Nonsteroidal Anti-inflammatory Drugs in Ophthalmology

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Nonsteroidal anti-inflammatory drugs (NSAIDs) have recently become commercially available throughout the world as ophthalmic eye drops [1]. This group of drugs has been widely used for the prevention and treatment of cystoid macular edema (CME) following cataract operations and in the management of postoperative ocular inflammation and prevention of intraoperative miosis associated with cataract surgery.

Chemistry and Classification of NSAIDs

The NSAIDs are a chemically heterogeneous group of compounds that can be grouped into six major classes: salicylates, fenamates, indoles, phenylalkanoic acids, phenylacetic acids, and pyrazolones. Their classification as NSAIDs emphasizes that their chemical structures do not include a steroid nucleus derived biosynthetically from cholesterol. This review will concentrate on the indoles, the phenylacetic acids, and the phenylalkanoic acids, all of which are available as topical ophthalmic preparations. The salicylates, fenamates, and pyrazolone derivatives are too toxic or unstable in solution for ocular application.

Indomethacin, the first topically administered NSAID widely used by ophthalmologists, is the only indole derivative currently available as an ophthalmic preparation. Although initially prepared as a solution, formulated in a sesame seed oil vehicle, it proved to be too irritating for most patients to use. Therefore, it is presently available in Europe and other parts of the world as an aqueous suspension consisting of indomethacin 1% (Indocid Ophthalmic Suspension, Merck Sharp & Dohme). This topical ophthalmic preparation is not approved for use in the United States.

The phenylalkanoic acids are water-soluble and have therefore been 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 operations and are commercially available in the United States. Ketorolac tromethamine 0.5% (Acular Ophthalmic Solution, Allergan) is available in Europe and other parts of the world as an eye drop preparation. It is the most recently approved NSAID for ophthalmic use in this country and will soon become available for the treatment of allergic conjunctivitis.

Diclofenac 0.1% (Voltaren, Ciba Vision Ophthalmics) is a phenylacetic acid derivative. It is approved by the FDA for use to inhibit postoperative inflammation following cataract surgery.

■ Pharmacokinetics

The NSAIDs are well absorbed from the gastrointestinal tract following oral administration. Peak serum levels are achieved in 1 to 3 hours. They are metabolized by the liver and excreted in urine and bile. Their plasma half-lives are variable, which probably relates to enterohepatic cycling. Furthermore, these agents are highly protein-bound (90 to 99%) and are therefore extensively bound to ocular tissues. Ocular instillation of the NSAIDs provides ocular tissue and aqueous humor levels adequate to inhibit prostaglandin synthesis. Although these agents have measurable ocular penetration after oral administration, NSAIDs appear to penetrate the eye better after topical application. These pharmacokinetic observations, coupled with the greater potential for undesirable systemic side effects with oral administration, probably make it unreasonable for ophthalmologists to administer NSAIDs systemically to achieve ocular therapeutic effects. However, it cannot definitely be concluded that the topical administration of NSAIDs is never associated with significant systemic absorption. Several studies [1] have shown that a significant percentage of topically applied drug can reach the systemic circulation via absorption from the nasolacrimal outflow system. Therefore, while the amount of NSAID absorbed is relatively small and variable following topical administration, and this method of drug administration is clearly associated with fewer systemic side effects as compared to oral treatment, it is unwise to assume the topical route lacks any possibility for systemic toxicity.

■ Pharmacodynamics

All the NSAIDs that are of ophthalmic interest have anti-inflammatory, analgesic, and antipyretic properties similar to the salicylates. In fact, some investigators choose to ignore the common pharmacodynamics and chemistry shared by the NSAIDs and prefer to emphasize the pharmacological effects that they share with aspirin, referring to them as *aspirinlike drugs*. Aspirin and other NSAIDs decrease the synthesis of prostaglandins by

inhibiting cyclooxygenase, the enzyme that catalyzes the formation of endoperoxides from arachidonic acid. Prostaglandins can produce several pharmacological effects within the eye, including miosis, increased vascular permeability of the blood-ocular barriers, conjunctival hyperemia, and changes in intraocular pressure. In addition, prostaglandins are known to possess chemokinetic activity and can serve as mediators of humoral and cellular phases of inflammatory responses. Finally, prostaglandins are involved in some allergic reactions.

