OCULAR SURGERY

September 1, 2005

Clinical Uses of NSAIDs in Ophthalmic Surgery

CME

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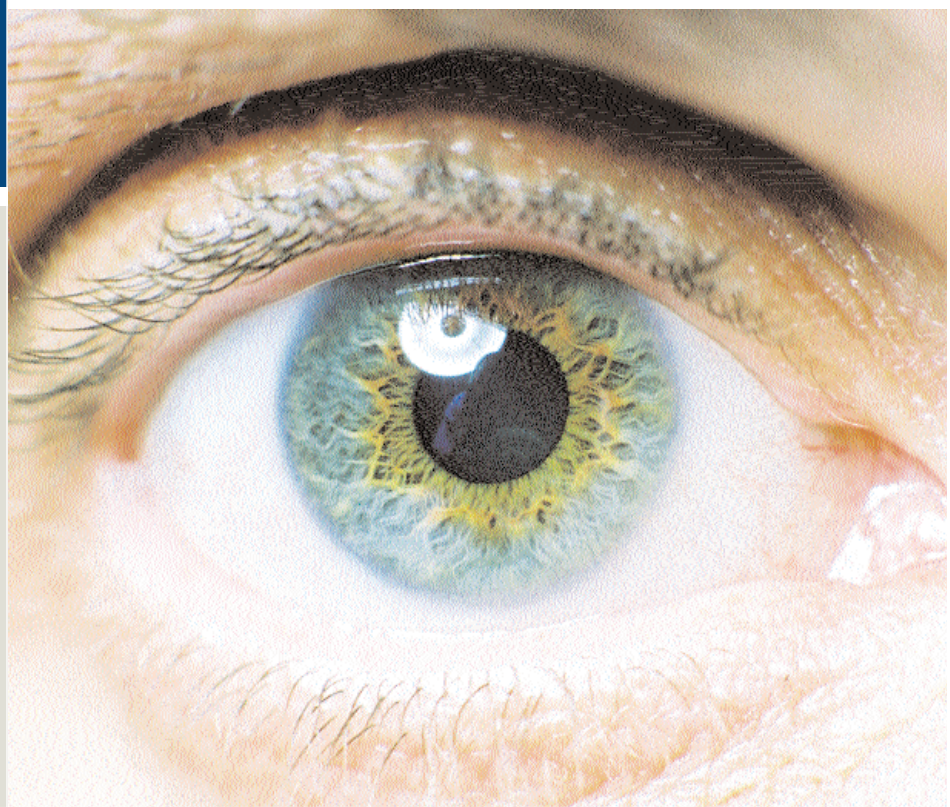

Learning Objectives

After reviewing the material, the participant should be able to:

- Discuss the use of NSAIDs in the prevention of cystoid macular edema.
- Review the use of NSAIDs for pain management following cataract and refractive surgery.
- Explain and recognize the implications of adverse events related to NSAID use.
- Elaborate on the effects of NSAIDs when used to maintain intraoperative mydriasis.

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Faculty

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Faculty Members Report the Following Relationship(s):

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Overview

Studies have shown that emerging treatment options for age-related macular degeneration (AMD) significantly benefit patients who have the choroidal neovascularization (CNV) form of AMD.
This activity is based on a meeting that was organized by SLACK Incorporated.

Target Audience

This activity is designed for ophthalmologists.

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Introduction

The applications of nonsteroidal anti-inflammatory drugs in ophthalmic surgery have grown considerably in the past few years. The multitude of clinical uses for nonsteroidals, including treatment of postoperative pain, ocular inflammation and photophobia and prevention of miosis intraoperatively, has made them an instrumental weapon in the ocular surgeon's armamentarium for patient care. Despite the subsequent increase in patient comfort and treatment, questions surround the efficacy of available NSAIDs and their association with adverse side effects.

At the Royal Hawaiian Eye Meeting 2005, Ocular Surgery News gathered leading ophthalmic surgeons to present and discuss various aspects of the latest NSAID formulations and their impact on patient care. The information available in this monograph is also available at www.OSNSuperSite.com.

I would like to thank the participating faculty for their insights.

Richard L. Lindstrom, MD
Chief Medical Editor
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Benefits of NSAIDs for CME prevention in cataract surgery

David F. Chang, MD

The benefits of nonsteroidal anti-inflammatory drugs for cataract surgery include their ability to prevent intraoperative miosis and to act as intraoperative and postoperative analgesics. The anti-inflammatory properties of NSAIDs provide protection against postoperative cystoid macular edema (CME) and iritis.

Clinically significant CME is defined as that with a symptomatic drop in vision to worse than 20/40 and up to a 3% incidence of the presence of visible perifoveal cysts in the macula. The incidence of perifoveal cysts ranges from 0.5% to 3%. In contrast, angiographic CME may be asymptomatic — patients will generally have vision that is 20/40 or better. Therefore, fluorescein angiography or optical coherence tomography (OCT) must be used to diagnose CME in these cases. Historically, studies have suggested that the incidence of angiographic CME after uncomplicated cataract surgery may be as high as 20% to 30%.

A fair question to ask is whether modern phacoemulsification methods reduce the incidence of angiographic CME compared with intracapsular and extracapsular surgical techniques. However, a study performed by Paul G. Ursell, MBBS, FRCOphth, MD, in 1999 showed that, even after uncomplicated phacoemulsifacation, the incidence of angiographic CME was still 19%.[1]

Philippe Sourdille, MD, performed a study of CME as diagnosed by OCT after routine cataract surgery and found that 11 of 41 eyes had an increase in macular thickness postoperatively.[2]

Dr. Binder presented data at the European Society of Cataract and Refractive Surgeons (ESCRS) Congress in 2004 on 71 eyes that were treated with a steroid for uncomplicated cataract surgery. OCT measurements were taken preoperatively and postoperatively. The study found that the average macular thickness increased at 1, 4 and 8 weeks postoperatively.[3]

Pathogenesis of CME after cataract surgery

Kensaku Miyake, MD, first proposed in the 1970s that surgical trauma causes the release of inflammatory mediators from cell membranes, most notably, the prostaglandins and leukotrienes.[4] Lens epithelial cells (LECs) may be the most important contributors to these mediators, which lead to the breakdown of the blood-aqueous barrier, resulting in aqueous flare and cell. Because the blood-aqueous barrier requires a significant amount of time to become re-established, a breakdown of the blood-retinal barrier occurs. Increasing capillary permeability around the fovea results in either angiographic or clinically significant CME.

David F. Chang, MD

A number of risk factors predispose eyes to CME following uncomplicated cataract surgery, and topical NSAIDs are indicated for these cases.

Within the arachidonic acid pathway, steroids and NSAIDs work at different points in the inflammation cascade. Steroids work at the top of the chain by blocking phospholipase A. Steroids block both subsequent arms of the pathway, including prostaglandin synthesis and leukotriene production, whereas NSAIDs come into play later and block prostaglandin synthesis.

