REVIEW

Critical appraisal of ophthalmic ketorolac in treatment of pain and inflammation following cataract surgery

Rahul Reddy
Stephen Jae Kim

Department of Ophthalmology, Vanderbilt University, Nashville, TN, USA

Background: The purpose of this review was to provide a critical appraisal of the literature supporting the efficacy of ophthalmic ketorolac (Acuvail®) in the treatment of pain and inflammation after cataract surgery.

Methods: Literature search and expert opinion of the authors.

Results: Recent studies indicate greater intraocular drug levels in the anterior chamber and iris-ciliary body after topical application of Acuvail in comparison with older formulations of ketorolac. A large randomized, multicenter, placebo-controlled study demonstrated significantly less inflammation and pain after cataract surgery using Acuvail.

Conclusion: Acuvail appears to be effective in reducing post-cataract surgery pain and inflammation.

Keywords: ketorolac tromethamine, Acuvail®, postsurgical, cystoid macular edema, nonsteroidal anti-inflammatory drugs

Introduction

Inflammation frequently complicates intraocular surgery and can result in pain, elevated intraocular pressure, and cystoid macular edema (CME).[1–3] CME is the most common cause of vision loss after uncomplicated cataract surgery and although its pathogenesis remains incompletely understood, inflammation is a known cause.[4] Excessive or persistent postoperative inflammation may also lead to prolonged compromise of the blood–ocular barrier and may increase the risk of chronic inflammation. Topical corticosteroids are effective for reducing and treating inflammation in the setting of cataract surgery, and have a long track record of ophthalmic use, but are limited by side effects, including elevated intraocular pressure, delayed wound healing, and increase risk of infection. Consequently, safer alternative anti-inflammatory agents to prevent and treat excessive postoperative inflammation and pain following cataract surgery would be advantageous.

Cyclo-oxygenase (COX) is an important enzyme in the inflammatory process and catalyzes the biosynthesis of prostaglandins and thromboxanes from arachidonic acid.[1] Two main isoforms, COX-1 and COX-2, have been well characterized. COX-1 is constitutively expressed in most mammalian cells, including the kidney, gastrointestinal tract, platelets, and vascular endothelium, and plays a pivotal role in normal physiological function. COX-2, on the other hand, is an inducible enzyme that is thought to be primarily responsible for inflammatory-mediated reactions.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes and thereby the synthesis of prostaglandins. While the anti-inflammatory

Correspondence: Stephen J Kim
Vanderbilt Eye Institute, 2311 Pierce Avenue, Nashville, TN 37232, USA
Tel +1 615 936 7126
Fax +1 615 936 1540
Email skim30@gmail.com

actions of corticosteroids are in part from the inhibition of phospholipase A_2 preventing the release of arachidonic acid from membrane-bound phospholipids, NSAIDs act more downstream in the cascade and directly inhibit COX-1 and COX-2 enzymes. Within the eye, it is firmly established that prostaglandins disrupt the blood–ocular barrier, increase vasodilation, facilitate leukocyte migration, and promote pain.[1] Consequently, their inhibition should have favorable effects on both intraocular inflammation and pain.

In support of this, several randomized, prospective, double-masked, and placebo-controlled studies have shown that topically applied indomethacin 1%, flurbiprofen 0.03%, ketorolac 0.4% and 0.5%, diclofenac 0.1%, nepafenac 0.1%, and bromfenac 0.09% reduce postoperative inflammation following cataract surgery.[1] Similarly, prospective randomized studies have demonstrated that diclofenac 0.1%, ketorolac 0.4%, nepafenac 0.1%, and bromfenac 0.09% reduce ocular discomfort after cataract surgery.[1]

