Topical Nonsteroidal Antiinflammatory Drugs in Ophthalmology

Allan Joseph Flach, M.D.

Topically applied nonsteroidal antiinflammatory drugs (NSAIDs) are widely used in the management of postoperative ocular inflammation and for the prevention and treatment of cystoid macular edema (CME) after cataract surgery. In addition, they are 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 after refractive surgery.[1,2] In this chapter, the current status of topically applied NSAIDs and their potential therapeutic benefit for ophthalmic disorders are summarized.

Chemical Classification and Commercial Preparations

Commercially available 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. The classification of this group of drugs as NSAIDs serves to underscore that their chemical structures lack a steroid nucleus that is biosynthetically derived from cholesterol. This ophthalmic clinical pharmacology review will emphasize the indoles, the phenylacetic acids, and the phenylalkanoic acids, because they are commercially available throughout the world as topically applied ophthalmic preparations. The salicylates, fenamates, and pyrazolone derivatives are either too toxic or too unstable in solution for commercial formulation as eye drops.

Indomethacin, an indole derivative, was initially formulated as a sesame seed oil solution. However, this preparation was locally irritating and unsuitable for widespread clinical use. Today topical indomethacin is commercially available outside of the United States as a 1% aqueous suspension (Indocid Ophthalmic Suspension, Merck, Sharp & Dohme). Al-

though a 0.1% indomethacin ophthalmic solution has been formulated, it is not commercially available.[3]

The phenylalkanoic acids are water-soluble. This pharmacological group includes flurbiprofen, suprofen, and ketorolac. Because of their favorable solubility characteristics, these acids are formulated as ophthalmic solutions. Flurbiprofen 0.03% (Ocufen Ophthalmic Solution, Allergan) and suprofen 1% (Profenal Ophthalmic Solution, Alcon) are approved by the US Food and Drug Administration (FDA) for intraoperative use to inhibit excessive 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 and postoperative inflammation after cataract surgery and for use after refractive surgery. It is the only topically effective NSAID that is available in a preservative-free formulation (Acular PF Ophthalmic Solution, Allergan).

Diclofenac 1% (Voltaren, Novartis Ophthalmics) is a phenylacetic acid derivative that is readily soluble in water and is, therefore, available as an ophthalmic solution. Its use is approved by the FDA for minimizing postoperative inflammation after cataract surgery and for minimizing pain and photophobia after refractive surgery.

Diclofenac 1% formerly was available also in a generic form (Falcon, Alcon) approved for treatment of postoperative inflammation after cataract surgery. This generic form of diclofenac was preserved with polyquad polyquaternium-1 and included tocophersolan and mannitol as emollients. These excipients differ from those present in Voltaren 1%, which is preserved with sorbic acid and edetate sodium and includes polyoxyl-35 as an emollient. The potential significance of these differences in formulation is not clear.

■ Pharmacokinetics

Pharmacokinetics can be defined as the action of one's body on a drug after the drug's administration. Although all NSAIDs are well absorbed after oral ingestion, with peak serum levels achieved in 1 to 3 hours, ocular instillation of topical NSAIDs provides ocular tissue and aqueous humor levels adequate to inhibit prostaglandin (PG) synthesis. In fact, commercially available, topically applied NSAIDs appear to penetrate the eye better after topical application than after oral administration. This observation makes it unreasonable for ophthalmologists to prescribe systemic NSAIDs to achieve most ocular therapeutic effects. This is particularly true in light of the enhanced likelihood for undesirable systemic side effects that can accompany the oral administration of these agents. NSAIDs 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 after topical or systemic administra-

tion. Topically applied NSAIDs can gain access to the systemic circulation after mucosal absorption from the nasolacrimal outflow system. Therefore, even local administration of NSAIDs can be accompanied by systemic toxicity, particularly if nasolacrimal occlusion and eyelid closure are not employed after eye drop instillation.