Treatment of CME

When I am beginning treatment of CME, one important consideration is whether an NSAID should be used concurrently with a steroid. While postoperative CME following uncomplicated surgery is a self-limited condition, treatment of symptomatic CME is commonly initiated in order to speed up the resolution. Many studies have shown that both NSAIDs and steroids, whether oral or topical, are effective in treating CME.

Jeffrey Heier, MD, performed a randomized prospective study on the effect of ketorolac alone, prednisolone alone or a combination of the two drugs for the treatment of CME. He found that ketorolac alone and the combination therapy were significantly more effective than prednisolone alone, with the combination being slightly superior to NSAID alone.[5] A more recent study of 10 patients did not find the combination to be better but, rather, found that ketorolac alone and ketorolac combined

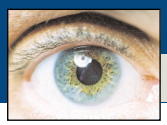

Figure 1

Risk Factors for CME

PATIENT RISK FACTORS

General Ocular

- Diabetes
- Uveitis
- Prior ocular surgery
- Chronic topical medications
  - glaucoma
  - preservatives

Retinal

- Prior CME in fellow eye
- Epiretinal membrane
- Existing macular edema
  - retinal vascular disease (BVO, CRVO, IT, DME)

SURGICAL RISK FACTORS

Uncomplicated Surgery

- Large incision
- Prolonged surgical time
- Iris trauma
  - surgical manipulation
  - iris prolapse
- Residual cortex
- Anterior chamber IOL, sulcus-fixated posterior chamber IOL

Complicated Surgery

- Posterior capsular rupture
- Vitreous loss
- Retained lens material
- Intraocular bleeding
- TASS

A number of patient and surgical risk factors predispose eyes to CME following cataract surgery. NSAIDs are indicated in these cases.

(Courtesy of David F. Chang, MD)

with prednisolone were equally effective.[6] A large prospective study by David S. Rho, MD, compared ketorolac and diclofenac and found no difference with respect to efficacy for treating CME.[7]

All of these studies were prospective randomized studies utilizing fluorescein angiography to objectively evaluate CME.

Prophylaxis for CME

Luca Rossetti, MD, and colleagues performed a meta-analysis of 36 studies on CME prophylaxis published through 1998. Prophylactically treated eyes had an average incidence of 11% of angiographic CME, compared to 32% incidence of angiographic CME in untreated eyes. Treated eyes had a 5% incidence of clinical CME, compared to 10% in untreated eyes. However, most of these studies were not randomized prospective trials.[8]

Following Dr. Rosetti's meta-analysis, several randomized prospective trials evaluating the ability of NSAIDs to prevent angiographic CME have been published. Claus-Dieter Quentin, MD, performed an early study comparing diclofenac vs. placebo and found that diclofenac had a protective effect against CME in patients undergoing intracapsular surgery with anterior chamber IOLs.[9] Allan J. Flach, MD, and Leon Solomon, MD, found a similar protective effect with ketorolac and flurbiprofen vs. placebo in two studies evaluating manual extracapsular surgery with posterior chamber IOLs.[10,11]

Clinicians may wonder whether the issue of CME is still relevant in light of less traumatic, small-incision phaco techniques. However, a number of randomized prospective trials have demonstrated that angiographic CME still occurs frequently enough following uncomplicated phaco. Two Italian randomized prospective studies showed that diclofenac was protective against angiographic CME compared to placebo both with or without concomitant steroid.[12,13]

Even more compelling were Dr. Miyake's prospective randomized angiographic studies demonstrating a greater CME protective effect of diclofenac compared to fluorometholone.[14,15] In one study, at 5 weeks postoperatively, angiographic CME was present in 5.7% of eyes treated with diclofenac only, compared to 54.7% of eyes treated with fluorometholone only.[15]

Postoperative NSAIDs for high-risk eyes

A number of risk factors predispose eyes to CME following uncomplicated cataract surgery, and topical NSAIDs are indicated for these cases. Patient risk factors for CME include diabetes, uveitis or previous ocular surgery and the chronic use of preserved topical medications, such as for glaucoma. Additional patient risk factors for CME include pre-existing macular edema from retinal vascular disease, the presence of an epiretinal membrane and previous postoperative CME in the fellow eye.

Surgical risk factors for CME include large incisions, prolonged surgical time, iris trauma, residual cortex, anterior chamber IOLs and sulcus-fixated posterior chamber IOLs. CME is more likely to occur following complications such as posterior capsular rupture, vitreous loss, retained lens material, intraocular bleeding and toxic anterior segment syndrome (Figure 1).

Many patients who undergo cataract surgery are

also taking glaucoma medications, and increased incidence of subclinical and symptomatic CME has been discovered in these eyes. Dr. Miyake published a landmark randomized prospective study in 1999 in which patients were stratified into four groups: latanoprost plus diclofenac, latanoprost plus fluorometholone, diclofenac only and fluorometholone only.[16] In comparing the two fluorometholone groups, concomitant latanoprost was associated with a statistically higher rate of angiographic CME. However, when comparing the two latanoprost groups, there was a statistically lower rate of angiographic CME when diclofenac was used. In other words, the NSAID blocked the CME-inducing effect of latanoprost.

Objective evidence from randomized clinical trials indicates that NSAIDs prevent both clinical and angiographic CME following routine or complicated cataract surgery.
— David F. Chang, MD

In 2002, Patrick C. Yeh, MD, and colleagues reported a strong association between latanoprost and clinically significant CME after routine cataract surgery in a retrospective study of 162 eyes.[17] This also seemed to confirm surgeons' concerns about using a prostaglandin analogue after cataract surgery.

However, in his 2002 ESCRS Binkhorst lecture, Dr. Miyake proposed a completely different mechanism, labeling the phenomenon pseudophakic preservative maculopathy.[18] Using LEC cultures, he compared latanoprost, preserved and nonpreserved timolol and preserved and nonpreserved vehicle. From these comparisons, he concluded that the preservative benzalkonium chloride was toxic to the LECs. Randomized prospective clinical trials with these agents (latanoprost and preserved vs. nonpreserved timolol or vehicle) subsequently confirmed that angiographic CME was associated with the preservative rather than the drugs.[18] Based upon these often overlooked studies, NSAIDs should be used whenever patients are taking chronic topical preserved medications.

Postoperative NSAIDs for routine cataract surgery

I began using postoperative NSAIDs routinely in 1999, based upon a randomized prospective study by Michael Raizman, MD. He used OCT to identify increased macular thickness following uncomplicated phacoemulsification. Patients receiving prednisolone had approximately a 25% incidence of CME diagnosed by OCT, compared with 0% of patients who received prednisolone with diclofenac. This was convincing objective evidence that NSAIDs prevent sub-clinical CME following uncomplicated cataract surgery.