Of all the commercially available ophthalmic NSAIDs, ketorolac tromethamine (ketorolac) possesses the greatest number of studies supporting its efficacy in preventing and treating postoperative inflammation and pain after cataract surgery (Table 1).[5–21] Ketorolac 0.5% (Acular®, Allergan Inc, Irvine, CA) is approved by the Food and Drug administration (FDA) for seasonal allergic conjunctivitis, inflammation following cataract surgery, and ocular discomfort after refractive surgery.[22] To reduce the incidence of burning and stinging, a 0.4% concentration of ketorolac (Acular LS®, Allergan Inc) was formulated, and appears to have a similar therapeutic effect.[18,23] Ketorolac 0.4% is approved by the FDA for the reduction of ocular pain and burning following corneal refractive surgery. Both the 0.5% and 0.4% preparations are dosed four times daily. More recently, a preservative-free 0.45% preparation of ketorolac (Acuvail®, Allergan Inc) in carboxymethylcellulose was approved by the FDA in 2009 for the treatment of pain and inflammation following cataract surgery and is dosed twice daily.[24] The specific intent of this review is to assess the available evidence supporting the efficacy of Acuvail in the treatment of pain and inflammation after cataract surgery.

Pharmacology of ketorolac

NSAIDs are a chemically heterogenous group of compounds that inhibit the formation of prostaglandins and lack a steroid nucleus biosynthetically derived from cholesterol. There are six major classes, but topical formulations are limited to the relatively water-soluble classes, ie, indole acetic, aryl acetic, and aryl propionic acids.[25]

Ketorolac tromethamine is an aryl acetic acid derivative. The chemical name is (±)-5-benzoyl-2,3- dihydro-1H-pyrrolizine-1-carboxylic acid, compounded with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). The molecular weight is 376.41 and the molecular formula is $C_{19}H_{24}N_2O_6$. Current preparations consist of a racemic mixture of R-(+) and S-(−) ketorolac tromethamine.

When administered systemically, ketorolac has proven analgesic, anti-inflammatory, and antipyretic activity.[1] Its mechanism of action, as with all NSAIDs, is presumed to be due to inhibition of prostaglandin biosynthesis. However, systemic administration is not thought to achieve sufficient intraocular drug levels to inhibit prostaglandin synthesis completely in the ciliary body and iris.[1] Topical administration of ketorolac, on the other hand, reaches adequate levels to inhibit prostaglandin synthesis in these target tissues. In one study, after a single topical application of ketorolac 0.4%, a peak aqueous concentration of 57.5 ng/mL was achieved after 60 minutes.[26] Another study demonstrated mean aqueous concentration of 1079 ng/mL after a total of 12 doses of ketorolac 0.4% administered over 2 days.[27]

The original ophthalmic formulation of ketorolac is a 0.5% solution marketed as Acular. A 0.4% formulation (Acular LS) was introduced in the US in 2003. The 0.5% and 0.4% preparations are supplied as an isotonic aqueous mixture with a pH of 7.4, and have an osmolality of approximately 290 mOsmol/kg. However, both the 0.4% and 0.5% solutions contain benzalkonium chloride (a preservative), the surfactant octoxynol-40, and sodium edetate (a metal-chelating agent), and are associated with a high incidence of burning and stinging on instillation (as high as 40%).[22,23,28]

In an effort to increase ocular bioavailability, a new formulation of ketorolac was developed to preserve the efficacy of prior formulations, while enhancing tolerability with a less frequent dosing regimen.[21] Compared with the ketorolac 0.4% formulation, the concentration of Acuvail is 12% greater (0.45%) and carboxymethylcellulose is added to the emulsion to allow greater drug retention on the ocular surface and improve comfort and drug penetration. Other key changes include lower pH and absence of surfactant, metal-chelating agents, and preservatives. As such, Acuvail is supplied as a sterile isotonic preservative-free solution with a pH and osmolality of approximately 6.8 and 285 mOsmol/kg, respectively, and is approved by the FDA for treatment of pain and inflammation following cataract surgery.

