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MAJOR REVIEW

Nonsteroidal Anti-inflammatory Drugs in Ophthalmology

Stephen J. Kim, MD,[1] Allan J. Flach, MD,[2] and Lee M. Jampol, MD[3]

[1]Department of Ophthalmology, Vanderbilt University, Nashville, Tennessee, USA; [2]Department of Ophthalmology, University of California and Veterans Administration, San Francisco, California, USA; and [3]Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

Abstract. Nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly employed in ophthalmology to reduce miosis and inflammation, manage scleritis, and prevent and treat cystoid macular edema associated with cataract surgery. In addition, they may decrease postoperative pain and photophobia associated with refractive surgery and may reduce the itching associated with allergic conjunctivitis. In recent years, the U.S. Food and Drug Administration has approved new topical NSAIDs, and previously approved NSAIDs have been reformulated. These additions and changes result in different pharmacokinetics and dosing intervals, which may offer therapeutic advantages. For example, therapeutic effects on diabetic retinopathy and age-related macular degeneration may now be achievable. We provide an updated review on NSAIDs and a summary of their current uses in ophthalmology with attention to potential future applications. (**Surv Ophthalmol** 55:108–133, 2010.

Key words. age-related macular degeneration • allergic conjunctivitis • cataract surgery • cyclooxygenase inhibitors • cystoid macular edema • diabetic retinopathy • mydriasis • nonsteroidal anti-inflammatory drugs • NSAIDs • postoperative inflammation • prostaglandins

I. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medications worldwide. Aspirin and other chemically related compounds, used systemically for many decades for their analgesic, antipyretic, and anti-inflammatory properties, have more recently been prepared in topical ophthalmic formulations. As such, they have proven useful to enhance mydriasis, reduce postoperative inflammation, and prevent and treat cystoid macular edema (CME) associated with cataract surgery. In addition, they can be used to decrease pain and photophobia after refractive surgery and to alleviate itching associated with allergic conjunctivitis.[91,92,94,268,274] A growing body of scientific evidence suggests that NSAIDs may be beneficial in diabetic retinopathy, age-related macular degeneration, and ocular tumors.[110,133,167,203,298,310] It has been more than a decade since the first comprehensive review of topical NSAIDs.[94] This was followed by a chapter in *Duane's Clinical Ophthalmology* in 1994, updated in 2006.[92] We provide a current review of the status of NSAIDs and their application in ophthalmology and discuss possible future applications.

II. Cyclooxygenase

Cyclooxygenase (COX), an important group of enzymes active in the inflammatory process, catalyzes the biosynthesis of eicosanoids from arachidonic acid

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to produce prostaglandins (PGs) and thromboxanes. NSAIDs are potent inhibitors of COX enzymes, and thereby the synthesis of PGs. Within the eye PGs cause vasodilatation, disruption of the blood–ocular barrier, and leukocyte migration. Consequently, their inhibition by cyclooxygenase inhibitors may have therapeutic effects.[92,94,217] Two main isoforms of COX, COX–1 and COX-2, have been identified.[285] A third isoform, COX–3, remains largely uncharacterized.[65] COX–1, a constitutive enzyme, synthesizes PGs that regulate physiologic processes. Present in most tissues, COX–1 is expressed in the gastrointestinal (GI) tract, kidneys, platelets, and vascular endothelium, where it plays a role in normal physiologic function. COX-2 is an inducible enzyme that is expressed throughout the body, primarily during inflammatory responses and in association with pain or fever, but may be constitutively expressed in the absence of inflammation in sites such as the brain and kidneys.[230]

Accumulating evidence suggests that COX-2 has important therapeutic implications in retinal diseases. For example, COX-2 is the predominant isoform in human retinal pigment epithelium cells and is significantly up–regulated in response to pro–inflammatory cytokines.[55] COX-2 is also present in choroidal neovascularization (CNV), as well as in other highly vascularized lesions, and its expression increases in diabetic retinopathy.[25,50,74,203,277,310] Furthermore, prostaglandins interact with and amplify many other soluble mediators and induce vascular endothelial growth factor (VEGF), important in the development of proliferative diabetic retinopathy and neovascular age-related macular degeneration.[11,13,25,54,155] In a variety of experimental systems COX-2 inhibition suppresses angiogenesis[68,157,224,273,350] and recent reports have demonstrated inhibition of CNV and prevention of diabetic retinopathy in animal models treated with NSAIDs.[158,167,310,311]

The development of NSAIDs that preferentially inhibit COX-2 provides the potential for relieving pain and inflammation without the adverse effects of COX–1 blockade,[335] but the advantages of this approach have been questioned.[246] Some studies indicate that patients have less GI toxicity while using COX-2 inhibitors, reporting a reduction of confirmed upper GI events from 1.4% to 0.6% in the VIGOR study and 1.2% to 0.44% in the CLASS study. Although these percentages translate into a large number of patients given the widespread use of NSAIDs, they reflect only a small absolute beneficial effect.[39,284] In addition, the two–fold increase of heart attacks and strokes in patients using rofecoxib (Merck & Co., Inc., Whitehouse Station, NJ) raised concerns about the cardiovascular safety of COX-2 inhibitors.[A] It is unclear whether other COX-2 inhibitors (celecoxib, Pfizer, Inc. New York, NY; valdecoxib, Pfizer) share this cardiovascular toxicity.[56,60,63,130,226] Finally, although COX-2 inhibitors may reduce GI toxicity, they appear to have equivalent nephrotoxicity to conventional NSAIDs.

III. Commercial Preparations

NSAIDs are a chemically heterogenous group of compounds that inhibit the formation of eicosanoids and lack a steroid nucleus biosynthetically derived from cholesterol. A discussion of the pertinent chemistry of NSAIDs including their chemical structures, is available elsewhere.[92] There are six major classes: salicylates, indole acetic acid derivatives, aryl acetic acid derivatives, aryl propionic acid derivatives, enolic acid derivatives, and fenamates (Table 1). The topical formulations of NSAIDs are limited to the relatively water soluble classes: indole acetic, aryl acetic, and aryl propionic acids.[12]

This review will focus on commercially available topical ophthalmic preparations. Indomethacin 1% (Merck Sharp & Dohme, Whitehouse Station, NJ) is an indole acetic acid derivative, currently only available outside of the United States. An 0.1% solution of indomethacin has been formulated, but is not commercially available.[324] Flurbiprofen 0.03% (Allergan, Inc., Irvine, CA) and suprofen 1% (Alcon Laboratories, Inc., Fort Worth, TX) are water–soluble aryl propionic acid derivatives approved by the U.S. Food and Drug Administration (FDA) for prophylaxis of surgical miosis. Suprofen 1% is no longer commercially available. Flurbiprofen 0.03% is administered four times, beginning 2 hours before surgery. Ketorolac tromethamine 0.5% (Allergan, Inc) is an aryl acetic acid derivative and is FDA–approved for seasonal allergic conjunctivitis, post–cataract inflammation, and ocular discomfort after refractive surgery. To reduce the incidence of burning and stinging, a 0.4% concentration of ketorolac tromethamine (Allergan, Inc) was formulated and appears to have a similar therapeutic effect.[272,336] In addition, a nonpreserved form of ketorolac tromethamine is used for the reduction of ocular pain following refractive surgery.[41,294] Diclofenac 0.1% (Novartis Ophthalmics, Duluth, GA), also an aryl acetic acid derivative, is FDA approved for reducing inflammation after cataract surgery and decreasing pain after refractive surgery. Both ketorolac and diclofenac are dosed four times daily following cataract surgery. Two other topical NSAIDs, both aryl acetic acid derivatives, are now FDA–approved for treatment of pain and inflammation associated with cataract surgery and can be dosed less frequently. Nepafenac 0.1% (Alcon Laboratories) is a prodrug that is rapidly

TABLE 1

Available NSAIDs in the United States

Generic	Brand name	Administration route
Salicylates		
Acetylsalicylic acid (aspirin)	Bayer, Ecotrin, St. Joseph, Bufferin, Anacin, Excedrin (others)	Oral, suppository
Choline Magnesium Trisalicylate	Trilisate, Tricosal	Oral
Salsalate	Amigesic, Disalcid, Salflex	Oral
Diflunisal	Dolobid	Oral
Acetic Acids		
Diclofenac	Cataflam, Flector, Solaraze, Voltaren	Oral, topical ophthalmic, topical dermatologic
Etodolac	Lodine	Oral
Indomenthacin	Indocin, Indocin SR	Oral, suppository, intravenous
Ketorolac	Toradol, Acular, Acular LS	Oral, topical opthalmic, topical dematologic intravenous, intramusular
Nabumetone	Relafen	Oral
Sulindac	Clinoril	Oral
Tolmetin	Tolectin, Tolectin DS	Oral
Bromfenac	Xibrom	Topical ophthalmic
Nepafenac	Nevanac	Topical ophthalmic
Propionic acids		
Flurbiprofen	Ansaid, Ocufen	Oral, topical ophthalmic
Ketoprofen	Actron, Orudis KT, Oruvail	Oral
Ibuprofen	Advil, NeoProfen, Cap-Profen, ElixSure, Motrin, Nuprin, (others)	Oral, intravenous,
Naproxen	Aleve, Anaprox, Anaprox DS	Oral
Fenoprofen	Nalfon	Oral
Oxaprozin	Daypro	Oral
Enolic acid derivative		
Piroxicam	Feldene	Oral
Meloxicam	Mobic	Oral
Fenamates		
Meclofenamate	Meclodium, Meclomen	Oral
Mefenamic acid	Ponstel	Oral
Cox-2 specific NSAIDs		
Celecoxib	Celebrex	Oral

converted to amfenac after passage through the cornea, is dosed three times daily and is the only suspension among the topical NSAIDs. Bromfenac 0.09% (ISTA Pharmaceuticals, Inc., Irvine, CA) is dosed twice daily.

