Topical Nonsteroidal Antiinflammatory Drugs for Ophthalmic Use

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Nonsteroidal antiinflammatory drugs (NSAIDs) formulated as ophthalmic eye drops are commercially available throughout the world [1, 2]. They have been used widely in the management of postoperative ocular inflammation and for the prevention and treatment of cystoid macular edema (CME) after cataract surgery. In addition, they have proved useful for the prevention of intraoperative miosis during cataract surgery, for the relief of symptoms of seasonal allergic conjunctivitis, and for the reduction of ocular discomfort following refractive surgery. This chapter summarizes the current status of topically applied NSAIDs and their potential therapeutic benefit for ophthalmic disorders.

■ Chemical Classification

NSAIDs consist of a chemically heterogeneous group of compounds that can be grouped into six major classes: salicylates, fenamates, indoles, phenylalkanoic acids, phenylacetic acids, and pyrazolones. Classification of these drugs as NSAIDs underscores that their chemical structures lack a steroid nucleus that is biosynthetically derived from cholesterol. In this chapter, the indoles, the phenylacetic acids, and the phenylalkanoic acids will be emphasized because they are commercially available as topical ophthalmic preparations. The salicylates, fenamates, and pyrazolone derivatives are either too toxic or too unstable in solution for commercial formulation.

Indomethacin is an indole derivative that was formulated initially as a sesame seed oil solution. However, this preparation proved to be locally irritating and unsuitable for widespread clinical use. Topical indomethacin is commercially available outside of the United States as a 1% aqueous suspension (Indocid Ophthalmic Suspension, Merck Sharp & Dohme). A 0.1% indomethacin ophthalmic solution has recently been formulated, but

it is not yet commercially available [3]. The phenylalkanoic acids are water-soluble and are formulated as ophthalmic solutions. Flurbiprofen 0.03% (Ocufen Ophthalmic Solution, Allergan) and suprofen 1% (Profenal Ophthalmic Solution, Alcon) are approved by the Food and Drug Administration (FDA) for intraoperative use to inhibit miosis during cataract surgery. Ketorolac tromethamine 0.5% (Acular Ophthalmic Solution, Allergan) is approved in the United States for the treatment of seasonal allergic conjunctivitis. Diclofenac 1% (Voltaren, Ciba Vision Ophthalmics) is a phenylacetic acid derivative that is approved by the FDA for use to minimize postoperative inflammation after cataract surgery.

■ Pharmacokinetics

Pharmacokinetics is defined most easily as the action of one's body on an administered drug. NSAIDs are well absorbed after oral administration, with peak serum levels achieved in 1 to 3 hours. These agents are metabolized by the liver and excreted in the urine and the bile. All these drugs are 90 to 99% protein-bound and, therefore, are easily recovered from ocular tissues. Ocular instillation of topical NSAIDs provides ocular tissue and aqueous humor levels adequate to inhibit prostaglandin (PG) synthesis. In fact, these NSAIDs appear to penetrate the eye better after topical application than after oral administration. This observation, coupled with a greater potential for undesirable systemic side effects with oral administration, makes it unreasonable for ophthalmologists to prescribe systemic NSAIDs to achieve most ocular therapeutic effects. However, topically applied NSAIDs can gain access to the systemic circulation via mucosal absorption. Therefore, even local administration of NSAIDs can be accompanied by systemic toxicity if nasolacrimal occlusion and eyelid closure are not employed following eye drop instillation.

■ Pharmacodynamics

Pharmacodynamics is the action of a drug on one's body. Aspirin and other NSAIDs decrease the synthesis of PGs within human tissues by inhibiting cyclooxygenase. This enzyme facilitates the formation of endoperoxides from arachidonic acid within the cascade of reactions that ultimately generate PGs within the human body. The resultant endogenous PGs can produce many ocular pharmacological effects including miosis, increased permeability of the blood-ocular barriers, conjunctival hyperemia, and changes in intraocular pressure. In addition, PGs are known to possess chemokinetic activity, can serve as mediators of humoral and cellular phases of inflammatory responses and are associated with the pain response and allergic reactions.