NSAIDs do not inhibit lipoxygenase and therefore have no direct ability to inhibit the generation of leukotrienes. This contrasts with the activity of corticosteroids which, by inhibiting phospholipase A_2, cause not only decreased prostaglandin synthesis but also decreased leukotriene formation. Nonetheless, while it is tempting to explain all the pharmacological properties of NSAIDs by their ability to inhibit cyclooxygenase, this is most likely an oversimplification. There is evidence that these drugs have a free radical scavenger activity that may be beneficial during inflammation. Furthermore, some NSAIDs appear to reduce the level of leukotriene formation in vitro by indirect means. However, inhibition of cyclooxygenase activity appears to relate to the potential therapeutic uses of topical NSAIDs within ophthalmology: the inhibition of intraoperative miosis, modification of postoperative inflammation, and prevention and treatment of CME associated with cataract operations and the symptomatic relief of ocular itching that can accompany seasonal allergic conjunctivitis.

■ Inhibition of Intraoperative Miosis

Although there are well-recognized differences among species in their miotic responses to prostaglandins, intraoperative inhibition of miosis with NSAIDs does occur in humans. Clinical studies reporting NSAID efficacy describe a small pharmacological effect on the intraoperative change in pupil size. Two NSAIDs, flurbiprofen 0.03% and suprofen 1%, are approved by the FDA for use in the United States as intraoperative inhibitors of miosis. This would appear to be of potential clinical benefit for patients 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. However, the published data and the FDA's *Summary Basis of Approval* for both flurbiprofen and suprofen suggest the pharmacological effect of NSAIDs on pupil size is small and varies from one surgical practice to another. Furthermore, changes in pupil diameters in vehicle-treated eyes among different studies [1] by the same surgeons are larger, in several instances, than any therapeutic effect on pupil size. This suggests that endogenous factors other than prostaglandin-induced miosis and surgical technique are playing important, and as yet undefined, roles in the etiology of surgical miosis.

Although there is evidence that NSAIDs have a statistically significant inhibitory effect on intraoperative miosis, it is not entirely clear that this effect is clinically significant for all ophthalmologists. The number of surgeons who have been unable to demonstrate an effect in double-masked clinical studies [1] is impressive. It appears that adequate intraoperative mydriasis is frequently achieved by some surgeons simply by using good surgical technique, some combination of preoperative parasympatholytic and sympathomimetic eye drop therapy, and the inclusion of a sympathomimetic in the intraocular irrigation solution used during irrigation and aspiration of cortical remnants. Based on these findings, it is probably unreasonable to suggest the routine use of preoperative NSAIDs for inhibiting intraoperative miosis during cataract surgery for all ophthalmic practices.

■ Postoperative Anti-inflammation and Cataract Operations

There are many well-designed clinical studies that provide evidence that NSAID ophthalmic preparations are potentially useful in managing postoperative inflammation following cataract surgery [2]. During the mid-1970s, double-masked clinical studies evaluated the effect of topically applied indomethacin suspensions and solutions on inflammation in the early postoperative period after ocular operations. Initially, the observed responses appeared variable. However, once studies were designed to evaluate the effectiveness of indomethacin given prior to and immediately after surgical procedures, the results were more consistent. Unfortunately, most subsequent studies included concurrent administration of corticosteroids. Therefore, it is difficult to conclude whether the observed effects on postoperative inflammation were related to NSAID treatment or a synergistic effect of indomethacin and corticosteroids. Furthermore, it is not possible to determine whether the concurrent steroid treatment masked indomethacin's tendency to cause ocular irritation.

Double-masked, randomized, placebo- and active-controlled studies [1] of patients undergoing cataract surgical procedures have reported anti-inflammatory effects from topically applied 1% indomethacin, 0.03% flurbiprofen, 0.5% ketorolac, and 0.1% diclofenac ophthalmic preparations [1]. These investigations report an anti-inflammatory effect from topical NSAID treatments as compared to placebo following intracapsular and extracapsular cataract extractions, both with and without implantation of an intraocular lens, and both with concurrent steroid administration and without the administration of concurrent or postoperative steroids. The correlation between slit-lamp observations and anterior ocular fluorophotometry appears reasonable. More recent studies using laser cell flare meter methodology provide further support for these observations. In addi-

tion, studies comparing NSAIDs to corticosteroids have demonstrated that these treatments are not significantly different 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 or laser cell flare meters.