■ Pharmacodynamics

Pharmacodynamics is defined as the action of a drug on one's body. Many investigators cite the pharmacodynamic relationship of NSAIDs and cyclooxygenase inhibitors. More specifically, aspirin and other NSAIDs decrease the synthesis of PGs within our tissues by inhibiting cyclooxygenase. This enzyme facilitates the formation of endoperoxides from arachidonic acid by participating in the cascade of reactions that ultimately generate PGs within our bodies. The resultant endogenous PGs can produce many 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 direct ability to inhibit the generation of endogenous leukotrienes, diclofenac appears capable of reducing the level of leukotriene formation in vitro by an indirect means.[4] There is evidence that NSAIDs have a free radical scavenger activity that may be beneficial during inflammation. Therefore, inhibition of COI activity is clearly not the only potential mechanism of activity for this group of drugs.[1]

■ Maintenance of Mydriasis During Cataract Surgery

Flurbiprofen 0.03% and suprofen 1% were the first NSAIDs approved by the FDA for use as intraoperative inhibitors of miosis during cataract surgery. This pharmacological activity is of clinical benefit because decreasing pupil size is a recognized risk factor for vitreous loss and zonular breaks during cataract surgery involving implantation of an intraocular lens.[1] Many clinical studies report that preoperative NSAID application provides a significant pharmacological effect to prevent excessive miosis during cataract surgery. All the commercially available topical NSAIDs appear to share this therapeutic benefit.[5–7] However, 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 suggests that endog-

enous factors other than PG-induced miosis and surgical technique are playing important, and as yet undefined, roles in the etiology of surgically induced miosis.

Although most ophthalmologists prefer using topical NSAIDs prior to performing cataract surgery, it is probably unreasonable to require the routine use of these agents for all ophthalmic practices, because adequate intraoperative mydriasis can frequently be achieved and maintained by the use of good surgical technique, a combination of preoperative parasympatholytic and sympathomimetic eye drop therapy, and a sympathomimetic in the intraocular irrigation solution used for irrigation and aspiration of cortical remnants.

■ Postoperative Inflammation After Cataract Surgery

Double-masked, prospective, randomized, active and placebo-controlled clinical studies provide good evidence that topical NSAIDs are potentially useful in limitating excessive postoperative inflammation after cataract surgery.[1,2] However, it is of historical interest that during the 1970s, several studies evaluated the effect of topically applied indomethacin on the inflammatory response in the early postoperative period after ocular surgeries, with inconsistent results. Once studies were designed to evaluate the effects of indomethacin given prior to and immediately after the surgical procedures, the results were more impressive. It is interesting that, at present, topically applied NSAIDs are officially approved by the FDA for only postoperative use. However, it has become the standard of care to use these agents both preoperatively and postoperatively to provide better antiinflammatory control and help to discourage undesired miosis during the surgical procedure. Well-designed studies support this preoperative dosage regimen.[6,7]

Many studies of NSAID effects on postoperative inflammation include the concurrent administration of corticosteroids. There is good evidence that NSAIDs and corticosteroids have a potential for synergistic activity.[8,9] Therefore, it is difficult to conclude from these studies whether the observed effects on postoperative inflammation are related to NSAID treatment alone or to a synergistic effect resulting from the combined pharmacological activities of the NSAID and corticosteroid. It is also possible that the concurrent corticosteroid treatment may mask the tendency for any given NSAID to cause ocular irritiation.

Double-masked, randomized, active and placebo-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 consistent. In addition, studies using laser cell flare meter methodology provide further support for this potentially beneficial therapeutic benefit.[10–12] Studies comparing NSAIDs to corticosteroids have demonstrated no significant difference in the results of these treatments as judged by slit-lamp examinations for cells, flare, and chemosis, but NSAID treatment appears to be more effective than topical steroids in reestablishing the blood-aqueous barrier, as quantitatively measured with anterior ocular fluorophotometry.[1,2,10] A double-masked, prospective, randomized study of 120 patients after cataract surgery and implantation of an intraocular lens showed no statistical difference between the antiinflammatory effects of postoperatively administered ketorolac 0.5% and diclofenac 0.1% ophthalmic solutions, as evaluated with slit-lamp examinations and laser cell flare measurements.[12]

In summary, many well-designed clinical studies provide evidence that topically applied NSAID ophthalmic preparations are potentially useful in the management of postoperative inflammation after cataract surgery. Furthermore, there is good evidence that this treatment is potentially beneficial even with the application of current surgical technology.[13] Although the various topical NSAID preparations previously mentioned are available and used throughout the world for avoiding excessive inflammation after cataract surgery, at the time of this writing diclofenac 0.1% (Voltaren) and ketorolac 0.5% (Acular) ophthalmic solutions are the only topically applied NSAIDs specifically approved by the FDA for this indication in the United States.