Although NSAIDs do not inhibit lipoxygenase and, therefore, have no ability to inhibit directly the generation of endogenous leukotrienes, diclofenac appears capable of reducing the level of leukotriene formation in vitro by indirect means [4]. There is evidence that NSAIDs have a free radical scavenger activity that may be beneficial during inflammation. Therefore, inhibition of cyclooxygenase activity clearly is not the only potential mechanism of activity for this group of drugs [1].

■ NSAIDs and Cataract Surgery

Maintenance of Intraoperative Mydriasis

Clinical studies reporting NSAID efficacy describe a small pharmacological effect on the intraoperative change in pupil size. Flurbiprofen 0.03% and suprofen 1% were first approved by the FDA for use as intraoperative inhibitors of miosis. Topical NSAIDs appear to share this therapeutic benefit [5]. This pharmacological activity is of potential clinical benefit because decreasing pupil size is a well-recognized risk factor for vitreous loss and zonular breaks during extracapsular cataract extractions with implantation of an intraocular lens [1]. The FDA's summary bases of approval for flurbiprofen and suprofen suggest that the pharmacological effect of these NSAIDs on pupil size varies from one surgical practice to another, as previously discussed [2]. This fact implies that endogenous factors other than PG-induced miosis and surgical technique are playing important, and as yet undefined, roles in the etiology of surgically induced miosis.

In summary, there is evidence that topically applied NSAIDs have a statistically significant inhibitory effect on intraoperative miosis. However, it is not clear that this effect is clinically significant for all surgeries. Adequate intraoperative mydriasis frequently is achieved and maintained by using good surgical technique, a combination of preoperative parasympatholytic and sympathomimetic eye drops, and the use of a sympathomimetic in the intraocular irrigation solution during irrigation and aspiration of cortical remnants. Therefore, it probably is unreasonable to suggest the routine use of preoperative NSAIDs for inhibiting intraoperative miosis during cataract surgery for all ophthalmic practices.

Reduction of Postoperative Inflammation

Many well-designed clinical studies provide evidence that topical NSAIDs are potentially useful in the management of inflammation after cataract surgery [1, 2]. During the 1970s, double-masked, randomized clinical studies evaluated the effect of topically applied indomethacin on the inflammatory response in the early postoperative period following ocular surgeries. Initially, the effects appeared variable. However, the results were more consistent once studies were designed to evaluate the effective-

ness of indomethacin given prior to and immediately after the surgical procedures. Unfortunately, many studies include concurrent administration of corticosteroids. Therefore, it is difficult to conclude whether the observed effects on postoperative inflammation are related to NSAID treatment or a synergistic effect of indomethacin and corticosteroids. It also is possible that the concurrent steroid treatment masks indomethacin's tendency to cause ocular irritation.

Several double-masked, randomized placebo- and active-controlled studies including patients undergoing cataract surgery have reported antiinflammatory effects from topically applied 1% indomethacin, 0.03% flurbiprofen, 0.5% ketorolac, and 0.1% diclofenac ophthalmic preparations [1, 2]. These investigations report a measurable antiinflammatory effect from topical NSAID treatments as compared to placebo after intracapsular and extracapsular cataract extractions, with and without implantation of an intraocular lens. The correlation between slit-lamp observations and anterior ocular fluorophotometry appears reasonably consistent. Studies using laser cell-and-flare meter methodology further support this potential therapeutic benefit [6, 7]. Studies comparing NSAIDs to corticosteroids have demonstrated that the results of these treatments show no significant difference as judged by slit-lamp examinations for cells, flare, and chemosis, but NSAID treatment appears more effective than topical steroids in reestablishing the blood-aqueous barrier as quantitatively measured with anterior ocular fluorophotometry [1].

In summary, many clinical studies provide evidence that topically applied NSAID ophthalmic preparations are potentially useful in managing inflammation after cataract surgery. These preparations are available and in use throughout the world for this indication. However, at the time this chapter was written, diclofenac 0.1% ophthalmic solution (Voltaren) was the only NSAID specifically approved by the FDA for use within the United States as a postoperative antiinflammatory agent following cataract surgery.

Prevention and Treatment of CME

Thoughtful reviews have summarized potential approaches to the prevention and treatment of CME after cataract surgery [8, 9]. These reviews stress the importance of placebo-controlled, double-masked, randomized trials in making decisions about the efficacy of potential treatments for CME after cataract surgery because this condition's natural history includes spontaneous resolution. Most reports emphasize the need to evaluate prophylactic therapy separately from the treatment of chronic CME and the importance of differentiating between angiographic CME and clinically significant CME (that associated with a reduction in vision).

