical NSAIDs help to prevent the development of angiographic CME in the postoperative period.[5,7] To date, however, there are few data available concerning the visual impairment associated with CME and the sustained benefit, if any, of pharmacological prophylaxis or treatment. Is the treatment of large numbers of patients with topical NSAIDs to prevent a relatively small number of patients from developing angiographic CME and possibly an even smaller number from developing visually significant clinical CME of sufficient value to approve these drugs for this clinical use? Without a clear answer to this question, clinical investigations have been focused on the therapy of established, visually significant CME. Evidence from retrospective studies has prompted some to conclude that postoperatively administered corticosteroids (topical, periocular, or oral) are beneficial in the treatment of established CME.[21,22] A recent study has concluded that a corticosteroid-induced rise in intraocular pressure may play a role in the beneficial response to topical corticosteroids.[23] However, no prospective, randomized studies have been performed with topical, systemic, or periocular corticosteroids alone for the treatment of postsurgical angiographic or visually significant CME.

Two prospective, randomized studies have been performed with topical ketorolac, an NSAID. In a randomized, prospective, masked, controlled pilot study involving 26 patients, Flach et al[24] demonstrated that eight of 13 patients with chronic CME treated with ketorolac four times daily for 60 days showed an improvement in visual acuity of 2 Snellen lines compared with one of 13 in a placebo group ($P$=.005). Furthermore, no patients in the ketorolac group had a decrease in visual acuity while two patients in the placebo group showed a decrease in visual acuity of 2 Snellen lines or more. The shortcomings of this study were the small number of patients involved and the relatively short follow-up period of 60 days. In a second randomized, prospective, multicenter, masked, controlled study of 120 patients, an improvement in visual acuity of at least 2 Snellen lines was demonstrated in patients with established CME after 30, 60, and 90 days of topical treatment with ketorolac, and then 30 days after treatment was stopped.[25] This study still did not attempt to demonstrate a benefit beyond 120 days after the initiation of treatment. In addition, there was no comparison made with the possible efficacy of topical corticosteroids, the present mainstay of therapy. These two studies suggest that ketorolac is effective for the treatment of visually significant chronic CME. Because NSAIDs may be more effective in stabilizing the blood-aqueous barrier than topical corticosteroids (at least as measured by fluorophotometry)[16-20] and may prevent angiographic CME,[5,7] it can be argued that topical ketorolac or a similar drug might be a better routine postoperative anti-inflammatory drug than topical corticosteroids. Alternatively, the two drugs

may have additive effects (when used concurrently) that might allow the doses to be reduced with fewer side effects. However, no direct comparison of NSAIDs and corticosteroids (or adjunctive study of the combined use) has been reported that measures either the presence of flare and cells in the anterior chamber or the development of CME.

Topical NSAIDs may have other possible benefits compared with topical corticosteroids. Corticosteroids can raise intraocular pressure, worsen herpes keratitis, and interfere with wound healing. There are only scant data so far on whether NSAIDs can raise intraocular pressure, effect herpes infection,[26] or influence wound healing. These are very important studies that need to be undertaken. Topical NSAIDs may also have a strong analgesic effect,[27] an added benefit. Besides these beneficial effects, topical NSAIDs also may have adverse consequences. By inhibiting the cyclooxygenase pathway, more substrate may be available for metabolism via the lipoxygenase pathway. This could lead to the increased biosynthesis and release of a proinflammatory substance such as leukotriene $B_4$. Topical NSAIDs can produce superficial punctate keratopathy, but in most patients this does not appear to interfere with therapy. Also, they could theoretically interfere with platelet function if systemic blood levels were achieved.

At present, NSAIDs are generally more expensive than corticosteroids, but as more experience is gained with NSAIDs, increased use and competition should decrease the price.