IV. Pharmacokinetics

All NSAIDs are well absorbed by the GI tract and reach peak serum levels in 1 to 3 hours. They are metabolized by the liver and excreted in the urine and bile and are highly protein–bound in plasma (typically > 95%), usually to albumin, so that their volume of distribution approximates that of plasma. This may be pertinent to topically applied NSAIDs, since systemic absorption may occur from mucosal surfaces of the nasolacrimal outflow system.

After a single topical application, 0.03% flurbiprofen and 0.1% diclofenac reach peak aqueous concentrations of 60 ng/mL and 82 ng/mL at 2.0 and 2.4 hours, respectively.[81] The concentration of diclofenac remains above 20 ng/mL for over 4 hours and is detectable after 24 hours. In contrast, flurbiprofen is undetectable after 7.25 hours. Although flurbiprofen reduces intraoperative miosis and inflammation after cataract surgery, it seems to be less effective than other available NSAIDs.[37,70,260,295]

Nepafenac is a prodrug that is rapidly converted into the more potent NSAID amfenac by intraocular hydrolases. Because nepafenac is noncharged, it may have greater corneal permeability than other NSAIDs, which have more polar acidic structures. In vitro studies have shown a six–fold greater corneal penetration by nepafenac compared to diclofenac.[164] Bromfenac is structurally identical to amfenac with the exception of a bromine atom at the C_4 position. This key alteration may increase bromfenac's penetration into ocular tissue, extend its duration of anti-inflammatory activity, and enhance its inhibitory effect on COX-2. In a comparative

study, after a single dose 0.1% nepafenac reached peak aqueous concentration in 30 minutes, compared to 60 minutes and 240 minutes for 0.4% ketorolac and 0.09% bromfenac, respectively.[334] Peak aqueous concentration of nepafenac and its active product amfenac was 205.3 ng/mL and 70.1 ng/mL, respectively, and the peak concentration of ketorolac and bromfenac was 57.5 ng/mL and 25.9 ng/mL, respectively. In contrast, another study demonstrated significantly higher mean aqueous concentration of 0.4% ketorolac (1,079 ng/mL) versus 0.1% nepafenac (353.4 ng/mL amfenac) after a total of 12 doses over 2 days.[47] Differences in dosing regimens may account for these conflicting results.

Although topical administration of NSAIDs provides aqueous humor levels adequate to suppress prostaglandin synthesis in the iris/ciliary body, their ability to suppress prostaglandin synthesis in the retina/choroid is less certain. In animal models, ketorolac 0.5% could not be detected in the vitreous after topical administration and 2% indomethacin and 0.1% diclofenac appeared to produce minimal inhibition of prostaglandin synthesis in the retina/choroid.[115,124,250] However, both newer NSAIDs, 0.1% nepafenac and 0.09% bromfenac, can be detected in the rabbit retina after topical administration, and in one study nepafenac inhibited 55% of retinal prostaglandin synthesis.[27,115] These studies, however, were performed using white New Zealand rabbits which lack pigment, blink infrequently, and have an unusually unstable blood–aqueous barrier, and therefore these results should be extrapolated with caution. Studies reporting reduction of retinal edema in rabbit models with topical nepafenac are also difficult to interpret because of the absence of a macula in rabbits.[161]

Other routes of delivery of NSAIDs have been investigated for posterior segment disease. In an animal model of experimental uveitis, periocular injection of ketorolac produced higher concentrations in the vitreous than either topical or systemic administration.[250] Similarly, periocular injection of celecoxib resulted in a 54–fold higher concentration in the retina than systemic administration and effectively reduced PGE_2 secretion, VEGF production, and blood–retinal barrier leakage in an animal model of diabetes.[17,26] Recent studies have also demonstrated the safety of intravitreal injections of both diclofenac and ketorolac.[171,204,279] In an animal model of endotoxin-induced uveitis, intravitreal injection of 3 mg ketorolac and 0.3 mg diclofenac significantly reduced aqueous leukocyte concentration and PGE_2 synthesis and achieved a peak vitreous concentration of 234 μg/mL and 73 μg/mL and retina/choroid concentration of 201μg/g and 4.1 μg/g, respectively.[B]

V. Pharmacodynamics

All NSAIDs inhibit COX enzymes and thereby the formation of excessive endogenous PGs including PGE_2, PGD_2, $PGF_{2\alpha}$, and PGI_2 (Fig. 1). These endogenous PGs act on iris smooth muscle to cause miosis, promote vasodilation, disrupt the blood–ocular barrier, increase leukocyte migration, stimulate pain, facilitate allergic responses, and regulate intraocular pressure (IOP).[91,92,94,217,232,331]

Some hypothesize that PGE_2 raises IOP by vasodilatation and increased permeability of the blood–aqueous barrier. In contrast, commercially available $PGF_{2\alpha}$ derivatives are thought to lower IOP by enhancing uveoscleral outflow. This appears to be the mechanism underlying their effectiveness in the treatment of glaucoma.[307] Fortunately, the non–selective inhibition of endogenous PG production appears to have no net effect on IOP.[308] In fact, NSAIDs may potentiate the hypotensive effect of PG analogs.[58,59] This lack of IOP elevation associated with topical NSAID administration is in contrast to corticosteroids, offering a distinct therapeutic advantage.[21]

NSAIDs do not inhibit lipoxygenase (LPO) and thus do not typically prevent generation of leukotrienes. This may explain in part their decreased anti-inflammatory effects compared to corticosteroids, which inhibit both LPO and COX. However celecoxib and diclofenac are notable exceptions and inhibit LPO by direct and indirect means, respectively.[181,184,201] In addition, NSAIDs appear to have anti-inflammatory and anti–angiogenic effects independent of their inhibition of COX.[18,92,125]

Several reports suggest that ketorolac is the most potent inhibitor of COX–1, while both bromfenac and amfenac have staked the claim as being the most potent inhibitor of COX-2.[12,115,259,334,337] Bromfenac is reported to be a 3 to 18 times more potent inhibitor of COX-2 than diclofenac, amfenac, and ketorolac.[12,337] Another study found that amfenac was the most potent inhibitor of COX-2.[334] COX-2 is an inducible enzyme and is thought to be primarily responsible for inflammation, and therefore the anti-inflammatory actions of NSAIDs are presumed to relate to their ability to inhibit this isoform. This relationship has not been consistently demonstrated in clinical trials, and the possibility exists that COX–1 also plays an important role in inflammation and, in the presence of substrate, may readily convert arachidonic acids into prostaglandins. Thus, the clinical importance of selective COX–1 and COX-2 inhibition for ocular disease remains to be established.

VI. Prevention of Surgically Induced Miosis

Suprofen 1% and flurbiprofen 0.03% were the first NSAIDs approved by the FDA for intraoperative

