CORNEA

Topical NSAIDs: Best Practices for Safe Use

BY LESLIE BURLING-PHILLIPS, CONTRIBUTING WRITER
INTERVIEWING JOSEPH I. MAGUIRE, MD, CHRISTOPHER J. RAPUANO, MD, AND IRA J. UDELL, MD

Although topical nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used without incident, some patient populations are predisposed to developing serious corneal complications. The first case that Ira J. Udell, MD, a cornea specialist in Great Neck, N.Y., saw was back in 2001. "I encountered a 62-year-old woman with a history of dry eye, suspected glaucoma, cataracts, and bilateral irritation. After developing persistent punctate staining, she had been prescribed preservative-free topical ketorolac. Within four days, she reported a decrease in vision, and her referring physician observed corneal ulceration and thinning. This was perplexing because there was nothing particularly notable about this patient's medical history. Searching for an explanation, we conducted some serological tests and found that she had a previously undiagnosed autoimmune disease."

In the years since that early case, a better understanding of the mechanisms underlying the development of topical NSAID-related side effects has evolved. Ophthalmologists who recognize these causative factors and keep a few best practices in mind may help protect patients who are susceptible to problems associated with these drugs.

Complications

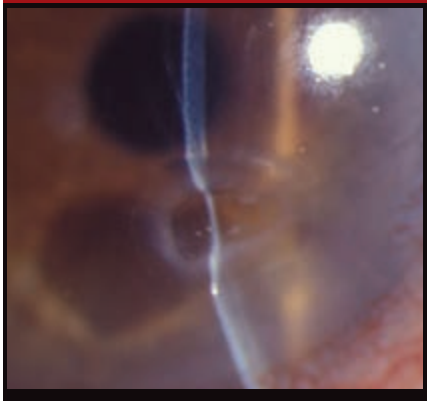
Side effects from NSAIDs are typically mild. "In general, this is a relatively safe group of drugs when applied topically, and complications are rare in my experience. Surface irritation tends to be the most common problem I encounter," said Wills Eye Institute retina specialist Joseph I. Maguire, MD.

Serious complications. According to Dr. Udell, keratitis and ulceration without loss of tissue, corneal and scleral melting, and corneal and scleral perforations are among the more serious complications associated with topical NSAID use. "In some cases, chronic epithelial defects have resulted in stromal loss and corneal haze with irregular astigmatism, which can prevent these patients from achieving spectacle-corrected vision. Fortunately, most patients will not experience these problems if the issue is identified and resolved early on during treatment."

Who is at risk? Patients with "normal" corneas are not typically at risk, but NSAIDs can cause problems in patients with a compromised or a less-than-optimal corneal surface, said Christopher J. Rapuano, MD, cornea specialist at Wills.

In addition to having an anti-inflammatory effect, NSAIDs act as mild anesthetics that can decrease corneal sensation, thereby impeding corneal healing. For this reason, said Dr. Maguire, "Patients at risk for developing complications are those with some type of decreased corneal sensation. Diabetics comprise the largest class of patients in this population. But people who have had previous herpetic disease—either zoster or simplex—with resulting corneal scarring are also at risk, as well as those with severe dry eye syndrome, Bell palsy, or rheumatologic disease. While you can still use NSAIDs with most of these patients, you should be more circumspect and follow them closely."

Corneal Melt



Ketorolac-associated corneal melting.

CHRISTOPHER J. RAPUANO, MD

Best Practices

Consider the patient. "Many cataract surgeons adhere to a standard pre- and postoperative regimen in which every patient receives the exact same treatment. While this might be reasonable for most patients, this routine may not be in the best interest of those who are at a higher risk for developing problems. Look at each patient's medical history and ocular exam to individually tailor treatment so that those who are at a higher risk for corneal healing problems receive a lower dose, a shorter treatment duration, or even no NSAID at all," Dr. Rapuano said.

Use NSAIDs with care in high-risk groups. Diabetic patients are at higher

risk for developing CME, which may present an added reason for using an NSAID. Diabetes, however, can have a deleterious effect on the ocular surface, so it is essential that this area is healthy enough to withstand the effects of the NSAID. "If the surface is not ideal prior to surgery, it can be primed and may be improved with [artificial] tears or punctal plugs. This group may also require closer postoperative follow-up," said Dr. Rapuano.

Avoid NSAIDs in others. For some patients, using an NSAID may be like adding gasoline to a fire. "Patients with sarcoidosis, rosacea, chemical burns, or local radiation around the eye; those who have undergone a bone marrow transplant and developed graft-vs.-host disease; and patients with neurotrophic corneas are all prone to corneal complications. Avoid this drug class in patients with epithelial defects, keratitis, or ulceration," said Dr. Udell. "Patients with rheumatoid arthritis, dry eye, or an ocular surface that appears unstable are probably not the best candidates for NSAID use either," added Dr. Rapuano.