For a time, I tried using NSAIDs without prednisolone following surgery, but a number of eyes exhibited significant inflammatory cells in the anterior chamber after 1 week, compelling me to prescribe both agents after routine surgery, despite the added cost and inconvenience.

Objective evidence from randomized clinical trials indicates that NSAIDs prevent both clinical and angiographic CME following routine or complicated cataract surgery. It is on this basis that I routinely use NSAIDs postoperatively, regardless of the presence of risk factors for CME. OSN

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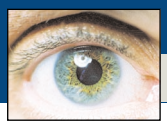

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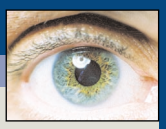
Discussion



Eric D. Donnenfeld, MD: One of the challenges encountered in the clinical trials for Xibrom (bromfenac sodium 0.1%, Ista Pharmaceuticals) was that the bar was raised higher in the clinical approval process than other nonsteroidal anti-inflammatory drugs previously approved by the Food and Drug Administration. In the past, Voltaren (diclofenac sodium, Novartis) and Acular (ketorolac tromethamine 0.5%, Allergan) were required to achieve a score of 1 on the postoperative inflammation chart, whereas the FDA required a score of 0 for Xibrom. Sixty-four percent of the 356 patients taking bromfenac achieved ocular inflammation scores of 0, compared to 43% of 171 patients on placebo. Additionally, the FDA also evaluated resolution of pain after cataract surgery, a measure that had not been reviewed previously. Patients taking bromfenac showed complete resolution of pain in fewer than 2 days after surgery vs. patients taking placebo, who took much longer to experience pain resolution. Postoperative photophobia was also significantly decreased with bromfenac in the FDA trials, showing that this NSAID is clinically effective.

It is difficult to compare NSAIDs because there are few head-to-head studies. However, there are clinical differences between them.

Preventing and managing CME

Donnenfeld: Dr. Chang, how do you define CME? Please differentiate between angiographic and clinical CME.

David F. Chang, MD: Clinical CME produces a symptomatic decrease in vision, which may be slight or very dramatic. In this context, angiographic CME refers to an asymptomatic patient in whom sub-clinical CME is detected by fluorescein angiography or OCT. While some of these eyes may be 20/25 or 20/30, Snellen acuity testing may not be sensitive enough to detect the functional change in other eyes. Testing contrast sensitivity or reading speed might better detect the more subtle impairment of sub-clinical CME.

Henry Perry, MD: In terms of CME diagnosis, there is no question that optical coherence tomography (OCT) has improved the clinician's ability to detect CME. With improved diagnoses, I believe that surgeons will be more prone to use NSAIDs to prevent the occurrence of CME.

Donnenfeld: I think that Snellen visual acuity may be the worst way to test postoperative results in cataract surgery. Low-contrast sensitivity and glare testing are equally important to measure the visual acuity of patients who have undergone cataract surgery. Under these conditions CME will cause significant visual degradation.

Dr. Chang, please comment on the data on the incidence of CME after cataract surgery without use of NSAIDs that Michael Raizman, MD, presented at Hawaii 1999: The Royal Hawaiian Eye Meeting.

Chang: Dr. Raizman's study addressed the obvious question of whether routinely adding a postoperative NSAID to the usual topical steroid regimen is necessary following uncomplicated cataract surgery. Using OCT in a prospective randomized study, he demonstrated that combination therapy prevented CME compared to steroids alone. Based upon his study, I began routinely prescribing combination therapy in 1999. This has dramatically decreased the incidence of clinical CME, which previously I would occastionally see following steroid cessation. The prevention of clinical and sub-clinical CME justifies the added cost and inconvenience of NSAIDs in my mind.

Pain management in cataract and refractive surgery

Henry Perry, MD

One of the most significant challenges that ophthalmologists face when performing cataract surgery involves managing patient expectations. Patients are not concerned with phaco time, technique or technology, but rather intraoperative comfort and postoperative results. Most patients do not want stitches, pain or injections. In order to achieve better outcomes, I routinely use nonsteroidal anti-inflammatory drugs (NSAIDs) for my cataract surgery cases.

NSAIDs vs. corticosteroids

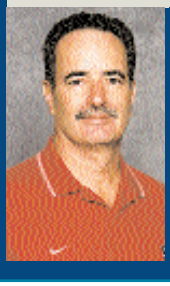
Several studies have been performed showing that NSAIDs reduce inflammation, pain and general discomfort after cataract surgery, including data from Kerry Solomon, MD, Robert Snyder, MD, PhD, and Calvin Roberts, MD.[1-3]

Based on the information in these and other studies, I have completely switched from using corticosteroids alone and rely on the addition of topical NSAIDs. As a result, my patients have had whiter eyes and less inflammation after surgery and have expressed higher satisfaction 1 day postoperatively. I also like to involve my patients in their care by providing them with information on the studies on NSAIDs so that they feel more confident and comfortable going into surgery.

In addition to cataract surgery, I find that NSAIDs are also useful for reducing pain in refractive surgery. Many patients who undergo refractive surgery have blepharospasm that results in striae after LASIK. NSAIDs help to reduce this complication.[4] Additionally, a longer acting NSAID will blunt the inflammatory and pain response for a longer period, which may be useful for postoperative recovery for LASIK.

Steroids affect postoperative results, but not patient comfort — they block inflammation, but do not have any significant effect on pain. NSAIDs, on the other hand, have an analgesic and anesthetic effect as well as being anti-inflammatory. The Food and Drug Administration has never approved corticosteroids for postoperative cataract surgery, although most surgeons have used them for this purpose.

I prefer not to use corticosteroids in certain patients because of their adverse effects, such as inhibition of epithelial healing and wound strengths, induction of ocular hypertension and the potentiation for secondary infections.[5]



Henry Perry, MD

When used in conjunction with contact lenses, NSAIDs result in faster recovery times for patients who had traumatic corneal abrasions.[6]

NSAIDs to reduce inflammation, increase recovery times

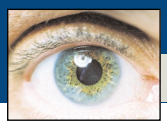
After surgical trauma is induced, the inflammatory cascade begins (Figure 1). Phospholipase A2 acts on the phospholipids to create arachidonic acid, which is the primary mediator of inflammation in cataract surgery via its connection to the cyclooxygenase (COX) pathway, or COX-1 and COX-2. Leukotrienes are also important in terms of the cellular changes that are seen in the anterior chamber, but the cyclooxygenases are the main catalysts in the inflammation process because of prostaglandin release.

In my opinion, using NSAIDs 3 days preoperatively will reduce the amount of naturally produced prostaglandins in the iris, resulting in fewer problems with vascular permeability, less effect on the blood-aqueous barrier, less vasodilation and miosis and a decrease in IOP.