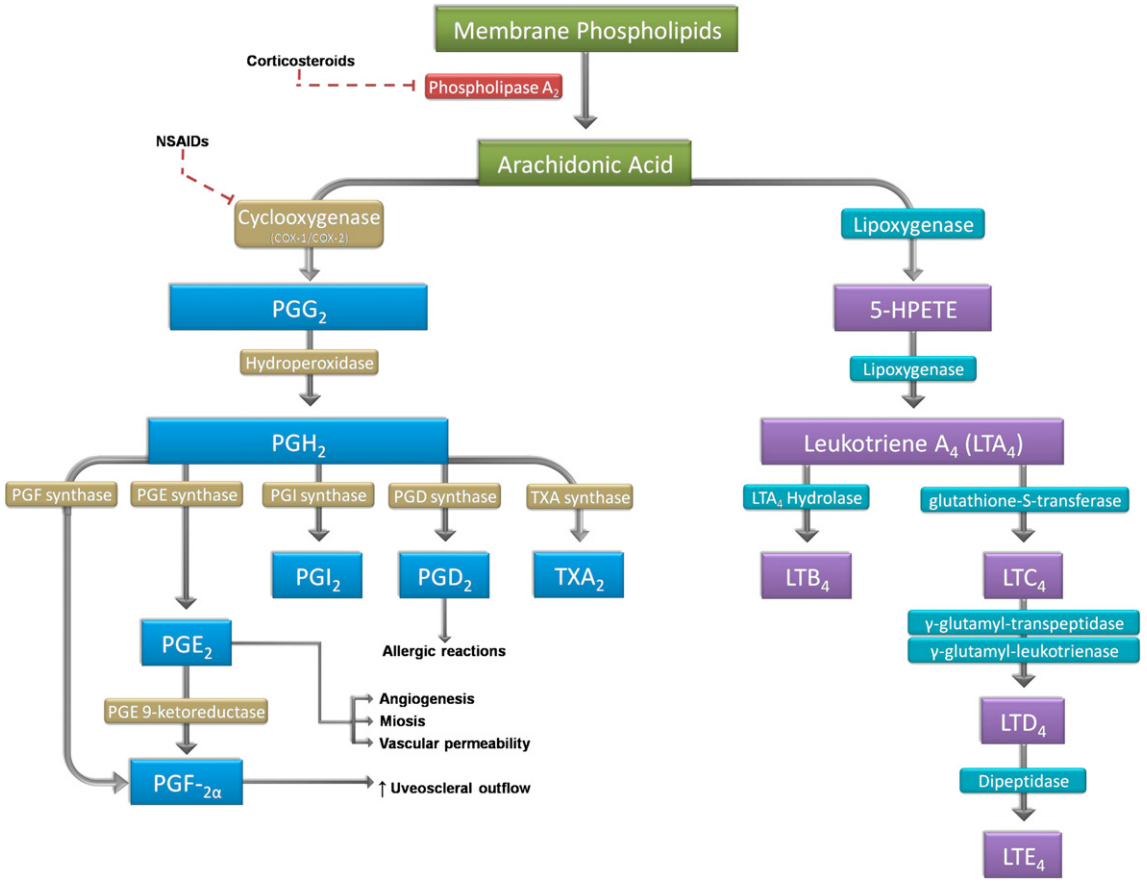

Fig. 1. Two pathways (cyclooxygenase and lipoxygenase) of eicosanoid biosynthesis from membrane bound arachidonic acid.

use to prevent miosis during cataract surgery.[91,92,94] Several clinical studies have subsequently demonstrated similar mydriatic properties for both 0.1% diclofenac and 0.4% and 0.5% ketorolac.[73,260,295,316] At least one study suggests that ketorolac tromethamine 0.5% may provide more stable mydriasis than diclofenac sodium 0.1%.[300] While the mydriatic effect of NSAIDs is most likely a class effect,[244] and this effect has been recently reported for bromfenac,[239] thus far no published studies have evaluated nepafenac.

Although topical NSAIDs are FDA–approved for inhibition of intraoperative miosis during cataract surgery, their benefit for the prevention of miosis during vitreoretinal surgery is less clear. Two studies observed no benefit on pupil stability with topical 0.03% flurbiprofen.[291,329] Similarly, in a recent randomized, doubled–masked, placebo-controlled trial, topical 0.4% ketorolac did not prevent miosis during vitrectomy.[174] However, two other studies found a mydriatic effect with topical 0.1% diclofenac.[185,215] The effectiveness of topical NSAIDs on pupil size appears to vary from one study to another,[92,94] and differences in study design, surgical technique, and outcome measurements may explain these inconsistencies.

VII. Postoperative Inflammation

A. CATARACT SURGERY

There is good evidence that topical NSAIDs reduce postoperative inflammation after cataract surgery.[90–92,94,268,274] Randomized, prospective, double-masked, placebo, and active drug–controlled clinical studies with adequate numbers of patients have shown that topically applied 1% indomethacin, 0.03% flurbiprofen, 0.4% and 0.5% ketorolac, 0.1% diclofenac, 0.1% nepafenac, and 0.09% bromfenac all decrease postoperative inflammation after cataract surgery without significant toxicity when used appropriately.[5,37,47,70,72,73,76,80,100,102,103,134,140,163,164,176,182,190,191,216,238,287,293,296,312,345] Only four of these drugs are FDA–approved for this use. Studies reviewed by the FDA during the approval process for diclofenac, ketorolac, nepafenac, and bromfenac are summarized in Table 2. At least two well–designed studies suggest treatment with topical NSAIDs also have a measurable beneficial effect upon visual acuity following cataract and retinal surgery.[73,174] Although studies directly comparing NSAIDs to corticosteroids have not consistently observed differences in reduction of intraocular inflammation after cataract surgery,[80,102,216,261,287] NSAIDs appear

TABLE 2

The Effects of NSAIDs on Postoperative Inflammation: Randomized, Double-masked, Phacebo-controlled Studies

Authors (# Eyes)	NSAID	Surgery (# Surgeons)	Drug Dosage	Results						Comments
				Cells	Flare	Ciliary Flush	Conjunctival Vasodilation	Lid Edema	Fluoro-photometry	
Solomon et al[293] (104)	0.05% ketorolac tromethamine solution	PE IOL (7)	1 gt q.i.d. beginning 1 day after surgery	p = 0.01	p = 0.001	p = 0.01	p = 0.01	N.D.	N.D.	Moderate or greater inflammation to enter study.
Heier et al[134] (103)	0.05% ketorolac tromethamine solution	PE IOL (6)	1 gt q.i.d. beginning 1 day after surgery	p = 0.05	p = 0.01	p = 0.005	p = 0.001	N.D.	N.D.	Moderate or greater inflammation to enter study. Tearing, photophobia, & pain P = 0.005, 0.001, 0.05
Flach et al[100] (100)	0.05% ketorolac tromethamine solution	ECCE (1)	1 gt t.i.d. beginning 1 day before surgery	p = 0.043	N.D.	p < 0.001	p < 0.001	p < 0.001	p < 0.001	No corticosteroids (paired comparison study)
Flach et al[103] (129)	0.05% ketorolac tromethamine solution	ECCE IOL (8)	1 gt t.i.d. beginning 1 day before surgery	p = 0.07[a]	N.D.	p = 0.002[a]	p = 0.06[a]	p = 0.001[a]	p = 0.02[a]	Need for steroids in placebo control greater than drug treatment group p < 0.001
Lane et al[190] (476)	0.1% nepafenac suspension	PE IOL (21)	1 gt t.i.d. beginning 1 day before surgery	p = 0.0001	p = 0.0001	N.D.	N.D.	N.D.	N.D.	Nepafenac group had higher cure rate (no flare, < 5 cells, p = 0.0001, also pain free 0.0001
Donnerfeld et al[72] (527)	0.09% bromfenac solution	PE ECCE IOL (39)	1 gt b.i.d. beginning 1 day after surgery	SOIS[b] = p = 0.0001	p = 0.0001	N.D.	N.D.	N.D.	N.D.	Time to resolution of ocular pain p = 0.0001
Kraff et al[183] (148)	0.1 diclofenac solution	PE ECCE IOL (4)	1 gt q.i.d. beginning 1 day after surgery	p = 0.001	p = 0.001	p = 0.001	p = 0.001	N.D.	N.D.	Moderate or greater inflammation to enter study

N.D. = not done; ECCE = extracapsular cataract surgery; IOL = intraocular lens; PE = phacoemulsification.
[a]Results favor drug treatment despite statistically significant greater use of corticosteroids in placebo control.
[b]SOIS = summed ocular inflammation score = cells + flare.

to be more effective at reestablishing the blood aqueous barrier as observed by flare on slit–lamp examination and quantitatively measured with ocular fluorophotometry.[91,92,94,102,140,215] Thus, there is good evidence that topical NSAIDs may be used in place of or in addition to topical corticosteroids after cataract surgery to avoid excessive inflammation and to improve visual recovery.[80,92,94,140,191,216,261,287]

Although none of the studies reviewed by the FDA used topical NSAIDs more than 24 hours before cataract surgery, well–designed studies suggest potential benefit of preoperative dosing regimens of up to 3 days.[47,73,174,295] Furthermore, several clinical studies have reported that concurrent administration of NSAIDs and corticosteroids results in additive effects.[73,93,134,174,345]

An important and frequently asked question is, Which topical NSAID is most effective in preventing excessive postoperative inflammation following cataract surgery? It is tempting simply to compare the results of studies supporting the efficacy of the newer NSAIDs, nepafenac and bromfenac, with the older studies that were used to gain FDA approval for ketorolac and diclofenac. Such retrospective comparisons may be misleading because enrollment criteria, surgical technique, surgical instruments, microscopes, phacoemulsification machines, co–existent medical treatments, indications for surgery, patient population (age, health, and coexistent problems), and even the cataract characteristics differ. Therefore, only prospective, double-masked, randomized comparisons of NSAIDs can adequately address this question. In this regard, diclofenac sodium 0.1% appears to be more effective in preventing postoperative inflammation than flurbiprofen 0.03% in a study of more than 100 patients.[70] In a well–designed study using an adequate patient population and evaluating inflammation with both slit lamp and laser cell flare meter to compare ketorolac's to diclofenac's ability to prevent excessive postoperative inflammation, both drugs were equally effective.[97] Furthermore, a subsequent comparison of these same NSAID–treated populations revealed no difference in effectiveness or complications, including CME and posterior capsular opacification, between diclofenac and ketorolac 3 years after surgery.[99] A subsequent study with fewer patients and shorter follow-up reached similar conclusions.[80] Therefore, at present, there is no evidence to suggest one topical NSAID treatment is better than another in controlling postoperative inflammation with the exception that flurbiprofen 0.03% appears less effective than other NSAIDs.