It is now clear that prospective head-to-head randomized therapeutic trials comparing topical NSAIDs with topical corticosteroids for their effects on postcataract aqueous flare and cell and their effects on visually significant CME are necessary. Since ketorolac has already been shown to be more efficacious for treatment of postoperative visually significant CME than placebo, at least for 120 days, short-term comparisons of corticosteroids with NSAIDs for therapy of CME do not require a placebo arm. However, long-term trials of NSAID therapy for CME should include a placebo arm.

The ophthalmologist must decide whether to use topical corticosteroids, the standard therapy, with their potential adverse effects on wound healing and intraocular pressure, or topical NSAIDs with their possible increased benefit, unknown effect on wound healing and intraocular pressure, higher cost, and limited track record. The choice will not be clear until further well-designed clinical trials are performed.

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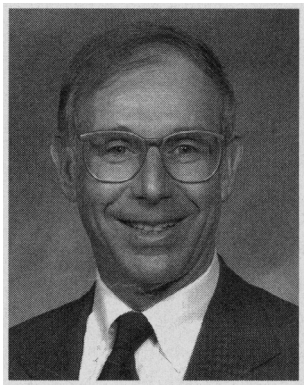
# A New Editor and a Birthday for the *Archives of Ophthalmology*

THIS YEAR, the *Archives of Ophthalmology* celebrates its 125th anniversary of continuous publication. It seems fitting, as we celebrate this milestone, to introduce a new chapter in the journal's long and distinguished history: the appointment of the new editor of the ARCHIVES, Daniel M. Albert, MD.

No one is more likely to appreciate the historical moment than is Dan Albert, who is widely known within ophthalmology not only for his many professional accomplishments but for his love of history. For many years, Dr Albert displayed in his office a rare copy of the first issue of *Archives of Ophthalmology and Otology*, the progenitor of the current ARCHIVES, founded in 1869 by Herman Knapp, MD. Early in his career, Dan Albert was a friend and colleague of David Cogan, MD, a former editor of the ARCHIVES, and later became the David G. Cogan Professor of Ophthalmology at Harvard Medical School. Dr Albert has served as a member of the ARCHIVES editorial board for the past 10 years and as editor of the journal's "Book Review" section, a job that gave him the opportunity to exercise his passion for editing, reviewing, and critiquing the latest literature. His editorial roots are thus deeply intertwined with the ARCHIVES, and his affection and enthusiasm for the journal are palpable.

## THE STATE OF THE ARCHIVES

Dr Albert inherits a journal that may be in the strongest shape in its 125-year history. This is due in major part to the tremendous efforts of Morton F. Goldberg, MD, who completed his 10-year term as editor with the June issue.[1] Mort is renowned for setting the highest possible standards in everything he does, and the ARCHIVES has flourished thanks to his personal vision and insistence on quality. During Dr Goldberg's tenure, manuscript submissions have grown from approximately 600 to 1100 per year. His extremely efficient editorial office, managed by Anne Meltzer, attained its goal of achieving the fastest possible turnaround time for manuscripts, with an average review time of fewer than 30 days and an average time from acceptance to publication of 4.1 months, a highly competitive performance for a monthly journal.



*Daniel M. Albert, MD*

Under Dr Goldberg's leadership, *Archives of Ophthalmology* has become known as the preeminent place to publish multicenter clinical trials in ophthalmology. Readership of the ARCHIVES is among the highest of any publication in its field, according to syndicated research, and the journal has a worldwide circulation of 20 000 in more than 40 countries. International editions were launched in Spain, China, and India during his tenure and continue to thrive. The ARCHIVES continues to be one of the most highly cited journals in ophthalmology, second only to *Investigative Ophthalmology and Visual Science*, and has published many of the seminal articles in the ophthalmic literature.[2]

Dr Goldberg has not been afraid to feature controversial articles or divergent opinions if they advanced legitimate dialogue within the specialty. He created a model for cooperation between government funding agencies and primary-source journals that worked in the best interest of patients without compromising the quality checks