NSAIDs also may be useful in treating corneal abrasions. Eric Donnenfeld, MD, and colleagues and I performed a study on traumatic abrasions and the effect of NSAIDs. We found that, when used in conjunction with contact lenses, NSAIDs result in faster recovery times for patients who had traumatic corneal abrasions.[6]

Conclusion

In order to meet higher patient expectations following cataract and refractive surgery, I have



switched from using corticosteroids alone to now using NSAIDs in combination to reduce inflammation, pain and discomfort postoperatively. NSAIDs block inflammation and ease patient discomfort, while steroids have no analgesic or anesthetic effect and a number of adverse effects. Using NSAIDs preoperatively will reduce prostaglandin response, resulting in subsequently fewer problems with vascular permeability, less effect on the blood-aqueous barrier, less vasodilation and miosis, and a decrease in IOP. NSAID use also results in faster recovery times for patients with traumatic corneal abrasions. OSN

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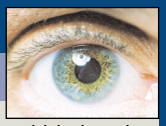
Discussion



NSAIDs in cataract surgery

Donnenfeld: The patient expectations for cataract surgery in 2005 include no pain, no complications, white, quiet eyes and rapid visual rehabilitation. Nonsteroidals allow ophthalmologists to achieve these patient expectations in many different ways.

Dr. Katsev, how do NSAIDs improve outcomes in cataract surgery?

Douglas Katsev, MD: NSAIDs reduce the incidence of postoperative CME. Intraoperatively, the most important issues that I encounter are maintaining pupil dilation for capsulorrhexis and patient comfort. NSAIDs are crucial for both of these functions.

Donnenfeld: I agree. I find one of the most challenging situations that I encounter during surgery is blepharospasm, or uncontrolled blinking. Using a lid speculum and an NSAID in conjunction with topical anesthetic dramatically reduces this phenomenon, making surgery easier for the surgeon and the patient.

NSAIDs vs. corticosteroids

Donnenfeld: What is the role of corticosteroids and what are the complications associated with their use after cataract and refractive surgery?

Chang: With cataract surgery, the more rapidly surgeons can eliminate inflammation and restore the blood-aqueous barrier, the better. In this regard, the benefits of corticosteroids and NSAIDs are additive because they work at different points along the arachidonic acid synthesis pathway. NSAIDs are more efficacious in preventing CME, while steroids are better at eliminating the inflammatory cells. I will use NSAIDs alone in steroid responders, advanced glaucoma patients and patients with prior ocular herpetic infections. However, the problem with routinely eliminating topical steroids postoperatively is that some eyes still exhibit prolonged iritis.

Perry: Wound healing can become critical in certain patients, and wound healing is significantly inhibited by corticosteroids. There is also the potentiation in terms of viral infections and corticosteroid-induced ocular hypertension. Five percent of patients on topical corticosteroids will have an increase in IOP between 5 mm Hg and 20 mm Hg. In glaucoma patients, 92% will have a hypertensive response to topical corticosteroids.

Donnenfeld: Corticosteroids are immunosuppressives whereas nonsteroidals are immunomodulators. One advantage of NSAIDs is that they can be stopped without any inflammatory sequelae, while corticosteroids must be tapered to avoid inflammatory rebound.

Pain management

Donnenfeld: How do you use NSAIDs to control pain in cataract and refractive surgery?

Katsev: In my LASIK practice, I give patients preservative-free ketorolac tromethamine 0.5% postoperatively and perform operations in the evening so patients can go home and go to sleep.

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Ketorolac helps control pain and counteracts the scratchy, burning feeling.

Terry Kim, MD: I use preservative-free ketorolac tromethamine 0.5% immediately before and after surface ablation surgery and then recommend its use as necessary until the point of epithelial healing. This regimen helps with postoperative pain and may also help with inflammation.

For cataract surgery, I dose ketorolac tromethamine 0.4% the day before surgery and in the preoperative holding area, along with dilating drops the day of surgery. This helps to maintain good analgesia and prevent intraoperative pupil constriction.

Postoperatively, I dose ketorolac tromethamine 0.4% four times a day for 4 weeks for routine cases, which addresses the problem of postoperative pain that a corticosteroid does not.

Donnenfeld: When you use topical nonsteroidals, what percentage of patients require additional medication stronger than over-the-counter oral NSAIDs?

Kim: In my surface ablation procedures, I have found that less than 10% of patients require stronger oral painkillers. Topical NSAIDs keep patients from having to go to stronger oral medications, whether prescription or nonprescription, and do not generate the unwanted side effects of oral narcotics.

Donnenfeld: In our practice, we find it helpful to pre-soak a bandage contact lens in NSAIDs. It acts as a depot to improve pain control.

Perry: If we can help break the cycle of blepharospasm — the patient leaving anesthetized but having a painful reaction later and experiencing subsequent blepharospasm — I think we will have less striae. Using an NSAID in the first postoperative 24 hours is helpful in breaking that cycle.

Donnenfeld: The use of NSAIDs dramatically blunts the increase in pain that occurs when an anesthetic wears off. Dr. Perry and colleagues and I have conducted studies that have shown that NSAIDs provide a gradual, slow curve of pain return, over 1 to 2 hours.[1]

Bromfenac seems to have a longer duration of action than other NSAIDs, which may be beneficial after refractive surgery, where you want the patient to be comfortable for 2 to 4 hours until re-epithelialization allows the clot to stay in place.

Chang: The analgesic effect of NSAIDs in cataract surgery is advantageous, but without the prophylactic CME benefits, I would not prescribe them solely for this reason. In addition, ketorolac and diclofenac both sting, which is a comfort tradeoff.[2,3] According to the Japanese literature, there is a lower incidence of stinging and burning with bromfenac than with ketorolac.

Donnenfeld: In my clinical experience, flurbiprofen is significantly weaker than the other medications in pain control. It provides less control of pain, less pupillary mydriasis and it has no significant effect on CME.

Corneal melting linked to use of topical NSAIDs

Terry Kim, MD

A number of reported complications are associated with nonsteroidal anti-inflammatory drugs, although they are fairly uncommon. Complications include superficial punctuate keratitis, stromal infiltrates, persistent epithelial defects and the more severe complication of corneal melting.

Corneal melting and NSAIDs

Numerous observations of corneal melting after routine anterior segment procedures and surgeries were first noted in a 1999 American Society of Cataract and Refractive Surgery survey. The melting was linked to the generic formulation of diclofenac made by Falcon Pharmaceuticals, which was subsequently recalled from the market. It was hypothesized that the vitamin E solubilizer, tocophersolan, which has been shown to inhibit epithe-

Terry Kim, MD

A number of reported complications are associated with nonsteroidal anti-inflammatory drugs, although they are fairly uncommon.

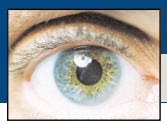

Figure 1

NSAID-Related Corneal Melts

Case Series in Literature	# Eyes	NSAID
Lin et al, 2000 *(Arch Ophthalmol)*	5	Falcon and Voltaren
Guidera et al, 2001 *(Ophthalmology)*	18	Falcon, Voltaren and Acular
Flach et al, 2001 *(Trans Am Ophth Soc)*	11	Falcon and Voltaren
Hargrave et al, 2002 *(Ophthalmology)*	3	Falcon

Reports of corneal melting have occurred with Voltaren (diclofenac sodium, Novartis) and Acular (ketorolac tromethamine 0.5%, Allergan) in addition to the generic diclofenac formulation (Falcon Pharmaceuticals).