B. GLAUCOMA SURGERY

The effect of topical NSAIDs in minimizing inflammation following glaucoma procedures appears modest, and thus far the FDA has not approved any for this indication. Yet, excessive inflammation can complicate glaucoma surgery and result in serious problems.[141,212,256] Published studies suggest that topical flurbiprofen 0.03% and diclofenac 0.1% decrease inflammation and may reduce pain following laser trabeculoplasty, and to a lesser extent after cyclocryotherapy, as summarized in Table 3.[38,138,142,144,340] In addition, there is recent evidence that 0.1% indomethacin and ketorolac 0.5% may share similar therapeutic effects.[35,120,165]

C. STRABISMUS SURGERY

Corticosteroids are commonly used following strabismus surgery to minimize postoperative inflammation and scarring. In up to 35% of some populations, healthy adult eyes may exhibit elevations of IOP with corticosteroid use.[22] Following strabismus surgery up to 82% of children who were treated with topical dexamethasone showed IOP elevations.[186,240] Topical diclofenac 0.1% was superior to dexamethasone 0.1% in terms of patient comfort, conjunctival inflammation, and chemosis up to 4 weeks after strabismus surgery.[292] In addition, eyes treated with diclofenac 0.1% had less conjunctival edema and erythema after surgery than eyes treated with prednisolone sodium phosphate 1%.[19] Others have demonstrated equivalent tolerance, comfort scores, and resolution of inflammation of diclofenac 0.1% and betamethasone sodium phosphate 0.1%.[348] In summary, several prospective, randomized studies have demonstrated that topical NSAIDs are at least comparable to corticosteroids in reducing pain and inflammation in pediatric patients after strabismus surgery.[19,62,168,292]

D. VITREORETINAL SURGERY

Two recent prospective, randomized, double-masked, placebo-controlled trials have demonstrated reduction of anterior chamber cell and flare after vitrectomy by 0.4% ketorolac and 0.1% diclofenac.[174,215] The anti-inflammatory effect of ketorolac was substantial, with four times as many patients compared to placebo demonstrating no inflammation after vitrectomy.[174] Furthermore only one ketorolac eye, versus six for placebo, demonstrated severe inflammation. This same study found that severity of inflammation significantly correlated with increased retinal thickness, which in turn resulted in reduced visual improvement.

VIII. Prevention and Treatment of CME

A. CATARACT SURGERY

Cystoid macular edema as a complication of cataract surgery has been recognized for over half

TABLE 3

NSAID Effects on Inflammation Following Glaucoma Surgery

Authors (# Eyes)	Procedure	Drug Dosage	Results[a]			Comment
			Cells	Flare	Conjunctival Vasodilation	
Hotchkiss et al[142] (70)	Argon laser trabeculoplasty	0.03% flurbiprofen (5 gtt, then 1 gt q.i.d. for 7 days)	N.S.	N.S.	$p < 0.005$	Less ocular discomfort with drug treatment as compared with phacebo
Weinreb et al[340] (130)	Argon laser trabeculoplasty	0.03% flurbiprofen (6 gtt, then 1 gt every 20 min for 2 hr)	N.S.	N.S.	$p = 0.05$[b]	Fewer eyes in drug treated group had inflammation at 35 days; $p = 0.024$
Blumenthal et al[38] (80)	Argon laser trabeculoplasty	0.03% flurbiprofen (6 gtt, then 1 gt every 20 min for 2 hr)	$p < 0.005$ (day 1)	$p < 0.05$ (days 1, 7)	$p < 0.05$ (hr 3, day 1)	5 placebo-treated and 1 drug-treated had uncontrolled inflammation at 2 weeks
Hurvitz et al[144] (39)	Cyclocryotherapy	0.03% flurbiprofen (2 gtt at 3, 2, & 1 hr preop, then 1 gt q.i.d. for 7 days [c]	N.S.	$p < 0.03$ (day 52 only)	N.S.	
Herbort et al[138] (53)	Argon laser trabeculoplasty	0.1% diclofenac (1 gt preop and postop, then q.i.d. for 4 days	N.D.	$p < 0.05$ (days 1, 2, 4, 7)	N.D.	

N.D. = not done; N.S. = not different statistically.
[a]All compared to placebo.
[b]Only different at 24 hours.
[c]Compared flurbiprofen 0.03% and dexamethasone 0.1% with placebo.

a century,[116,146,255] and although there have been reviews, symposia, and seminars on CME,[6,156] only one major review has focused exclusively upon CME following cataract surgery.[104] CME remains the most common cause of vision loss after cataract surgery. Despite its significance, the pathogenesis of this syndrome, and its relationship to and its associations with CME in other diseases, is not completely understood.[104] However, clinicians and investigators have long agreed that inflammation appears to be at least part of the pathogenesis and, therefore, it was reasonable to attempt to minimize the inflammatory response with corticosteroids.[116,146] Subsequently, the idea developed that the production of prostaglandins within the anterior segment might be reduced by NSAIDs and provide therapeutic effects.[353] Unfortunately, topical preparations of NSAIDs did not exist at this time, and oral indomethacin was ineffective for the treatment of chronic CME.[351] This negative result likely reflects the fact that systemic NSAIDs provide insufficient drug levels to inhibit PG production in the anterior segment, especially when compared to topical administration.[131,196,270]

CME can be classified as angiographic (leakage detected on fluorescein angiography), clinical (biomicroscopic or angiographic leakage in combination with visual impairment), and, most recently, in terms of retinal thickening as measured by optical coherence tomography (OCT). Incidence rates of CME vary substantially throughout the literature even within these three groups.[104,172,173,210,255] In fact, the true incidence of CME following cataract is not precisely known.[104] Despite this continued uncertainty, recent studies have reported incidences following small–incision cataract surgery as high as 9–19% using fluorescein angiography and 41% as measured by OCT.[173,198,328]

It has long been recognized that the natural history of CME usually includes spontaneous resolution.[151] Therefore, reviews summarizing approaches to the prevention and treatment of CME after cataract surgery emphasize the importance of placebo–controlled, double-masked, randomized trials.[104,152,153] Although

there is no FDA–approved treatment for the prevention or treatment of CME following cataract surgery, an extensive review of the world literature, with special attention to randomized, controlled clinical trials published in 1998 that culminated in a meta–analysis concluded that prevention and treatment of CME with NSAIDs is beneficial.[264] These authors stressed the need for more studies of NSAIDs and other potential treatments, in particular corticosteroids, for which there is not a single properly designed study supporting their use in the prevention and treatment of this syndrome. Most therapeutic reviews consider prophylaxis of CME and treatment of manifest CME following cataract surgery separately because there is no proof that their pathogenesis is the same.[104,264]

B. PROPHYLACTIC TREATMENT OF CME FOLLOWING CATARACT SURGERY

The many clinical studies indicating that topically applied NSAIDs are effective in the prophylaxis of angiographic CME following cataract extraction have been summarized in detail previously.[92,94,104] The placebo-controlled investigations are summarized in Table 4.[105,183,219,297,352] However, none of these studies documented an effect for even one year following prophylactic treatment. The longest study using 1% indomethacin in sesame seed oil, a preparation no longer available, lost angiographic statistical significance between 7 and 12 months following cessation of treatment.[219] Furthermore, this is the only study that showed even a transient effect on Snellen visual acuity, which was not sustained beyond 3 months after treatment. A different randomized, double-masked, placebo-controlled trial reported that prophylactic use of 0.5% ketorolac was effective in reducing angiographic CME in aphakic patients without the use of corticosteroids.[105] Interpretation of the conclusions of all the other studies listed in Table 4 is difficult due to concurrent application of corticosteroids.[92,104] More recently, a multicenter, prospective study compared the effects of topical 0.1% diclofenac and 0.1% fluorometholone (FML) on prevention of CME in eyes undergoing modern, small–incision phacoemulsification.[218] Five weeks after surgery, angiographic CME was present in 5.7% of diclofenac–treated eyes and 54.7% of FML–treated eyes. FML has limited intraocular penetration; therefore, these results may approximate the effectiveness of diclofenac as compared to placebo. Several more recent, prospective, randomized studies have suggested the effectiveness of topical NSAIDs at preventing CME after cataract surgery.[16,92,94,345,355] A large, randomized, double-masked, placebo-controlled trial demonstrated that 0.03% flurbiprofen and 1% indomethacin were effective at preventing CME during a 6–month period after cataract surgery, but the effect was not sustained.[297] Although the meta–analysis published in 1998 concluded there is benefit from prophylactic treatment of CME following cataract surgery,[264] it remains unclear whether prophylactic treatment prevents the onset of chronic CME or in some way decreases its severity. Therefore, the long-term benefit of prophylactic treatment remains unproven, making this FDA–unapproved indication controversial.