Topical NSAIDs are effective in the prophylaxis of angiographic CME. However, a statistically significant, sustained effect on visual acuity has not

been demonstrated [1]. Unfortunately, most of the studies of prophylactic NSAID therapy include the concurrent use of corticosteroids. Insofar as corticosteroids inhibit the generation of PGs by a different mechanism than do NSAIDs it appears possible that a synergistic effect occurs when these drugs are used together. A randomized, double-masked clinical trial, using Snellen and contrast-sensitivity measurements, compares 0.03% flurbiprofen, 1% indomethacin, and placebo regarding their ability to prevent CME during a 6-month period after cataract surgery [10]. The incidence of clinical CME as determined by contrast-sensitivity scores is significantly lower for the drug- treated groups. However, these effects were not sustained, and this study included concurrent corticosteroids.

Only one randomized, double-masked study of prophylaxis of CME with NSAIDs without concurrent corticosteroid therapy is found in the literature [11]. It reports less postoperative angiographic CME in the group treated with ketorolac 0.5% compared to the placebo group [11]. Though there are fewer studies of the treatment of chronic CME, two double-masked, placebo-controlled, randomized studies demonstrate that ketorolac 0.5% ophthalmic solution, one drop given four times daily for up to 3 months, improves vision in some patients with chronic CME (of 6 or more months' duration) after cataract surgery [12, 13]. Hence, there is evidence that topical NSAID treatment offers benefit to some patients for the prevention and treatment of CME following cataract surgery.

■ Allergic Conjunctivitis

Topical corticosteroids commonly are used in an attempt to reduce the signs and symptoms of allergic conjunctivitis. Unfortunately, their use can be accompanied by local toxicity, including secondary open-angle glaucoma, cataracts, superinfections with viruses or fungi, and impaired wound healing. There is evidence that ketorolac 0.5% ophthalmic solution, administered as one drop four times daily, is effective in reducing the ocular pruritus that often accompanies seasonal allergic conjunctivitis [14]. Therefore, the FDA has approved this preparation (Acular) for use in the United States. In addition, some studies suggest that diclofenac is effective in the treatment of seasonal allergic conjunctivitis [15], and there are reports of potentially useful effects following suprofen treatment of giant papillary conjunctivitis and vernal conjunctivitis [16, 17].

■ Reduction of Discomfort After Refractive Surgery

The topical NSAIDs are not approved for use following radial keratotomy or photorefractive keratectomy within the United States. However,

there are reports that pain following refractive surgeries is reduced with the use of topical ketorolac and diclofenac ophthalmic solutions [18–20].

■ Local and Systemic Toxicity of Topical NSAIDs

The most common adverse reactions after topical instillation of the NSAIDs are transient burning, stinging, and hyperemia of the conjunctiva. Manufacturers have used various formulation methods to minimize this potential discomfort. Indomethacin solution in sesame seed oil was abandoned in favor of an aqueous suspension. Suprofen is prepared with 1% caffeine because it is less irritating in this form. Ketorolac is formulated as the tromethamine salt because the tromethamine moiety enhances the aqueous solubility and results in a solution that is less irritating to the eye. Despite these improvements, some patients will experience local discomfort after instilling these preparations. In addition, allergies and hypersensitivity reactions have been reported with all the NSAIDs.

Systemic administration of NSAIDs can be accompanied by serious side effects such as gastrointestinal, central nervous system, hematologic, renal, liver, dermatological, and metabolic changes. It appears, though, that these effects are largely avoided by topical administration. The possibility of systemic absorption exists after topical application, but it is not clear whether this represents a clinically significant problem [1]. The literature clearly describes less toxicity associated with the topical use of NSAIDs than with topically applied corticosteroids, but NSAIDs have been used far less extensively. Furthermore, there are some theoretical objections to the inhibition of only the cyclooxygenase pathway for PG generation. Although an aggravation of ocular inflammation has not been observed in any of the clinical studies of NSAID use thus far reported, it is premature to assume that this treatment is completely safe. Therefore, NSAID use must be carefully monitored for adverse events, as is good practice with any new drug treatment.

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