(Courtesy of Terry Kim, MD)

lial cell proliferation and induce apoptosis in cells, in the generic formulation induced corneal melting.[1] Other reports of corneal melting have occurred with the brand diclofenac, Voltaren (diclofenac sodium, Novartis), as well as with Acular (ketorolac tromethamine 0.5%, Allergan),[1-4] raising the concern that other factors may contribute to corneal melting (Figure 1).

Matrix metalloproteinases and NSAID-related corneal melting

Matrix metalloproteinases (MMPs) are a family of proteases or collagenolytic enzymes that have multiple functions that include degradation of the extracellular matrix components, such as collagen, lamina and proteoglycans. MMPs are also involved in cell-cell and cell-matrix communication. In normal tissues, MMPs are rarely detected. MMP expression is typically seen in human tissues during rapid matrix turnover, such as tissues undergoing metastatic tumor invasion or wound healing. MMP expression has been found in corneal tissue during the wound-healing process as well.

In the eye, MMPs are involved in many physiologic and pathophysiologic conditions such as age-related macular degeneration, diabetic retinopathy, IOP regulation and glaucoma. Specifically in the cornea, MMPs have been detected in bacterial, chemical and thermal corneal ulcerations. MMP expression has also been reported in corneas following PRK surgery, and it is thought to play a role in the pathophysiology of keratoconus.

What role can these MMPs play in NSAID-related corneal melts? Corneal melting occurs when an imbalance exists between extracellular matrix deposition and degradation. MMP expression that occurs normally in wound healing may become unregulated with NSAID use, creating an imbalance and subsequently corneal melting.

Based on a number of studies,[5,6] a link between MMPs and corneal melts has been shown. As research continues, MMPs are being found to play a greater role in the eye. However, the exact role of each MMP is still unknown.

Clinical factors to consider in using NSAIDs

It has been shown that topical NSAIDs decrease normal corneal sensation,[7,8] hence their efficacy in decreasing postoperative pain following PRK or other surface ablation procedures. Topical NSAIDs can affect normal corneal epithelial healing,[9,10] but this is a topic of controversy; other studies have shown that topical NSAIDs may not have as adverse an effect on wound healing as topical corticosteroids.[11,12]

As has been demonstrated, potential problems with NSAID use exist, but can be limited if used properly. Long-term use of NSAIDs and dosing more frequently than four times daily should be avoided, and patients should be carefully evaluated for risk factors linked to corneal melting. Patients who have the following characteristics should be observed carefully during NSAID use: severe dry eye; recurrent epithelial keratopathy; active bacterial keratitis or neurotrophic situations from previous herpes simplex or zoster keratitis; severe ocular surface disease, such as ocular cicatricial pemphigoid or chemical burn; potential long-term use of concurrent topical steroids; and systemic disorders such as diabetes and rheumatoid arthritis. Compliance with regard to medication dosing and follow-up is important to ensure that normal wound healing occurs and corneal melting is avoided. In the setting of a corneal melt, infection should always be ruled out.

Conclusion

Complications associated with NSAID use are uncommon and typically benign.

While corneal melting represents a rare but severe complication potentially related to NSAIDs, the mechanism is unclear and probably involves

multiple factors. MMPs serve as a starting point in defining these mechanisms, but more study is needed to elucidate their role in corneal melting. In the meantime, by adhering to established guidelines, eye care practitioners can use NSAIDs safely and benefit greatly from their use in CME prevention and treatment, postoperative inflammation management, postoperative pain reduction and other ocular conditions. OSN

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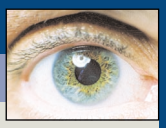
Discussion



Adverse events with NSAIDs

Donnenfeld: There are no data in the United States on any long-term toxicity issues with Xibrom (bromfenac sodium, Ista), although it has been available in Japan for many years and has been shown to be a well-tolerated drug in that country's literature.[4] There appear to be minimal short-term side effects associated with bromfenac based on the FDA clinical trials.[5] What adverse events have been associated with other NSAIDS?

Kim: The most well-known adverse event associated with topical NSAIDs, corneal melting, occurred with the generic form of diclofenac. Subsequently, the same issue has been recently seen in case reports with Acular (ketorolac tromethamine 0.5%, Allergan) and Voltaren (diclofenac sodium, Novartis).[6,7] These uncommon cases were not reported until after a few years of NSAID use. While the incidence of corneal melts is more widespread with generic formulations, these studies show that the branded NSAIDs are not immune to the complication. However, it is important to note that this complication is rare and may be associated with other variables.

Donnenfeld: In the studies performed that look at toxicity with NSAIDs, the affected patients almost always had some type of ocular surface disease. Do you believe that NSAIDs should be used routinely after cataract surgery in patients who have ocular surface disease, or should they be reserved for special cases?

Kim: I agree that the exact mechanism of NSAID-related corneal toxicity is unclear and that factors such as ocular surface disease can contribute. However, NSAIDs can be used safely and effectively in these patients after cataract surgery as long as practical guidelines are followed. The degree or severity of ocular surface pathology should be assessed, and if the decision is made to institute therapy, these patients should be followed closely. Patients with predisposing conditions such as severe keratoconjunctivitis sicca, persistent epithelial defects, neurotrophic keratopathy, ocular cicatricial pemphigoid and certain systemic disorders like rheumatoid arthritis are at higher risk for corneal complications and should be identified prior to NSAID therapy.

Otherwise, I strongly advocate the use of NSAIDs routinely after cataract surgery to protect against CME. I typically start NSAID therapy the day before surgery, continuing for 1 month. For those who are at a higher risk for developing CME after

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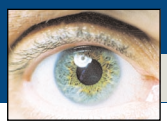

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cataract surgery, such as patients with diabetic retinopathy, central retinal vein occlusion or branch retinal vein occlusion, uveitis or a previous history of CME, I start NSAID therapy 1 week prior to surgery and continue dosing for 2 months to 3 months. However, the use of NSAIDs after cataract surgery should not be reserved only for these patients at a higher risk for developing CME.

Katsev: When the reports of corneal melting with generic diclofenac first became public, I was routinely using NSAIDs for my cataract surgeries. As soon as I discontinued using NSAIDs, my CME rate rose dramatically. A high volume cataract practice can expect an additional five to six cases of CME when the clinician is not using NSAIDs. Not only does this flood a practice with dissatisfied patients, but it also places additional time demands on the clinical staff.

As soon as it was clear that the corneal melts were due mostly to generic diclofenac only, I went back using ketorolac routinely and my rate of CME subsided. I have never had a case of corneal melting in my practice, before or since the initial reports.