C. TREATMENT OF CME FOLLOWING CATARACT SURGERY

CME associated with cataract surgery may be treated early (less than 6 months) or late (6 months or more) following its diagnosis. These two groups

TABLE 4

Prophylaxis of CME with Topical NSAID Treatment: Double-masked, Randomized, Placebo-controlled Studies

Authors	Drug Dosages	Examination Time	Angiographic CME[b]	Improved Vision[b]	Drug Treatment
Miyake et al[219] [a]	1 gt t.i.d for 2 weeks after surgery	1–2 months	Decreased	Yes	1% indomethacin in sesame seed oil[a]
		4–7 months	Decreased	No	
		12–18 months	Same	No	
Yannuzzi et al[352] [a]	1 gt q.i.d. for 4–6 weeks after surgery	5 weeks	Decreased	No	1% indomethacin suspension[a]
		10 weeks	Same	No	
		52 weeks	Same	No	
Kraff et al[183] [a]	1 gt q.i.d. for 9 months after surgery	2–12 months	Decreased	No	1% indomethacin suspension[a]
Flach et al[105]	1 gt q.i.d. for 19 days after surgery	1 month	Decreased	No	0.5% ketorolac solution
Soloman et al[297] [a]	1 gt q.i.d. 2 days before surgery and for 3 months after surgery	21–60 days and 120–240 days	Decreased	Yes (contrast sensitivity) No (Snellen)	0.3% flurbiprofen 1% indomethacin suspension[a]

[a]Studies included corticosteroids concurrently.
[b]NSAID treatment vs. placebo treatment.

TABLE 5

NSAID Treatment of Chronic Symptomatic CME: Randomized, Placebo-controlled Trials

Authors	Drug Dosages	Results[a]	Comments
Yannuzzi et al[351] (20 patients)	Oral indomethacin (25 mg t.i.d. for 3 wk)	No effect	Accepted cases 4 months after surgery
Burnett et al[48] (14 patients)	1% fenoprofen solution (1 gt t.i.d. for 8 wk)	No effect	On–off effect impressive in two patients
Flach et al[98] (30 patients)	0.5% ketorolac solution (1 gt t.i.d. for 2 mo)	Improved vision[b]	On–off impressive in three patients (all double-masked, randomized, placebo controlled)
Flach et al[101] (120 patients)	0.5% ketorolac solution (1 gt t.i.d. for 3 mo)	Improved vision[b]	Statistically significant improvement in vision maintained 1 month after treatment cessation (all double-masked, randomized, placebo controlled)

[a]Compared with placebo.
[b]Improved vision = two or more lines on Snellen testing.

are distinguished as *acute* and *chronic* CME.[104] The treatment of chronic CME following cataract surgery has been previously summarized and discussed.[92,94,104] Pertinent studies are summarized in Table 5.[48,98,101,351] A more recent study reported an effect from ketorolac on macular edema noted more than 24 months following cataract surgery, but the study was uncontrolled.[341] Finally in a study limited by its small number of patients and uncontrolled design, both topical ketorolac and diclofenac were equally effective at resolving chronic CME after uneventful phacoemulsification.[257] Therefore, although a meta–analysis concluded that treatment of chronic CME following cataract surgery with NSAIDs is beneficial, more controlled studies are desirable.[210,353]

Investigators have wondered if earlier treatment of CME following surgery might be more beneficial than waiting 6 months or longer. One study of the treatment of acute CME with ketorolac 0.5% showed no benefit in terms of visual improvement,[104] but another reported a significant short–term benefit.[135] This latter study also demonstrated a synergistic effect from corticosteroids and ketorolac 0.5%,[135] which has been previously discussed.[93] A more recent study of only 10 patients showed no difference between ketorolac alone and ketorolac with corticosteroids.[288]

In summary, although there is no FDA–approved therapy for the prevention and treatment of CME following cataract surgery, available evidence suggests that topical NSAIDs may prevent and treat CME when used alone or concurrently with corticosteroids. Furthermore, although not yet investigated with properly designed studies, corticosteroids, acetazolamide, and hyperbaric oxygen may all have roles in the treatment of this syndrome.[104,148,221] Finally, given the relatively low incidence of clinically significant CME, the cost–benefit of routine prophylactic use of NSAIDs in cataract surgery is a matter of ongoing debate.[170,322,345]

D. CME FOLLOWING VITREORETINAL SURGERY

Although advances in modern vitreoretinal surgery have improved visual outcomes, postoperative CME remains frequent. The reported incidence of CME following retinal detachment repair with scleral buckling ranges from 9% to 43% and may delay visual recovery.[197,211,265] Topical indomethacin may reduce the incidence of CME after scleral buckling surgery.[220] Although a more recent prospective, randomized, double-masked, placebo-controlled study, did not report a benefit with postoperative oral valdecoxib, the study was underpowered due to the low incidence of CME.[32] Furthermore, oral administration is less likely than topical administration to achieve therapeutic intraocular levels. Despite this, the study did observe a significantly reduced incidence of residual submacular fluid in the oral valdecoxib group.

Persistent angiographic CME may occur in up to 70% and 80% of eyes after vitrectomy surgery for epiretinal membrane (ERM) and macular hole, respectively.[207,301] A recent prospective study reported an incidence of post–vitrectomy CME detected on OCT of 64% one month after ERM surgery.[175] Furthermore, this same study demonstrated that postoperative inflammation was a risk factor for retinal thickening and that increased retinal thickening delayed visual recovery. Only one prospective, randomized, placebo-controlled trial to date has evaluated the effects of topical 0.4% ketorolac on retinal thickness after vitrectomy surgery. Although this study found that ketorolac reduced both center point thickness and central

subfield thickness by 9% and 8%, respectively, and reduced total macular volume by 6% as measured by OCT, this did not reach the level of statistical significance.[174]

IX. Relieving Discomfort and Pain after Ocular Surgery and Trauma

Pain often occurs after radial keratotomy (RK) and excimer laser photorefractive keratectomy (PRK). Both 0.4% and 0.5% ketorolac tromethamine and 0.1% diclofenac sodium are FDA–approved to reduce pain and photophobia after refractive surgery.[79,91,92,94,356] Several reports have shown that diclofenac and ketorolac also decrease normal corneal sensitivity and reduce pain after corneal abrasions.[92,94,160,267,276,309]

A retrospective, placebo–controlled, unmasked study of 20 patients suggested 0.1% diclofenac given as one drop four times daily reduced eye pain after PRK in humans.[79] Subsequently, a multicenter, randomized, double-masked, parallel–group study compared 0.03% flurbiprofen ophthalmic solution to vehicle in 105 patients undergoing RK.[128] Subjects received treatment before surgery and every four hours after surgery for two weeks. Significant differences in pain relief favoring flurbiprofen were present at 2, 3, and 4 hours after surgery. These early studies stimulated interest in the use of topically applied NSAIDs for ocular discomfort after refractive surgery. Presently the FDA has approved only diclofenac 0.1% and ketorolac 0.4% and 0.5%.[79,356] Although diclofenac's anesthetic effect appears to be more pronounced and longer lasting than ketorolac's, this difference does not appear to correlate with postoperative pain relief. Two recent prospective, randomized, double-masked trials have shown similar analgesic properties with 0.1% nepafenac,[49,71] however, thus far neither nepafenac nor bromfenac have been approved by the FDA for postoperative discomfort.

Although ketorolac is available as a preservative–free preparation that is as effective as the preserved preparation,[356] a significant difference in toxicity has not been proven. In addition, the original Acular Ophthalmic Solution, available as a reformulation called Acular PF (Allergan, Inc.) which contains 0.4% in place of 0.5% ketorolac, is buffered to 7.4, and has less benzalkonium chloride (0.006% in place of 0.01%), appears to produce less stinging and burning.