■ Prevention and Treatment of CME After Cataract Surgery

Excellent reviews have summarized potential approaches to the prevention and treatment of CME after cataract surgery.[14,15] These reviews stress the importance of placebo-controlled, double-masked, randomized trials in influencing decisions about the efficacy of potential treatments for CME after cataract surgery, because this syndrome's natural history includes spontaneous resolution. In addition, evaluating prophylactic therapy separately from the treatment of chronic CME is emphasized, as is the importance of differentiating between asymptomatic angiographic CME and clinically significant CME, which is associated with a reduction in vision.

There is no FDA-approved therapy for the prevention and treatment of CME after cataract surgery. However, a recently completed metaanalysis concludes that application of a topical NSAID for this indication is potentially beneficial.[16] This metaanalysis is in agreement with a recent review article on this subject.[17]

Although NSAIDs are effective in the prophylaxis of angiographic CME, a significant and sustained effect on visual acuity has not been demonstrated.[1,2,14,15,17] In addition, 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, the possibility exists for a synergistic effect when these drugs are used together.

A large, randomized, double-masked clinical trial has compared 0.03% flurbiprofen, 1% indomethacin, and placebo for their ability to prevent CME during a 6-month period after cataract surgery, as assessed by Snellen and contrast sensitivity measurements.[18] The incidence of clinical CME as determined by contrast sensitivity scores was significantly lower for the drug-treated groups, but the effects were not sustained. In addition, this study involved concurrent use of corticosteroids. To date, there is only one randomized, double-masked study of prophylaxis of CME using NSAIDs without concurrent corticosteroids: It reports less postoperative angiographic CME in the group treated with ketorolac 0.5% as compared to the placebo group.[19]

Although there are fewer studies of the treatment of chronic CME (defined as reduced vision associated with CME that has been present for at least 6 months), two double-masked, placebo-controlled, randomized studies in which corticosteroids were not used demonstrate that ketorolac 0.5% ophthalmic solution, administered as a single drop four times daily for up to 3 months, improves vision in some patients with chronic CME after cataract surgery.[20,21]

These studies provide evidence that this topical NSAID treatment offers benefit to some patients for the prevention and treatment of CME after cataract surgery. In addition, it has recently been demonstrated that the concurrent administration of corticosteroids and NSAIDs may provide a synergistic activity resulting in more rapid resolution of symptomatic CME.[8] The potential application of topical NSAIDs for the treatment and prevention of CME is discussed in greater detail and compared to other potential treatments (including corticosteroids, carbonic anhydrase inhibitors, and hyperbaric oxygen) in a recent publication.[17]

■ Allergic Conjunctivitis

On the basis of evidence that ketorolac 0.5% ophthalmic solution administered as one drop four times daily is effective in reducing the ocular pruritis that often accompanies seasonal allergic conjunctivitis,[22] the FDA has approved this preparation (Acular) for use in the United States. In addition, some studies suggest that diclofenac (Voltaren) also is effective in treating seasonal allergic conjunctivitis,[23] and there are reports of potentially useful effects after suprofen (Profenal) treatment of

giant papillary conjunctivitis and vernal conjunctivitis.[24,25] 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. Therefore, topically applied NSAIDs offer a potentially safer alternative to minimizing the signs and symptoms of allergic eye disease.