Prescribe with the patient in mind. NSAIDs today are all effective, perform well, and have similar pharmacological actions. Beyond this, said Dr. Udell, "There is not enough data to make comparative statements about or between NSAIDs with regard to their overall efficacy or potential for side effects. As a class, they are all capable of causing harmful side effects."

Pairing an NSAID with a particular patient usually boils down to accessibility, cost, and convenience. Dr. Maguire typically begins by prescribing the drug that is on a patient's insurance plan formulary. "Ketorolac is a first-generation NSAID [administered four times daily], and it is listed on most insurance formularies because it is less expensive. However, Bromday [bromfenac 0.09 percent] is administered just once per day, making its use more convenient, which improves patient compliance." Two relative newcomers, Prolensa (bromfenac 0.07 percent) and Ilevro (nepafenac) are also once-daily drops.

Know the truth about proprietary NSAIDs. There is a general misconception that only generic NSAIDs cause corneal problems. Indeed, corneal melting and other serious ocular surface complications were widely reported in the literature shortly after the generic version of Voltaren (diclofenac) was introduced to the market nearly 15 years ago. "Most, but not all, of the corneal melts were seen in patients who used generic Voltaren. When diclofenac was removed from the market, the problems decreased but did not subside completely. Most NSAIDs, including the brand name medications, have been linked to adverse complications. It should therefore never be assumed that this class of drugs is benign when applied to the corneal surface," said Dr. Rapuano.

Prescribe judiciously; follow up. There is no single "optimal" pre- and postoperative regimen for cataract surgery; many patient variables should be considered before creating a treatment plan. According to the package insert, the recommended treatment duration after cataract surgery for all NSAIDs is two weeks. Dr. Udell said, "Once you go beyond this FDA-approved dosing period, follow up with patients frequently enough to monitor for the development of corneal problems, particularly if there is any suspicion of ocular surface disease. Certainly, never allow a patient to go for a month or two without reevaluation."

Exercise care with off-label use. NSAIDs are regularly used off-label for pain control in patients with corneal abrasions and in those undergoing various ocular procedures. According to Dr. Rapuano, these patients should receive only a short-term dosing regimen and then be followed closely to ensure proper healing. "NSAIDs are used for several days after photorefractive keratectomy, for example. Limit use to the period when the patient is most likely to experience pain. Dosing should not continue for many days or weeks. It is not necessary, and it increases the probability of encountering side effects," he said.

An NSAID prescribed for postoperative CME can be discontinued as soon as the edema resolves. Most patients do not need extended treatment, said Dr. Maguire, "but some eyes are predisposed to CME relapse due to structural irregularities that create localized inflammation and therefore increase CME." Among these structural problems are iris–intraocular lens (IOL) chafe, iris to the wound, vitreous in the anterior chamber, or anterior chamber IOL malposition. "In these rare situations, a minimal nontherapeutic dose may create benefit, but corneal complications should not be discounted in higher-risk eyes. I recommend a maximal six-week examination interval for all long-term NSAID-managed CME cases," he added.

What to look for during follow-up. In addition to checking for the absence or resolution of CME, Dr. Maguire looks for NSAID-related corneal complications, including superficial punctate keratopathy, epithelial defects, and corneal thinning.

Know when to refer to a cornea specialist. If you encounter a poorly healing cornea, reduce the dose or stop the NSAID as a first measure, Dr. Rapuano said, and then "refer patients to a cornea specialist if you continue to observe a poorly healing surface or if there is significant corneal thinning, melting, or perforation." ■

Christopher J. Rapuano, MD, *is director of the cornea service and codirector of the refractive surgery department at Wills Eye Institute and professor of ophthalmology at Thomas Jefferson University in Philadelphia. Financial disclosure: Is a consultant and speaker for Allergan, Bausch + Lomb, and Merck; is a speaker for Alcon; and has equity ownership in Rapid Pathogen Screening.*

Joseph I. Maguire, MD, *is attending surgeon at Wills Eye Hospital and associate professor of ophthalmology at Thomas Jefferson University Hospital in Philadelphia. Financial disclosure: Consults for Genentech and is a speaker for and receives grant support from Genentech and Regeneron.*

Ira J. Udell, MD, *is professor of ophthalmology at the Hofstra North Shore–Long Island Jewish School of Medicine. Financial disclosure: None.*