Topically applied NSAIDs also appear to minimize ocular discomfort following cataract and retinal surgery. Prospective, randomized studies have demonstrated that topical 0.1% diclofenac, 0.4% ketorolac, 0.1% nepafenac, and 0.09% bromfenac have this effect.[72,73,113,190,249,294] Furthermore, in vitreoretinal surgery, intravenous ketorolac significantly reduces postoperative pain and nausea[85,330] and recent prospective, randomized studies have demonstrated similar benefits with prophylactic use of topical 0.1% diclofenac and 0.4% ketorolac.[174,215] Finally, both diclofenac and ketorolac have some benefit following laser photocoagulation procedures.[82,339]

X. Allergic Conjunctivitis

Topical 0.5% ketorolac is the only NSAID that is FDA–approved for the treatment of seasonal allergic rhinoconjunctivitis.[320] Allergic conjunctivitis incorporates several diagnoses: seasonal allergic rhinoconjunctivitis, contact allergic blepharoconjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, and vernal keratoconjunctivitis.[109] Seasonal allergic rhinoconjunctivitis, the most common type of allergic conjunctivitis, is often referred to as hay fever conjunctivitis.[34] Ocular pruritus is the hallmark of allergic conjunctivitis, which may be associated with conjunctival hyperemia, chemosis, papillary hypertrophy, and giant papillae.[150]

Although the pathogenesis of allergic conjunctivitis and its subdivisions is complicated, most agree that the mast cell with its chemical mediators is an important component.[109] These mediators include autacoids such as histamine, eosinophil chemotactic factors, eosinophil granule major basic protein, platelet activating factor, and many different PGs. Among the PGs isolated from ocular tissue are PGE_1, PGE_2, $PGF_{2\alpha}$, and PGD_2. Although PGD_2 is most likely the primary PG produced by the mast cell during type I hypersensitivity reactions,[193] both PGE_1 and PGE_2 lower the threshold of human skin to histamine-induced itching[123] and $PGF_{2\alpha}$ is present in tears from patients suffering from vernal conjunctivitis.[69]

Ketorolac tromethamine 0.5% ophthalmic solution is approved for the relief of ocular itching in patients with seasonal allergic rhinoconjunctivitis. Two multicenter studies verify the efficacy of this treatment.[28,320] One double-masked, placebo-controlled study of 148 patients evaluated treatment given four times daily over a 7–day period and showed that ketorolac was significantly better than placebo in regards to ocular itching, conjunctival inflammation, conjunctival injection, swollen eyes, foreign–body sensation, and ocular discharge.[28] A second study of 93 subjects with similar design, but lacking slit–lamp observations, reported ketorolac was significantly more beneficial than placebo in reducing conjunctival inflammation and photophobia after 7 days of treatment.[320] Although no other

topical NSAID has been approved for allergic conjunctivitis, there are studies suggesting that 0.1% diclofenac and 0.09% bromfenac may also be effective.[187,213,222,314]

The mast cell has also been associated with vernal keratoconjunctivitis, and PGD_2 is a major PG produced by this cell.[194] This autacoid can cause redness, chemosis, mucous discharge, and eosinophil chemotaxis in the eye. In addition, tears from patients with vernal keratoconjunctivitis also contain $PGF_{2\alpha}$.[69] Aspirin therapy has been reported to be effective for treating vernal keratoconjunctivitis, and studies have reported that indomethacin 1%, ketorolac 0.5%, diclofenac 0.1%, and bromfenac 0.09% are all effective in treating vernal keratoconjunctivitis.[8,64,127,278,326]

Giant papillary conjunctivitis is an allergic reaction to contact lenses, ocular prostheses, or sutures.[15] Suprofen 1% ophthalmic solution used four times daily for 28 days was more effective than placebo in a multi–center, double-masked study of 80 patients.[347] Both physicians and patients favored the response to suprofen as compared to placebo, and the investigators concluded that NSAID treatment may be useful in contact lens-associated giant papillary conjunctivitis.

There is evidence that both systemic flurbiprofen and topical 0.03% flurbiprofen are beneficial for signs and symptoms of hay fever.[42–44] Systemic flurbiprofen proved almost as effective in reducing signs and symptoms as orally administered chlorpheniramine.[43] In a different study, oral flurbiprofen provided additional benefit to patients using oral antihistamines.[42] Finally, topical flurbiprofen's usefulness in allergic disease has been demonstrated in animal models.[9,169] Despite these observations, no prospective, randomized studies have evaluated the role of flurbiprofen in the treatment of allergic eye disease.

XI. Uveitis and Other Inflammatory Ocular Diseases

A. UVEITIS

Although topical NSAIDs are effective in reducing postoperative inflammation, there are few clinical studies evaluating their role in uveitis and other inflammatory diseases of the eye. Two prospective, randomized studies involving patients with acute, nongranulomatous uveitis found higher cure rates among patients treated with 0.5% prednisolone disodium phosphate and 0.1% betamethasone disodium phosphate (both weaker corticosteroid preparations than 1% prednisolone acetate) versus a non–commercially available NSAID preparation, 5% tolmetin sodium dihydrate.[75,357] At present, NSAIDs are not indicated for primary treatment of anterior uveitis in view of the greater experience with and efficacy of corticosteroids and despite the fact that NSAIDs do not cause cataracts or increase intraocular pressure. Corticosteroid side effects may be decreased by using alternative, less potent corticosteroids such as rimexolone 1% (Vexol, Alcon Laboratories, Inc.).[36]

Finally, there are anecdotal reports that oral NSAIDs may have a favorable effect on chronic childhood anterior uveitis associated with juvenile idiopathic arthritis.[242]

B. ORBITAL PSEUDOTUMOR

Orbital pseudotumor or idiopathic orbital inflammation is a disorder of unclear etiology that consists of infiltration of the orbit with mixed inflammatory cells and fibrosis.[223] It is the third most common orbital disease after thyroid eye disease and lymphoproliferative disorders.[358] Systemic NSAIDs have been used to treat orbital inflammatory disease since the 1970s,[159] and there is one case report of orbital myositis treated with oral indomethacin.[233] There are also anecdotal reports of rapid resolution of pain and orbital swelling after administration of intravenous ketorolac. Although no randomized trials using systemic NSAIDs have been conducted, their use in patients with contraindications to corticosteroids seems reasonable. There are no data to suggest that topical NSAIDs would be of benefit.

C. EPISCLERITIS AND SCLERITIS

Episcleritis is a benign, painless, self–limited inflammation of the highly vascular tissue lying deep to Tenon's capsule and superficial to the sclera.[14,149,241] Although often requiring no therapy, it may respond to topical medications, including NSAIDs.[325,338] Whereas topical corticosteroids are frequently helpful in relieving this superficial inflammation, topical NSAIDs appear to be less effective. Systemic NSAIDs are of value in those unusual cases where topical treatments are ineffective.[149,199,343]

Scleritis is a severe granulomatous inflammation of the scleral coat of the eye that is associated with systemic disease in roughly 50% of cases.[14,149,241] Although topical NSAIDs are not effective, systemic NSAIDs are used as first line agents. An overall response rate of 30–92% has been reported with diffuse and nodular anterior scleritis.[149,266] Although many NSAIDs may be effective, indomethacin at 25–50 mg three times daily is most commonly used. Side effects include gastric upset that may require concurrent use of a H_2–blocker or proton pump inhibitor.[149,263] A recent report indicated that the COX-2

selective NSAID celecoxib at daily doses ranging from 200–800 mg was effective in controlling diffuse anterior scleritis in 92% of patients without producing any gastrointestinal side effects.[30]

D. INFLAMED PINQUECULA AND PTERYGIA

Pinquecula and pterygia are considered manifestations of chronic ocular irritation by solar radiation, repeated micro trauma, and other factors.[154] Many patients complain of chronic ocular discomfort, foreign–body sensation, pain tearing, itching, and redness, signs and symptoms that are commonly treated with lubricants, vasoconstrictors, or corticosteroids. There is also evidence that NSAIDs are useful in the treatment of inflamed pinquecula and pterygia.[112] Topical indomethacin provided "dramatic relief" of signs and symptoms during 14 days of treatment compared to placebo. More recently, a randomized, prospective, double-masked study compared 0.1% topical indomethacin to 0.1% dexamethasone phosphate in 50 patients with pinqueculae or pterygia.[111] Both treatments significantly decreased signs and symptoms, but by day 30 outcome measures favored indomethacin over dexamethasone.

E. VIRAL CONJUNCTIVITIS

In hospitalized patients with severe measles conjunctivitis, a randomized study compared topical ketorolac 0.5% and indomethacin 0.1% to artificial tears.[321] Ketorolac and indomethacin were more effective in decreasing conjunctival hyperemia, but burning, foreign–body sensations, and photophobia were unaffected. In a different randomized study of 117 patients, topical ketorolac 0.5% used four times daily was no better than artificial tears in relieving signs (conjunctival injection, chemosis, mucus, and lid edema) and symptoms (itching, foreign body sensation, tearing, redness, lid swelling, and overall discomfort) of viral conjunctivitis.[283]

In a rabbit ocular model to evaluate antiviral activity, neither 0.5% ketorolac nor 0.1% diclofenac demonstrated inhibitory activity on viral replication or the formation of subepithelial immune infiltrates.[122] In contrast, 1% prednisolone acetate prolonged viral shedding.

In conclusion, there is limited current evidence to support the use of topical NSAIDs in viral conjunctivitis.

F. OCULAR INFLAMMATION IN DRY EYE PATIENTS

Although the cause of dry eye is multifactorial, inflammation is believed to play a prominent role. Consequently, topical corticosteroids and NSAIDs have been considered as an alternative to conventional tear replacement and preservation strategies in dry eye patients.[24,51] However, corneal perforations and melts have been reported.[247,251] Therefore the routine use of topical NSAIDs in dry eye patients may increase the risk of these adverse events.