In a study by Attar et al evaluating the pharmacokinetics of ketorolac 0.45% versus 0.4%, the addition of carboxymethylcellulose in combination with the 12% increase in concentration

Table 1 Clinical studies with ketorolac in post-cataract surgery inflammation and pain

Author	Year	Patients/Eyes	Ketorolac	Dosing regimen	P = cells/flare	P = pain	Conclusions
El Harazi et al[5]	1988	58 pts	0.50%	4 × daily 1 wk then BID × 3 wks			Ketorolac = diclofenac = prednisolone 1% for inflammation
Flach et al[6]	1988	118 pts	0.50%	1 gtt 3 × daily	0.001		Ketorolac > placebo for inflammation
Flach et al[7]	1989	127 pts	0.50%	Pre and postoperatively	0.53		Ketorolac = dexamethasone for inflammation
Ostrov et al[8]	1997	157 pts	0.50%	1 day preop and 4 wks postop			Ketorolac = prednisone 1% = dexamethasone for inflammation
Heier et al[9]	1999	102 pts	0.50%	4 × daily	0.030/0.025	0.049	Ketorolac > placebo for inflammation and pain
Simone et al[10]	1999	59 pts	0.50%	1 to 2 drops 4 times daily × 1 wk then tapered			Ketorolac = prednisolone 1% for inflammation and pain
Snyder et al[11]	2000	26 pts	0.50%	Pre and postoperatively			Ketorolac = flurbiprofen/prednisolone 1% for inflammation
Soloman et al[12]	2001	104 eyes	0.50%	4 × daily starting 24 hrs after surgery	0.0002/0.001	0.043	Ketorolac > placebo for inflammation
Soloman et al[13]	2001	36 pts	0.50%	4 × daily starting 24 hrs after surgery	0.17/0.48		Ketorolac = rimexolone 1% for cell/flare
Holzer et al[14]	2002	60 pts	0.50%	4 times a day × 1 wk then BID × 3 wks			Ketorolac = loteprednol for inflammation
Trinivarat et al[15]	2003	120 pts	0.50%	4 × daily	0.008		Prednisolone > ketorolac for inflammation
Price and Price[16]	2004	25 pts (50 eyes)	0.40%	4 × daily starting 3 days prior and 1 day after CE		0.02	Ketorolac > placebo for pain
Donnenfeld et al[17]	2006	4 grps of 25	0.40%	4 times daily pre and post operatively	0.001	0.001	Preoperative ketorolac decreased inflammation
Sandoval et al[18]	2006	40 eyes total	0.4%/0.5%	4 × daily × 1 wk then BID × 3 wks			Comparative study revealed 0.5% > stinging/burning
Duong et al[19]	2007	193 eyes	0.40%	4 × daily	0.33	0.025	Ketorolac > nepafenac for pain
Maca et al[20]	2010	100 pts	0.50%	4 × daily		0.001	Diclofenac = ketorolac for inflammation
Donnenfeld et al[21]	2011	511 pts	0.45%	2 × daily	0.001	0.001	Ketorolac > placebo for pain and inflammation

resulted in a 35% enhancement of bioavailability in the aqueous humor of the 0.45% preparation.[29] Furthermore, decreasing the pH from 7.4 to 6.8 in combination with addition of carboxymethylcellulose enhanced bioavailability in the aqueous humor by two-fold and in the iris-ciliary body by three-fold.