Donnenfeld: In our practice, we typically see 100,000 patients per year and we have had no cases of corneal melting from NSAIDs. This zero incidence underscores the importance of using nonsteroidals in a careful and controlled manner for patients who have ocular surface disease.

Perry: Evidence suggests that the preoperative use of NSAIDs for patients with ocular surface disease, such as keratoconjunctivitis sicca (KCS), rheumatoid arthritis and Sjögren's disease, will lessen the inflammation that these patients experience.[8,9]

Chang: I generally will not use an NSAID postoperatively in eyes at higher risk for corneal melting. This includes eyes with concurrent pterygium removal, large epithelial defects or neurotrophic corneas. In addition, I try to avoid NSAIDs if there is severe dry eye or keratoconjunctivitus sicca.

However, there are occasions when I see unexpected corneal epithelial toxicity associated with postoperative use of topical NSAIDs. It will be interesting to see if twice-daily dosing reduces this type of problem.

The importance of NSAIDs in maintaining pupil dilation

By Douglas Katsev, MD

The number of cataract surgeries performed is increasing and, as the number of surgeries rises, so do patient expectations; patients expect virtually painless procedures, minimal recovery time and excellent visual acuity. In order to meet these higher expectations, complications must be avoided. However, not all cataract surgeries are the same, and many surgical decisions need to be made in the operating room. Maintaining mydriasis helps a surgeon to see as much as possible. Noting zonular dehiscense, capsular breaks or vitreous presentation early can save the case, making intraoperative mydriasis important to avoid complications.

Douglas Katsev, MD

Nonsteroidal anti-inflammatory drugs have been proven effective in maintaining intraoperative pupil dilation through prostaglandin inhibition.

Nonsteroidal anti-inflammatory drugs have been proven effective in maintaining intraoperative pupil dilation through prostaglandin inhibition. In normal physiologic processes, cyclooxygenase (COX)-1 activity produces normal quantities of prostaglandins, and therefore normal pupil dilation, without inflammation. With the trauma of surgery, subsequent COX-2 activity produces excessive quantities of prostaglandins, leading to inflammation and vasodilation, vascular permeability, blood-aqueous barrier disruption, cystoid macular edema (CME), miosis and overall patient discomfort. Other surgical uses of NSAIDs include the reduction of discomfort, inflammation and photophobia in patients. NSAIDs are also used to treat CME and allergic conjunctivitis.

Preventing mydriasis with NSAIDs

Flurbiprofen sodium 0.3% and suprofen 1.0% are the only NSAIDs approved by the Food and Drug Administration for maintenance of intraoperative mydriasis, but neither is easily available. Others, including diclofenac sodium 0.1%[1,2] and ketorolac

tromethamine 0.5%,[3-5] have been shown to be effective in mydriasis maintenance, but are not approved for this indication.

I performed a study with Robert C. Drews, MD, showing that flurbiprofen sodium 0.3%, which is the first NSAID available in drop form, prevented miosis in all cataract surgery cases, but, most importantly, the prevention was most effective in patients with small pupils.[6] Patients with small pupils benefit most from miosis prevention. Pupillary constriction in patients with larger pupils does not present as much of a problem as in patients with smaller pupils, as the surgeon initially has more area with which to work. The study showed as much as a 30% decrease in pupil surface area in small pupils when an NSAID was not used. Even a 1-mm decrease in the radius of the pupil makes a dramatic difference, as surface area is determined by squaring the radius and multiplying by Pi.

Conclusion

Inflammation is inhibited with the use of any vailable NSAID, preventing excessive release of prostaglandins and vasodilation, vascular permeability, blood-aqueous barrier disruption, CME, miosis and overall patient discomfort.

Preventing intraoperative miosis is important to prevent complications. Noting zonular dehiscense, capsular breaks or vitreous presentation early can prevent complications. Maintaining mydriasis makes it easier for a surgeon to detect such complication-causing phenomena, particularly in patients with small pupils. Ketorolac and diclofenac are efficient at maintaining mydriasis and have proven so in clinical tests, but have not joined flurbiprofen 0.3% and suprofen 1.0% in receiving FDA approval for this indication. OSN

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Discussion

Pupillary dilation

Donnenfeld: Data show that preoperative NSAIDs significantly improve pupillary dilation during surgery.[10,11] Dr. Perry and I performed a study in which we did an NSAID dose response curve at 3 days, 1 day, 1 hour and no NSAID. We found that there was a significant improvement in mydriasis and less postoperative inflammation in administering NSAIDs 3 days before surgery as compared to 1 day, 1 hour or at control.[12]

What is the importance of pupil size in cataract surgery?

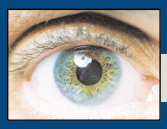
Katsev: With surface area determined by squaring the pupil radius and multiplying by Pi, every millimeter is important. Creating a capsulorrhexis with a smaller pupil is more difficult. If I have a good capsulorrhexis, without engaging the capsule, I can always put the lens in the sulcus and achieve a great result. NSAIDs maintain pupil dilation near preoperative size.

Chang: A small or constricting pupil decreases the red reflex, limits the ability to see and access the peripheral nucleus and impedes cortical cleanup. As a result, this increases the risk of posterior capsular rupture, as demonstrated in the intraoperative floppy iris syndrome.

Perry: By using an NSAID and by making sure patients are dilated before they get to the surgical center, I have decreased the need for pupil stretching or iris hooks.

Chang: Nevertheless, at times a small pupil must be stretched or mechanically manipulated. With either iris prolapse or surgical manipulation, there will be more prostaglandin release, and that warrants combination NSAID and steroid use to reduce postoperative iritis and prevent CME.

Perry: Studies have shown that NSAIDs increase patient comfort, reduce inflammation and improve visual acuity, with the greatest efficacy occurring when treatment begins at 3 days preoperatively.[13-15] There is prostaglandin release with surgery, but this will be less with treatment beginning 3 days preoperatively, which decreases the amount of naturally formed prostaglandins in the eye.



Twice-daily bromfenac more effective than other topical NSAIDs

Eric D. Donnenfeld, MD

Nonsteroidal anti-inflammatory drugs are versatile pharmacologic agents. Available NSAIDs include bromfenac sodium 0.1%, diclofenac sodium, ketorolac tromethamine 0.5%, ketorolac tromethamine 0.4% and flurbiprofen sodium.

Eric D. Donnenfeld, MD

The ideal NSAID would have decreased dosing requirements for increased convenience and patient compliance, improved tolerability and rapid onset of response.

NSAIDs are attractive agents in ophthalmology because of the variety of indications for use and the diverse effects that these agents have in the eye. The primary mechanism of action for NSAIDs is to inhibit prostaglandin synthesis and intraoperative miosis in the cyclooxygenase (COX)-1 and COX-2 pathways. NSAIDs not only reduce postoperative inflammation and pain but also minimize itching from allergic conjunctivitis.