■ Reduction of Discomfort After Refractive Surgery

Ketorolac and diclofenac are approved for use within the United States to reduce pain and photophobia after refractive surgery.[26–28] In addition, some practitioners use topically applied NSAIDs to reduce pain after corneal abrasions. One randomized, double-masked, placebo-controlled study of 100 patients has shown that the healing time was not significantly different for patients who were patched after noninfected, non–contact lens–related, traumatic, or foreign-body removal–related corneal abrasions measuring less than 10 mm as compared to patients who received topical ketorolac 0.5% four times daily without patching. All patients also received topical antibiotics.[29]

■ Miscellaneous Potential Uses of Topical NSAIDs

Clinical studies have suggested a potential application for topical NSAIDs for the treatment of inflamed pinguecula and pterygia, argon laser trabeculoplasty, glaucoma, strabismus, refractive errors, and the management of pain and inflammation associated with corneal abrasions.[30–35] Laboratory studies have suggested that diclofenac might have a unique effect in preventing posterior capsule opacification after cataract surgery.[36] However, a randomized, double-masked, prospective clinical comparison of diclofenac 0.1% and ketorolac 0.5% given as one drop four times daily after cataract surgery and implantation of an intraocular lens did not demonstrate a difference in these drugs abilities to prevent posterior capsule opacification, as determined 3 years postoperatively.[37]

■ 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. For example, 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. 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 instillation of these preparations. In addition, allergies and hypersensitivity reactions have been reported with all the NSAIDs.

Corneal complications after topical NSAID use are uncommon. However, superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported after use of these agents.[38–41] This is not surprising, because most preserved eye-drops can cause minor, transient corneal changes.[42,43]

The recent reports of corneal melting *is* surprising and of great interest.[44] Although we await a complete and careful analysis of these cases of severe toxicity, thus far any potentially severe corneal toxicity appears to be more likely associated with generic diclofenac (Falcon, Alcon). However, even in these cases, the inconsistent and variable dose-toxicity relationships do not suggest a simple drug toxicity. Furthermore, the lack of a definitive diagnosis and indication for treatment, the concurrent presence of ocular disease, and use of additional medications in many of these cases complicates the analysis.[45–48] For example, many of the reported cases occur in patients with insufficient tear production who are concurrently using corticosteroids. These are important considerations, because corneal perforations have been reported in symptomatic and asymptomatic patients with dry eyes and in patients using only corticosteroids.[49–52] Practitioners can minimize the occurrence of corneal toxicity by attempting to make a definitive diagnosis before initiating antiinflammatory treatment and by conducting careful postoperative follow-up examinations.

Systemic administration of NSAIDs can be accompanied by serious side effects, such as gastrointestinal, central nervous system, hematological, renal, liver, dermatological, and metabolic changes. However, such effects appear to be largely avoided by topical NSAID administration. The possibility of systemic absorption exists after topical application, but whether this represents a clinically significant problem is not clear.[1] Although the literature describes less toxicity associated with the topical use of NSAIDs than with topically applied corticosteroids, NSAIDs have been used far less extensively. Furthermore, there are some theoretical objections to the inhibition of only the cyclooxygenase inhibitor 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.

This work was supported by a Department of Veterans Affairs merit review grant; a That Man May See, Inc., grant; and a department core grant from the National Institutes of Health and the University of California at San Francisco Department of Ophthalmology.