At the time of writing, the pharmacokinetics of Acuvail have not been assessed in humans, but both Acular LS and Acuvail formulations were directly compared after a single topical application of 35 µL.[29] Peak concentration in the aqueous humor and iris-ciliary body was 389 ng/mL and 450 ng/g,

respectively, for Acuvail, and 211 ng/mL and 216 ng/g, respectively, for Acular LS. This study concluded that Acuvail delivered significantly higher concentrations of ketorolac to the aqueous humor and iris-ciliary body. Waterbury et al directly compared the peak and trough intraocular levels of Acuvail, bromfenac 0.9% (Xibrom®, ISTA Pharmaceuticals Inc, Irvine, CA), and placebo after three applications (35 μL) every 20 minutes in an animal model of lipopolysaccharide-induced inflammation.[30] Peak concentrations in the aqueous humor and iris-ciliary body were 738 ng/mL and 556 ng/g, respectively, for Acuvail and 94 ng/mL and 46 ng/g, respectively, for bromfenac 0.9%. Trough concentrations in the aqueous humor and iris-ciliary body were 127 ng/mL and 59 ng/g, respectively, for Acuvail, and 17 ng/mL and 8 ng/g, respectively, for bromfenac 0.9%. The study concluded that Acuvail achieved aqueous and iris-ciliary body concentrations that exceeded its inhibitory concentration of 50% (IC_{50}) values for COX-1 and COX-2 at both peak and trough (Table 2).[1,26,31,32] In addition, while both NSAIDs inhibited lipopolysaccharide-induced aqueous prostaglandin E_2 elevation, only Acuvail significantly prevented vascular leakage, as measured by fluorescein isothiocyanate-dextran leakage at trough levels.

Although suggestive, the number of animals used in both studies was small, and therefore additional studies with larger sample sizes are needed to confirm these initial results. Furthermore, both studies used New Zealand white rabbits which lack pigment, blink infrequently, and have an unusually unstable blood–aqueous barrier, so these results should be extrapolated to humans with caution.

Given the favorable pharmacokinetic data of Acuvail, approval was granted for twice-daily dosing in contrast with four times daily dosing for Acular LS. This reduced dosing regimen offers a distinct therapeutic advantage for Acuvail because in addition to patient convenience, several studies have suggested increased patient compliance with less frequent dosing.[33]

Efficacy studies

The efficacy of Acuvail was assessed in two identical multicenter, double-masked, randomized, placebo-controlled, parallel studies and specifically conducted to evaluate the effects of Acuvail on relief of pain and inflammation after cataract surgery.[21] The results of these parallel studies were analyzed together and collectively involved 511 patients.

Patients were randomized in a 2:1 ratio to receive either Acuvail or vehicle in the operative eye for 16 days. Patients were dosed twice daily the day before surgery. On the day of surgery, patients had one drop upon awakening, three drops each 20 minutes apart starting two hours before surgery, one drop before discharge, and one drop 12 hours after the first dose upon awakening, resulting in a total of six drops of the study medication. Patients continued one drop twice daily of the study medication for 14 days after surgery. No patients were exposed to topical corticosteroids during the study period.

All patients underwent elective unilateral, uncomplicated, extracapsular cataract extraction with posterior chamber intraocular lens implantation. Patients were evaluated on postoperative days 1, 3, 7, and 14. The primary efficacy endpoint was the percentage of patients with a summed ocular inflammation score (SOIS) of 0 for anterior chamber cell and flare on day 14. The main secondary efficacy endpoint was the percentage of patients with no pain (grade = 0) on postoperative day 1.

In this study, anterior chamber cell was graded on a six-point scale and anterior chamber flare was graded on a five-point scale. The SOIS was calculated as the sum of scores for anterior chamber cell and flare. To assess the degree of pain, patients called an interactive voice response system diary twice daily during the two weeks after the day of surgery and were instructed to rate their level of ocular pain on a five-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = intolerable).

The Acuvail group had a significantly higher percentage of patients with a SOIS score of 0 compared with vehicle at days 7 and 14. At day 7, Acuvail and vehicle had a SOIS score of 0 for 32% (102/318) and 17% (26/155) of patients, respectively ($P < 0.001$). At day 14, Acuvail and vehicle had a SOIS score of 0 for 53% (167/318) and 27% (41/155) of patients, respectively ($P < 0.001$).