XII. Retinal and Choroidal Disease

A. DIABETIC RETINOPATHY

There is growing evidence that immunologic mechanisms play a prominent role in the pathogenesis of diabetic retinopathy (DR).[10] Both animal and human studies have demonstrated elevated levels of prostaglandins in eyes with DR[155,189,228,229,342] and treatment with NSAIDs in animal models prevents or delays its progression.[25,158,166,167]

Rheumatoid arthritis patients taking salicylates had a reduced incidence of DR.[248] This observation was later examined in two clinical trials, the Early Treatment Diabetic Retinopathy Study (ETDRS), which examined the effect of 650 mg aspirin on advanced DR, and the Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) Study, which tested the impact of 990 mg aspirin in patients with early DR.[3,4] Although no benefit was found in patients with more advanced DR in ETDRS, a significant effect was seen in the DAMAD study, where higher doses of aspirin were found to slow the development of retinal microaneurysms. This latter observation is supported by a recent prospective, randomized study where treatment with the NSAID sulindac prevented development and progression of DR.[133]

Therapeutic inhibition of COX-2 in the retina may now be achievable with topical 0.1% nepafenac and 0.09% bromfenac.[27,55,115] In an animal study topical 0.1% nepafenac inhibited diabetes-induced retinal microvascular disease.[167] Other routes, including periocular and intravitreal, are currently being investigated that may allow greater therapeutic effects.[17,171] However, awaiting further studies, there is insufficient evidence to recommend using NSAIDs as prophylaxis for, or as primary treatment of, diabetic retinopathy.

Diabetic macular edema (DME), the most common cause of visual impairment in diabetics, affects approximately 75,000 new patients in the United States every year.[33] The pathogenesis of DME is complex and multifactorial, but ultimately is the result of disruption of the blood–retinal barrier, an influx of fluid that exceeds the pump capacity of the retinal pigment epithelium, and subsequent accumulation within the macula. Inflammatory mediators such as intercellular adhesion molecule–1, interleukin–6, VEGF, monocyte chemotactic protein–1, and pigment epithelium–derived factor are

associated with retinal vascular permeability and elevated in eyes with DME.[114] While prospective, randomized studies have demonstrated the efficacy of intravitreal triamcinolone acetonide in reducing DME and improving visual acuity,[2,118] only anecdotal or uncontrolled retrospective case studies have reported benefit with NSAIDs.[132] Therefore, there is insufficient evidence to recommend using NSAIDs to treat DME.

B. AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is a leading cause of blindness for individuals aged 55 and over.[179] While the etiology and pathogenesis of AMD are complex and remain poorly understood, there is considerable evidence from human and animal studies that inflammatory and immunological events play a central role.[245] In particular, a host of recent genetic analysis in human AMD patients support the role of complement factor H in the pathogenesis of up to 50% of cases of AMD.[78,129,180,315] The complement system is a component of the innate immune system and comprises over 30 soluble and membrane–bound proteins that initiate pro–inflammatory responses.[332,333] Studies in animal models of laser-induced CNV demonstrate that CNV complexes accumulate C3 and the C5b–9 membrane attack complex and that these complement components are capable of up–regulating VEGF.[40,234] Similarly, in Alzheimer disease complement proteins are present in the neurofibrillary tangles and neuritic plaques that characterize this disorder,[354] and epidemiological studies indicate that NSAIDs reduce the age-related prevalence of this disease.[208] The risk of developing Alzheimer disease was reduced by about one–third for those patients using NSAIDs 2 years or less and by 60% for those with more than 2 years of use.[145,305]

A prospectively followed cohort of patients with rheumatoid arthritis had a very low prevalence of AMD, and it was hypothesized that long term anti-inflammatory treatment may have been responsible.[209] In one large retrospective study, patients taking aspirin were significantly less likely to develop neovascular AMD, but this observation has not been confirmed.[178,344]

Considerable evidence indicates, however, that COX-2 is a promoter of angiogenesis and can be detected in human choroidal neovascular membranes.[25,74,203,224,277,310] Furthermore, inhibition of COX-2 by NSAIDs reduces VEGF production and directly inhibits CNV in both trauma-induced and ischemic-induced animal models.[17,25,143,310,311] With the recent availability of newer topical NSAIDs with potentially greater retinal penetration and more potent COX-2 inhibition, a therapeutic effect may now be adequately tested. However, at present, there is insufficient evidence to recommend using NSAIDs for prophylaxis or treatment of AMD.

C. OCULAR TUMORS

Use of systemic NSAIDs reduces the incidence of colon cancer by 40–50%, and several epidemiological, clinical, and experimental studies have established NSAIDs as promising cancer chemopreventative agents.[126,253,290,318] COX-2 expression is increased in both uveal melanoma and retinoblastoma.[61,87,110,162,298] Experimental studies have shown that nepafenac (amfenac) inhibits proliferation of human retinoblastoma cell lines, reduces progression of uveal melanoma, and increases its radiosensitivity.[67,86,205] In addition, COX-2 expression appears to correlate with tumor malignancy. Enucleated eyes with retinoblastoma demonstrated high expression of COX-2, particularly in areas of tumor invasion.[298] Similarly, in 32 enucleated eyes with uveal melanoma, the degree of expression of COX-2 was found to correlate with the risk of death from metastases.[61] Future studies investigating the therapeutic potential of NSAIDs in treatment and prevention of ocular tumors are indicated.

XIII. Toxicity of NSAIDs

One in seven Americans receives a prescription for orally administered NSAIDs each year.[45] Many more use over–the–counter NSAIDs. The widespread use of NSAIDs has meant that the adverse events of these relatively safe drugs have become increasingly prevalent.

A. TOXICITY WITH SYSTEMIC NSAIDs

The most well known side effects accompanying systemic NSAID use relate to the GI and central nervous systems (CNS). The CNS adverse drug reactions (ADRs) commonly responsible for patient intolerance to oral NSAIDs include headache, somnolence, dizziness, depression, fatigue, anxiety, confusion, insomnia, and psychotic episodes. GI toxicity includes nausea, anorexia, vomiting, dyspepsia, diarrhea, constipation, and peptic ulceration and bleeding. Often the GI toxicity can be partially ameliorated by adding a H_2–receptor antagonist; proton pump inhibitor, or prostaglandin analogue; [20] however, many patients will require discontinuation of the medication. Although it was hoped that COX-2 selective NSAIDs would reduce gastrointestinal adverse events,[39] evidence of cardiovascular side effects, including an increased risk of myocardial infarction

and stroke, have resulted in the withdrawal of both rofecoxib and valdecoxib and heightened concerns about the remaining COX-2 NSAID celecoxib.[29,235]

NSAIDs are also associated with a risk of renal ADRs including acute renal failure, salt and water retention, hypertension, hyperkalemia, papillary necrosis and interstitial nephritis, nephrotic syndrome, and acute tubular necrosis. Prostaglandins cause vasodilation of afferent glomerular arterioles and, under normal conditions, help regulate glomerular perfusion and filtration. Inhibition of renal prostaglandins may lead to renal impairment, especially when used in combination with angiotensin–converting enzyme inhibitors and diuretics.[317]

Other NSAID-induced ADRs include hematologic toxicity (aplastic anemia, red–cell aplasia, hemolytic anemia, thrombocytopenia, and prolonged bleeding time), hepatic toxicity (abnormal liver function tests, Reye syndrome, and hepatitis), dermatologic reactions (bullous eruptions, benign morbilliform eruptions, photosensitivity, fixed drug eruptions, urticaria, pustular psoriasis, exfoliative dermatitis, and erythema multiforme, including Stevens–Johnson syndrome), metabolic changes (fluid retention, edema, weight gain), and hypersensitivity responses including rashes, bronchospasm, and anaphylactoid reactions. NSAIDs are not recommended during pregnancy because they can cause premature closure of the fetal ductus arteriosus and renal ADRs in the fetus.[45,53,137,206,237,286,302] Thus, the systemic side effects that can accompany systemic NSAID treatment include life–threatening reactions. These complications, including potential drug interactions, must be considered in determining the risk–benefit relationship for an individual patient.

Systemic absorption can occur following topical application of any NSAID. There is a report of a patient with chronic asthma, rhinosinusitis, and nasal polyps where topical ketorolac exacerbated her asthma, necessitating hospital admission.[289] The authors concluded that NSAID eye drops are contraindicated in patients with the combination of asthma and nasal polyps unless the patient is known to tolerate aspirin.

Flurbiprofen can inhibit platelet aggregation by inhibiting thromboxane synthesis, but it does not change bleeding time, prothrombin time, platelet adhesiveness, or platelet count.[66] Furthermore, in one animal study, prolonged topical use of ketorolac did not produce gastrointestinal ulceration.[202] Although no properly designed study has shown that the use of topical NSAIDs before or following ocular surgery increases the bleeding tendencies of ocular tissues, all NSAIDs package inserts include a caution describing this possibility.