■ References

1. Flach AJ. Nonsteroidal anti-inflammatory drugs. In: Tasman W, ed. Duane's foundations of clinical ophthalmology. Philadelphia: Lippincott, 1994:1–32
2. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. Surv Ophthalmol 1992;36:259–284
3. Trinquand C, Richard C, Arnaud B. Three-arm, double-masked study of two ophthalmic formulations of 0.1% indomethacin and 0.1% diclofenac in controlling inflammation after cataract surgery. Invest Ophthalmol Vis Sci 1996;37:S590
4. Ku ED, Lee W, Kothari HV, et al. Effect of diclofenac sodium on the arachidonic acid cascade. Am J Med 1986;80:18–23
5. Roberts CW. A comparison of diclofenac sodium to flurbiprofen for maintaining intraoperative mydriasis. Invest Ophthalmol Vis Sci 1993;35:1967
6. Roberts CW. Pretreatment with topical diclofenac sodium to decrease postoperative inflammation. Ophthalmology 1996;103:636–639
7. Solomon KD, Turkalj JW, Whiteside SB, et al. Topical 0.5% ketorolac vs 0.03% flurbiprofen for inhibition of miosis during cataract surgery. Arch Ophthalmol 1997;115:1119–1122
8. Heier JS, Topping TM, Baumann S, et al. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular-edema. Ophthalmology 2000;107:2034–2038
9. Flach AJ. Discussion: ketorolac vs prednisolone vs combination therapy in the treatment of acute pseudophakic CMD. Ophthalmology 2000;107:2039
10. Roberts CW, Brennan KM. A comparison of topical diclofenac with prednisolone for postcataract inflammation. Arch Ophthalmol 1995;113:725–727
11. Diestelhorst M, Thull D, Krieglstein GK. The effect of argon laser trabeculoplasty on the blood-aqueous barrier and intraocular pressure in human glaucomatous eyes treated with diclofenac 0.1%. Graefes Arch Clin Exp Ophthalmol 1995;233:559–562
12. Flach AJ, Dolan BJ, Donahue ME, et al. Comparative effects of ketorolac 0.5% or diclofenac 0.1% ophthalmic solutions on inflammation after cataract surgery. Ophthalmology 1998;105:1775–1779
13. Solomon KD, Cheetham JK, DeGryse R, et al. Topical ketorolac tromethamine 0.5% ophthalmic solution in ocular inflammation after cataract surgery. Ophthalmology 2001;108:331–337
14. Jampol LM. Pharmacologic therapy of aphakic cystoid macular edema: a review. Ophthalmology 1982;89:891–897
15. Jampol LM. Pharmacologic therapy of aphakic and pseudophakic cystoid macular edema: 1985 update. Ophthalmology 1985;92:807–810
16. Rossetti L, Chaudhuri J, Dickersin K. Medical prophylaxis and treatment of cystoid macular edema after cataract surgery—the results of a meta-analysis. Ophthalmology 1998;105:397–405
17. Flach AJ. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc 1998;96:557–634
18. Solomon LD, Flurbiprofen-CME Study Group I. Efficacy of topical flurbiprofen and indomethacin in preventing pseudophakic cystoid macular edema. J Cataract Refract Surg 1995;21:73–81

19. Flach AJ, Stegman RC, Graham J, et al. Prophylaxis of aphakic cystoid macular edema without corticosteroids. Ophthalmology 1990;97:1253–1258
20. Flach AJ, Jampol LM, Yannuzzi LA, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac ophthalmic solution. Am J Ophthalmol 1991;112:514–519
21. Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic cystoid macular edema. Am J Ophthalmol 1987;103:479–486
22. Tinkelman DG, Rupp G, Kaufman H, et al. Double-masked, paired-comparison clinical study of ketorolac tromethamine 0.5% ophthalmic solution compared with placebo eyedrops in the treatment of seasonal allergic conjunctivitis. Surv Ophthalmol 1993; 38:141–148
23. Laibovitz RA, Koester J, Schaich L, et al. Safety and efficacy of diclofenac sodium 0.1% ophthalmic solution in acute seasonal allergic conjunctivitis. J Ocul Pharmacol Ther 1995;11:361–368
24. Wood T, Steward R, Bowman R. Suprofen treatment of contact lens associated GPC. Ophthalmology 1988;96:822–829
25. Tauber J, Raizman MB, Ostrov CS, et al. A multicenter comparison of the ocular efficacy and safety of diclofenac 0.1% solution with that of ketorolac 0.5% solution in patients with acute seasonal allergic conjunctivitis. J Ocul Pharmacol Ther 1998;14: 137–145
26. Yee RW, Ketorolac Radial Keratotomy Study Group. Analgesic efficacy and safety of nonpreserved ketorolac ophthalmic solution following radial keratotomy. Am J Ophthalmol 1998;125:472–480
27. Eiferman RA, Hoffman RS, Sher NA. Topical diclofenac reduced pain following photorefractive keratectomy. Arch Ophthalmol 1993;111:1022
28. Szerenyi K, Sorken K, Garbus JJ, et al. Decrease in normal human corneal sensitivity with topical diclofenac sodium. Am J Ophthalmol 1994;118:312–315
29. Kaiser PK, Pineda R II. A study of topical nonsteroidal antiinflammatory drops and no pressure patching in the treatment of corneal abrasions. Ophthalmology 1997;104: 1353–1359
30. Frucht-Pery J, Siganos CS, Solomon A, et al. Topical indomethacin solution versus dexamethasone solution for treatment of inflamed pterygium and pinguecula: a prospective randomized clinical study. Am J Ophthalmol 1999;127:148–152
31. Goethals M, Missotten L. Efficacy and safety of indomethacin 0.1% versus flurbiprofen 0.03% eyedrops in inflammation after argon laser trabeculoplasty. Doc Ophthalmol 1994;85:287–293
32. Kent AR, Dubiner HB, Whitaker R, et al. The efficacy and safety of diclofenac 0.1% versus prednisolone acetate 1% following trabeculectomy with adjunctive mitomycin-C. Ophthalmic Surg Lasers 1998;29:562–569
33. Apt L, Voo I, Isenberg SJ. A randomized clinical trial of the nonsteroidal eyedrop diclofenac after strabismus surgery. Ophthalmology 1998;105:1449–1452
34. Rajpal RK, Cooperman BB. Analgesic efficacy and safety of ketorolac after photorefractive keratectomy. J Refract Surg 1999;15:661–667
35. Szucs PA, Nashed AH, Allegra JR, Eskin B. Safety and efficacy of diclofenac ophthalmic solution in the treatment of corneal abrasions. Ann Emerg Med 2000;35:131–137
36. Nishi O, Nishi K, Fujuwara T, et al. Effects of diclofenac sodium and indomethacin on proliferation and collagen synthesis of lens epithelial cells in vitro. J Cataract Refract Surg 1995;21:461–465
37. Flach AJ, Dolan BJ. Incidence of postoperative posterior capsular opacification following treatment with diclofenac 0.1% and ketorolac 0.5% ophthalmic solutions: 3 year randomized, double-masked, prospective clinical investigation. Trans Am Ophthalmol Soc 2000;98:101–107