NSAIDs are important in prophylaxis for and in the treatment of cystoid macular edema (CME) following cataract surgery and are also effective for treating postoperative uveitis. Although steroids can help reduce postoperative inflammation, preoperative loading will not have any effect, whereas loading the eye with NSAIDs preoperatively is a helpful strategy to reduce the incidence of postoperative CME and uveitis.

Side effects associated with NSAIDs include burning and stinging (a 20% to 40% incidence with ketorolac 0.5% in the Food and Drug Administration trials[1]) and corneal melting, particularly found with generic diclofenac and, in some cases, the branded diclofenac.[2] To address the burning and stinging issues associated with ketorolac tromethamine 0.5%, Allergan introduced a reformulation at a reduced concentration, 0.4%.

Although flurbiprofen is an NSAID that has few to no side effects, it works at a lower concentration level, which results in the lowest rate of efficacy of all the available NSAIDs.[3-5]

Corticosteroids are also used in ophthalmic surgery. The most commonly used steroids include loteprednol, prednisolone acetate and dexamethasone. Like NSAIDs, steroids are used for the prevention of postoperative inflammation, reduction of postoperative pain and the treatment of uveitis. While effective, steroids have several adverse effects that must be noted. Steroids work by inhibiting the entire network of anti-inflammatory pathways and, thus, inhibit wound healing.[6,7] Steroids can increase the risk of viral infection and can also worsen fungal, amoebic and bacterial infections,[8] whereas NSAIDs actually have an antiviral effect in some cases.[9] Additionally, steroids have been shown to cause cataracts in some patients.[10-12]

Figure 1

Percentage of Patients Reaching Score of Zero

Combined (Cells & Flare) Score of Zero

Days Post Surgery	Bromfenac n = 356	Placebo n = 171	*P* Value
Day 3 *(first post-surgery treatment check)*	8.4%	1.2%	0.001
Day 8	34.8%	13.5%	0.001
Day 15	59.3%	26.9%	0.001
Day 22	65.7%	39.2%	0.001
Day 29	80.1%	49.7%	0.001

Figure 1. In phase 3 of its U.S. clinical trials, Xibrom (bromfenac sodium ophthalmic solution 0.1%, Ista Pharmaceuticals) cleared inflammation at statistically significant rates at days 3, 8, 15, 22 and 29 postoperatively.

(Courtesy of Ophthalmic Consultants of Long Island)

Profile of the ideal NSAID

Today's cataract surgeon has the advantage of improved surgical techniques, smaller incision sizes and foldable IOLs. These technological advances translate to improved clinical outcomes for patients. As a result, patients expect more from their surgery, including reduced pain during and after the procedure and fast postoperative visual rehabilitation. The use of NSAIDs has also contributed to increased patient expectations by significantly decreasing pain, increasing patient comfort and reducing the incidence of side effects.

The ideal NSAID would have decreased dosing requirements for increased convenience and patient compliance, improved tolerability and rapid onset of response.

In March 2005, bromfenac 0.1% was approved by the Food and Drug Administration for the treatment of ocular inflammation following cataract surgery. The advantages to bromfenac include higher potency, which allows twice-a-day dosing compared to four-times-daily dosing with other available NSAIDs.

Figure 2

Common Adverse Events

Adverse Event	Bromfenac	Placebo
Iritis	7.0%	18.1%
Abnormal sensation in eye	6.5%	8.2%
Eye pain	4.2%	11.7%
Eye pruritus	3.9%	2.9%
Posterior capsule opacification	3.9%	4.1%
Partial vision loss	3.1%	9.4%
Eye irritation (burning & stinging)	2.5%	4.7%
Eye redness	2.2%	7.6%
Conjunctival hyperemia	2.2%	11.1%
Photophobia	2.0%	11.1%
Macula edema	2.0%	4.7%
Increased lacrimation	1.7%	4.7%
Conjunctival edema	1.4%	5.3%
Ocular discomfort	1.4%	0.6%

Figure 2. Adverse events occurred less frequently in patients treated with bromfenac than in those on placebo.

(Courtesy of Ophthalmic Consultants of Long Island)

Japanese studies

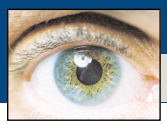
The first studies on topical bromfenac for ophthalmic use were performed in Japan. In 1995, a study was performed on the effect of bromfenac on ocular inflammation. The study found that bromfenac inhibited prostaglandin synthesis from the rabbit ciliary body by 50% and that bromfenac was 3.8 times more potent than indomethacin and 10.9 times more potent than pranoprofen.[13]

In a double-masked trial, the anti-inflammatory effect of bromfenac sodium ophthalmic solution 0.1% instilled twice a day was compared to that of pranoprofen 0.1% instilled four times daily to treat anterior uveitis following cataract surgery. The only adverse drug reaction in the bromfenac group was bulbar conjunctiva injection in one eye (0.9%), but in this case it was not accompanied by any remarkable changes in IOP or laboratory test values.[14]

Another study compared twice-a-day bromfenac to four-times-daily panoprofen and found that the efficacy of the two drugs was similar at these dosing schedules, indicating that bromfenac is more potent than pranoprofen.[15]

U.S. clinical trials

Phase 3 of the U.S. clinical trials included the pooled results of two trials comprising 527 patients who had undergone cataract surgery and who scored 3 on the ocular inflammation scale. The double-masked study evaluated how well twice-daily bromfenac treated postoperative inflammation and reduced eye pain and photophobia after surgery. The primary endpoint of the study was an ocular inflammation score of 0. Patients were also tested for liver function because of the potential systemic effects of bromfenac. Secondary endpoints of the trial included time to resolution of ocular inflammation and ocular pain; mean change in ocular inflammation score; proportion of patients with summed ocular inflammation of 1 or less; percentage of improvement of anterior chamber cell and flare scores; and percentage of patients with adverse ocular events, for example, photophobia or CME.



In the analysis of efficacy for the primary endpoint of total clearance of ocular inflammation, 64% of the 356 patients taking bromfenac achieved ocular inflammation scores of 0, compared to 43% of 171 patients on placebo ($P<.01$). A breakdown of total clearance of inflammation at days 3, 8, 12, 15, 22 and 29 shows that bromfenac cleared inflammation at rates that were statistically significant at all time points (Figure 1). There was also significant pain reduction for patients taking bromfenac. Pain was resolved in 1.9 days with bromfenac compared to 5.9 days with placebo.

In regard to adverse effects, liver function tests were normal for both groups and other side effects, including iritis, pain, burning and stinging, conjunctival hyperemia and photophobia, were lower in the group taking bromfenac than in those on placebo (Figure 2).

Conclusion

The studies that have been performed on bromfenac show that this agent is safe, tolerable and effective. The twice-daily dosing of bromfenac is a significant advantage over the other available NSAIDs, and the drug's total clearance of inflammation can greatly enhance patients' experience with ophthalmic surgery.