Bromfenac's oral formulation was withdrawn after post–market surveillance indicated an increased risk of hepatic toxicity.[121] A recent prospective, randomized, placebo-controlled trial observed no adverse events or changes in liver chemistries in a large number of patients treated twice–daily for 14 days with topical bromfenac.[303] The off–label use of topical NSAIDs for durations longer than this is common and clinicians should be vigilant for potential systemic toxicity. In addition, because eyelid closure and nasolacrimal occlusion can decrease systemic absorption of topically applied medications by almost 70%,[108,359] explaining these techniques to all patients seems prudent.[89]

B. TOXICITY WITH TOPICALLY APPLIED NSAIDs

Transient burning, stinging, and conjunctival hyperemia are common ocular side effects after the topical instillation of NSAIDs,[92] and differences exist in the discomfort produced by the various commercially available formulations.[200] Properly controlled, prospective, double-masked clinical studies have failed to demonstrate significant differences in patient acceptance, however.[97] As with all commercially available eye drops, allergic and hypersensitivity reactions occur with topical NSAIDs.[92] In addition, superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported.[119,280,282] Although one prospective, randomized, double-masked trial observed increased corneal haze and delayed wound healing after surface ablation in eyes treated with topical 0.1% nepafenac,[323] this has not been confirmed.[49,71,77] At present, there is no evidence that one NSAID is less toxic than another.

Postcataract surgery atonic mydriasis has been reported in some patients receiving topical NSAIDs prior to surgery.[C] This potential adverse event is mentioned in the package insert of flurbiprofen and suprofen. Apparently, the NSAID-induced mydriasis that is helpful during cataract extraction and lens insertion may be resistant to reversal from parasympathomimetics such as acetylcholine and carbachol. The pharmacodynamics of this are poorly understood, but atonic mydriasis may also occur without NSAID use following uncomplicated cataract surgery.[188]

Severe corneal toxicity has been reported with 0.1% diclofenac, 0.5% ketorolac, 0.1% nepafenac, and 0.09% bromfenac.[23,31,57,95,147,195,346] Although uncommon, these dramatic events are frequently referred to as corneal melts. It is helpful to review the history leading to their original recognition.

Severe corneal complications, including corneal melting, in some patients using topical NSAIDs were reported by members of the American Society of

Cataract and Refractive Surgery during 1999.[D,E] Because of these reports, Falcon, a generic form of diclofenac ophthalmic solution (Alcon Laboratories, Inc.), was recalled.[F] Although some concluded that the generic form of diclofenac was responsible,[G] others emphasized the importance of reviewing all reported cases with careful attention to possible confounding variables before concluding that drug toxicity alone accounted for these adverse events.[57,88,95]

An analysis of 140 patients with corneal toxicity associated with the use of topical NSAIDs[57] included many cases of mild, transient keratitis, and all 34 cases of severe corneal toxicity. The authors concluded that multiple factors could have influenced development of corneal toxicity, and the strengths and weaknesses of this report have been reviewed.[95]

A comprehensive review of the medical records and histories of 11 cases of corneal melts thought related to topical NSAIDs (paying special attention to the indications for NSAIDs, doses and duration of treatment, and onset and extent of corneal toxicity) was analyzed. Briefly, seven of these patients received generic diclofenac, and four received brand name diclofenac. Duration of treatment varied from 6 days to 17 months. Associated ocular and systemic diseases and their treatments complicated the analysis. The specific indication for topical NSAID was often unclear or inappropriate. Inconsistent and variable dose–toxicity relationships suggest that factors other than simple NSAID toxicity, including concurrent corticosteroid use, may be contributory. This report underscores the importance of making a sound clinical diagnosis before beginning NSAIDs and the need to follow patients appropriately.[95] The over two dozen cases of corneal perforations reported with the introduction of topical corticosteroids over 30 years ago were likely related to improper clinical use and patient follow-up.[319] Thus, many topical medications have the potential for toxicity if unmonitored or used inappropriately.

In conclusion, despite proposed theories to explain their pathogenesis,[236] a definite link between NSAID use and corneal melt remains tenuous. Application of topical NSAIDs for reasonable lengths of time in appropriate patients with proper monitoring appears safe. There is, however, evidence of the continued misuse of these medications.[96,258]

C. NSAIDs AND CORTICOSTEROIDS: RELATIVE TOXICITY

Many clinicians believe that topical NSAIDs should be substituted for topical corticosteroids in the treatment of postoperative inflammation following cataract surgery and in some ocular allergies to minimize side effects. Topical corticosteroids have been associated with elevations of IOP, the formation of posterior subcapsular cataracts, slow wound healing, and precipitation or worsening of ocular infections.[46,231,252,262,275,299,304,327,349] Even the newer, less potent corticosteroids may elevate IOP.[1,83,84,192] It remains to be seen whether the newer corticosteroid delivery systems will overcome some of these toxicities.[52,313]

Corticosteroids have been compared to topical NSAIDs in an effort to establish their relative toxicities. Topical flurbiprofen had less effect on elevating IOP compared with topical dexamethasone in one study of steroid–responsive patients.[117] In a different study, IOPs did not differ in two groups of 46 patients given placebo or diclofenac 0.1% pre– and postoperatively.[308] However, one report describes a small, but statistically significant, increase in IOP in eyes receiving both topical corticosteroids and indomethacin compared with corticosteroids and placebo.[271] One study using rabbits demonstrated that topical flurbiprofen had undesirable effects on corneal wound healing.[214] This study compared the effects of equipotent anti-inflammatory doses of topical flurbiprofen and prednisolone acetate four times a day for ten postoperative days on healing (as measured by the wound bursting pressure) of 4–mm incisions. The results suggested that flurbiprofen and prednisolone might not be different in their effects on wound healing. In a different rabbit study, diclofenac 0.1%, prednisolone 1%, and flurbiprofen 0.03% delayed wound healing compared with placebo.[139] However, there are no studies demonstrating that topically applied NSAIDs interfere with wound healing after contemporary cataract surgery.[281] Finally, although animal studies suggest that NSAIDs do not worsen viral infections,[106,107,136] flurbiprofen and suprofen ophthalmic solutions are FDA–labeled as being contraindicated in epithelial *Herpes simplex* keratitis.[H,I]

Although NSAIDs are not known to cause cataracts, it required long-term and widespread clinical use of corticosteroids before their cataractogenic properties were first recognized. Some studies have even observed a protective effect on development of nuclear cataracts with use of NSAIDs.[7,177]

In summary, although the literature describes less toxicity with topical NSAIDs than with corticosteroids, NSAIDs have been used far less extensively. Moreover, the selective inhibition of cyclooxygenase might stimulate lipoxygenase and consequently increase formation of leukotrienes.[227,243,269,306] At least one laboratory study suggests that NSAIDs may enhance the granulomatous process by this mechanism.[254] A different laboratory study concluded

that inhibition of the cyclooxygenase pathway by NSAIDs might be detrimental in *Pseudomonas* keratitis because corneal ulceration seemed to be accelerated by flurbiprofen,[225] while inhibition of lipoxygenase might be beneficial. It seems only prudent, therefore, as with any relatively new drug treatment, that attentive monitoring of eyes exposed to topical NSAIDs be continued.

XIV. Conclusions

Systemic and topical NSAIDs have proven effective in treating many inflammatory ocular disorders. With our growing understanding of pathogenesis, including the contribution of prostaglandins in eye disease, the clinical indications for NSAIDs, both systemic and topically applied, may continue to expand. In addition, newer topical formulations with increased potency and different pharmacokinetics may allow important therapeutic advances. Finally, other routes of NSAID delivery may be necessary to achieve their optimal therapeutic effects with minimal toxicity.

XV. Method of Literature Search

A PubMed literature search was performed for all years through March 2009 using the following search terms: *nonsteroidal anti-inflammatory drugs, NSAIDs, cyclooxygenase, COX II, prostaglandins, cystoid macular edema, ketorolac, diclofenac, nepafenac,* and *bromfenac.* Relevant articles were retrieved and analyzed. English abstracts were used for non–English articles. Cross–referencing was employed and reference lists from selected articles were used to identify additional pertinent articles. In addition, Dr. Flach referred to an extensive personal comprehensive file consisting of copies of all the pharmacological articles relating to nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, prostaglandins, cystoid macular edema, and each individual NSAID preparation published and copied from *Archives of Ophthalmology, American Journal of Ophthalmology, Survey of Ophthalmology, Ophthalmology, Journal of Cataract and Refractive Surgery and Investigative Ophthalmology,* and related material from other journals accumulated and, subsequently, stored during the past 30 years.

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Reprint address: Steven J Kim, MD, Vanderbilt University, Ophthalmology, 2311 Pierce Avenue, Nashville, TN 37232, United States. e-mail: skim30@gmail.com.

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