38. Gills JP. Voltaren associated with medication keratitis [letter]. J Cataract Refract Surg 1994;20:110
39. Sher NA, Krueger RR, Teal R, Jans RG. Role of topical corticosteroids and nonsteroidal anti-inflammatory drugs in the etiology of stromal infiltrates after excimer photorefractive keratectomy. J Refract Corneal Surg 1994;10:587–588
40. Probst LEV, Machat JJ. Corneal subepithelial infiltrates following photorefractive keratectomy [letter]. J Cataract Refract Surg 1996;22:281
41. Shimazaki J, Saito H, Yang HY, et al. Persistent epithelial defect following penetrating keratoplasty: an adverse effect of diclofenac eyedrops. Cornea 1995;14:623–627
42. Wilson FM. Adverse external ocular effects of topical ophthalmic medications. Surv Ophthalmol 1979;24:57–88
43. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. Surv Ophthalmol 1980;25:15–30
44. Flach AJ. Topically applied nonsteroidal anti-inflammatory drugs and corneal problems: an interim review and comment [editorial]. Ophthalmology 2000;107:1224–1226
45. Lin JC, Rapuano CJ, Laibson PR, et al. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. Arch Ophthalmol 2000;118: 1129–1132
46. Congdon NG, Schein OD, von Kulajta P, et al. Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. J Cataract Refract Surg 2001;27:622–631
47. Guidera AC, Luchs JI, Udell IJ. Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. Ophthalmology 2001;108:936–944
48. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. Trans Am Ophthalmol Soc 2001 (in press)
49. Donzis PB, Mondino BJ. Management of noninfectious corneal ulcers. Surv Ophthalmol 1987;32:94–110
50. Pfister RR, Marphy GE. Corneal ulceration and perforation associated with Sjögren's syndrome. Arch Ophthalmol 1980;98:89–94
51. Radtke N, Meyers S, Kaufman HE. Sterile corneal ulcers after cataract surgery in keratoconjunctivitis sicca. Arch Ophthalmol 1978;96:51–52
52. Thygeson P. Controversies in ophthalmology. Philadelphia: Saunders, 1977:450–469