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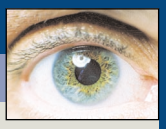
Discussion



Dosing regimens with NSAIDs

Donnenfeld: Dr. Chang, how do the available NSAIDs differ in dosing?

Chang: The dosing for all of the ophthalmic NSAIDs has been four times daily, until the arrival of Xibrom (bromfenac sodium ophthalmic solution, Ista Pharmaceuticals), which is approved for twice-daily dosing. A twice-daily regimen is an advantage for patients in terms of convenience and compliance.

By using bromfenac, an ophthalmologist cuts the total drops administered by one half, allowing the achievement of therapeutic goals with less drug. Less frequent dosing could lower the risk of side effects such as corneal epithelial toxicity.

Kim: Patients who took bromfenac in the clinical trials reached the targeted inflammatory endpoint in 15 days with twice-daily dosing. If an ophthalmologist can decrease dosing and duration of treatment with any medication, this is an advantage to the patient.

Donnenfeld: Dr. Kim, does the use of an

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NSAID twice a day reduce the incidence of side effects more effectively than four times-daily dosing?

Kim: Dosing has not been specifically addressed in any of the human studies on adverse effects such as corneal melting. However, data from animal studies show that frequent dosing of NSAIDs, particularly diclofenac, may induce apoptosis.[16] Generally speaking, it seems logical that decreasing the frequency of NSAID dosing would minimize the potential for toxicity and other potential side effects like corneal melting. For this reason, I recommend that topical NSAID dosing not exceed four times-daily frequency with available formulations like Acular LS (ketorolac tromethamine 0.5%, Allergan) or Voltaren (diclofenac sodium, Novartis).

Perry: Several large studies have been performed with various medications, mostly for glaucoma, that compare four times-daily dosing vs. two times-daily dosing. Reduced frequency of dosing has consistently been found to have a positive effect on patient compliance.[17]

Donnenfeld: When I trained 20 years ago, most of the glaucoma drops were dosed four times daily and compliance was a significant issue. Currently, there are no glaucoma medications dosed more than twice daily and, as compliance has improved, so have clinical outcomes. I expect the same will hold true for the NSAIDs.

Dr. Perry, what is your dosing regimen for NSAIDs in routine cataract surgery?

Perry: Routinely at my practice, we use Acular LS (ketorolac tromethamine 0.4%, Allergan) on our patients 3 days preoperatively in conjunction with an antibiotic four times daily. We dose NSAIDs on the day of surgery along with dilating drops. Postoperatively, I have patients continue NSAIDs for at least 2 to 4 weeks, with the exception of patients with diabetes or chronic uveitis. I have these patients continue taking NSAIDs for up to 3 months postoperatively, and sometimes longer, depending on the clinical situation. Patients who have pre-existing CME will most likely continue taking NSAIDs indefinitely.

Katsev: I have my patients begin taking ketorolac tromethamine 0.5% four times daily, 2 to 3 days preoperatively. On the day of surgery, I either administer a dilating drop or have the patient instill the drop at home and add an NSAID to maintain pupillary dilation during surgery.

Donnenfeld: We also use NSAIDs prior to surgery to improve clinical outcomes. NSAIDs are important preoperatively because they inhibit prostaglandin synthesis and reduce the release of formed prostaglandins at the time of surgery.

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CME TEST

1. Which of the following is not a patient risk factor for cystoid macular edema (CME)?
   A. Diabetes
   B. Prior ocular surgery
   C. Epiretinal membrane
   D. Age
   E. Chronic topical medications

2. Which of the following is not a surgical risk factor for CME?
   A. Elevated IOP
   B. Intraocular bleeding
   C. Large incision
   D. Prolonged surgical times
   E. Iris trauma

3. Data from objective randomized clinical trials indicates which of the following?
   A. The use of NSAIDs prevents only clinical CME, not angiographic CME, following cataract surgery.
   B. The use of NSAIDs prevents only angiographic CME, not clinical CME, following cataract surgery.
   C. The use of NSAIDs prevents both clinical and angiographic CME following cataract surgery.
   D. The use of NSAIDs does not prevent clinical or angiographic CME following cataract surgery.

4. Which of the following statements is not true?
   A. Surgical trauma induces the inflammatory cascade.
   B. Arachidonic acid is the primary mediator of inflammation in cataract surgery.
   C. Leukotrienes are the main catalysts in the inflammation process.
   D. Phospholipase A2 acts on the phospholipids to create arachidonic acid.

5. Using NSAIDs preoperatively to reduce prostaglandin response will not result in which of the following?
   A. An increase in IOP
   B. Fewer problems with vascular permeability
   C. Less vasodilation
   D. Less miosis
   E. Less effect on the blood-aqueous barrier

6. Which of the following will not help limit potential problems associated with NSAID use?
   A. Limiting long-term use of NSAIDs
   B. Dosing more frequently than 4 times daily
   C. Following up with patients
   D. Carefully observing patients with characteristics such as severe dry eye, recurrent epithelial keratopathy or severe ocular surface disease
   E. Evaluating patients for risk factors linked to corneal melting

7. Functions of matrix metalloproteinases (MMPs) include which of the following?
   A. Degradation of the extracellular matrix components.
   B. Involvement in cell-cell and cell-matrix communications.
   C. Expression in wound healing.
   D. A and B
   E. All of the above

8. Which of the following is approved by the United States Food and Drug Administration for maintenance of intraoperative mydriasis?
   A. Diclofenac sodium 0.1%
   B. Suprofen 1.0%
   C. Bromfenac sodium 1.0%
   D. Flurbiprofen sodium 0.3%
   E. B and D

9. Which of the following adverse events have been associated with the use of NSAIDs?
   A. Corneal melting
   B. Burning and stinging
   C. Persistent epithelial defects
   D. A and B
   E. All of the above

10. In phase 3 of the U.S. clinical trials for bromfenac sodium 1.0% (Xibrom, Ista Pharmaceuticals), what percentage of patients achieved zero clearance by day 29 postoperatively?
   A. 49.7%
   B. 65.7%
   C. 80.1%
   D. 93.6%

11. Which of the following would be characteristics of an ideal NSAID?
   A. Decreased dosing requirements
   B. Rapid onset of response
   C. Improved tolerability
   D. All of the above

12. Advantages of a twice-daily dosed NSAID include all but which of the following?
   A. Improved patient compliance
   B. Reduced potential for resistance to develop
   C. Reduced risk for toxicity
   D. Decreased patient costs

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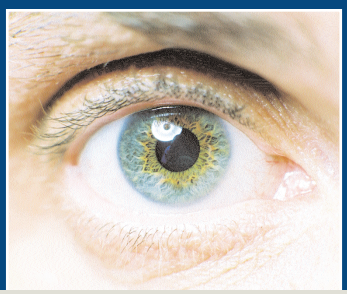

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