Thus, there are many clinical studies providing evidence that NSAID ophthalmic preparations are potentially useful in the management of postoperative inflammation associated with cataract operations. These preparations are available and in use elsewhere in the world for this indication. At the time of this writing, only diclofenac 0.1% ophthalmic solution has been approved by the FDA for use in postoperative inflammation after cataract surgery in the United States. Unfortunately, the investigations supporting this indication have not been published in the peer-reviewed literature to date, and the *Summary Basis of Approval* supplied by the FDA is not significantly detailed to permit a critical analysis of this drug's efficacy.

■ CME Following Cataract Extraction

There are excellent reviews of the therapy of CME after cataract extraction [3, 4]. These reviews stress the importance of using placebo-controlled, double-masked, randomized trials to make decisions concerning the efficacy of any potential treatment for a condition such as postcataract extraction CME, whose natural history includes spontaneous resolution. Furthermore, an emphasis is placed on the desirability of evaluating prophylactic therapy separately from treatment of chronic CME and the need to differentiate between angiographic (presence of CME documented with a fluorescein angiogram) and clinically significant (associated with a reduction in vision) CME.

Topical NSAIDs are effective in the prophylaxis of angiographic CME. However, a statistically significant, sustained effect on visual acuity has not been demonstrated. Although this lack of a sustained effect of prophylactic treatment on visual acuity is discouraging, no study has carefully evaluated non-Snellen parameters of visual function. More complete vision testing might reveal more impressive beneficial effects.

Most of the reported studies [1] of prophylactic NSAID therapy include the concurrent use of corticosteroids in the postoperative period. Insofar as corticosteroids inhibit the generation of prostaglandins by a different mechanism than NSAIDs, there may be a synergistic effect when these drugs are used together. However, there is one published study of NSAID therapy without concurrent corticosteroid use that documented less postoperative angiographic CME in the group treated with ketorolac 0.5% as compared to placebo [5]. In addition, two double-masked, placebo-controlled, randomized studies have demonstrated that ketorolac 0.5%

ophthalmic solution improves vision in some patients with chronic CME (present 6 or more months) following cataract extraction [6]. This provides some evidence that NSAID treatment may be somewhat beneficial for the prevention and treatment of CME after a cataract operation. However, the clinical significance of any therapeutic effect from NSAID administration for the prevention or treatment of CME must be evaluated in relation to other possible pathogenic factors and potential treatments.

■ Seasonal Allergic Conjunctivitis

Topical corticosteroids are commonly 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 is effective in reducing the ocular pruritis that often accompanies seasonal allergic conjunctivitis. Therefore, the FDA has approved this preparation for use in the United States. The studies supporting this indication have not been published, but are reviewed in the FDA's *Summary Basis of Approval* for this preparation.

■ Toxicity

After topical instillation of the NSAIDs, the most common adverse reactions appear to be 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 proved less irritating. Ketorolac is formulated as the tromethamine salt because the tromethamine moiety enhances aqueous solubility and results in a solution that is less irritating to the eye. Despite these improvements, some patients will complain of transient burning and stinging after instillation of any of these preparations. In addition, allergies and hypersensitivity reactions have been reported with all of the NSAIDs, and there is a potential for cross-sensitivity with aspirin. A postoperative atonic mydriasis has been reported in some patients who receive topical NSAIDs before a cataract operation [1]. The pharmacodynamics of this adverse event are poorly understood. In addition, its relationship to the dilated, atonic pupil that has been reported after uncomplicated cataract extraction in patients who have never received NSAIDs has not been studied [7].

Although systemic administration of NSAIDs can be accompanied by serious side effects (gastrointestinal, central nervous system, hematological,

renal, liver, dermatological, and metabolic changes), it appears these can be largely avoided by topical administration. However, there is the possibility of systemic absorption after topical application, and it is not clear whether this represents a clinically significant problem. Furthermore, while it is clear that the literature describes less toxicity associated with the topical use of NSAIDs than with topically applied corticosteroids, NSAIDs have been used far less extensively. There are some theoretical objections to the inhibition of only the cyclooxygenase pathway for prostaglandin 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.

■ References

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