Acuvail was also significantly superior to vehicle in resolving ocular pain after cataract surgery. A pain score of 0 on day 1 was reported in 72% (233/322) of Acuvail patients versus 40% (62/156) in vehicle patients ($P < 0.001$). The median time to postoperative ocular pain resolution was one day in patients treated with Acuvail and two days in patients treated with vehicle ($P < 0.001$).

Although the combined results of these controlled studies demonstrate the efficacy of Acuvail for the prevention and

Table 2 Reported ranges of IC_{50} for COX-1 and COX-2 of ocular NSAIDs

Drug	COX-1 IC_{50} μm (ng/mL)	COX-2 IC_{50} μm (ng/mL)
Amfenac	0.14 to 0.25 (35.6 to 63.6)	0.002 to 0.15 (0.51 to 38.1)
Diclofenac	0.12 to 0.95 (38 to 302.1)	0.03 to 0.09 (9.5 to 28.6)
Ketorolac	0.014 to 0.02 (5.3 to 7.5)	0.09 to 0.12 (33.9 to 45.2)
Bromfenac	0.09 to 0.53 (3.4 to 203.1)	0.007 to 0.023 (2.7 to 8.8)

Abbreviations: COX, cyclooxygenase; IC_{50}, half-maximum inhibition relative to control values.

treatment of postoperative inflammation and pain after cataract surgery, these results should be interpreted with caution. The importance of achieving a median of one less day of pain with Acuvail versus placebo needs to be assessed in the appropriate context of treatment cost, clinical impact, and in the absence of concomitant corticosteroid use. Moreover, cell and flare were combined together in contrast with grading each outcome independently, and their summation may have amplified the treatment differences observed between the Acuvail and vehicle group. In addition, because corticosteroids were not used concomitantly, no information can be discerned about the additive benefits of Acuvail with a corticosteroid in regards to inflammation and pain following cataract surgery. In a study comparing the efficacy of ketorolac 0.5% with prednisolone acetate 1%, Simone et al observed that prednisolone acetate was more effective at reducing intraocular inflammation by day 7 after cataract surgery than ketorolac, although this difference resolved by day 28.[10] Several studies have demonstrated an additive benefit of a topical NSAID with a corticosteroid and their combined use, therefore, is common in clinical practice.[1] Therefore, the results of this study cannot be directly applied in the setting of concomitant corticosteroid use. Nevertheless, previous studies have demonstrated an additive benefit of ketorolac 0.5% or 0.4% when used in conjunction with corticosteroids in reducing inflammation, pain, and CME following cataract surgery. Thus, given the favorable pharmacokinetics of Acuvail in comparison with these older formulations, similar therapeutic benefit may be likely.[5–21]

Selective COX-1 versus COX-2 inhibition

Several in vitro studies indicate that ketorolac is the most potent inhibitor of COX-1, while both amfenac (active component in Nevanac®, Alcon Laboratories Inc, Fort Worth, TX) and bromfenac have been reported as being the most potent inhibitors of COX-2.[1,26,31,32] Bromfenac may be a 3–18 times more potent inhibitor of COX-2 than diclofenac, amfenac, and ketorolac.[25,32] Another study found that amfenac was a more potent inhibitor of COX-2 than bromfenac. Differences in experimental testing and design may explain these conflicting findings. COX-2 is an inducible enzyme and is thought to be primarily responsible for inflammation. Therefore, the anti-inflammatory actions of NSAIDs are presumed to relate to their ability to inhibit this isoform. However, this paradigm 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 versus COX-2 inhibition for ocular disease remains unproven.

Although ketorolac is approximately six times more potent as an inhibitor of COX-1 than COX-2 (Table 2), it is nevertheless a potent inhibitor of COX-2, with an IC_{50} in the range of 0.09–0.12 μM (33.9–45.2 ng/mL).[32] This allows ketorolac to inhibit COX-2 in the iris-ciliary body after topical application, an important fact that can be overlooked if the relative COX-1/COX-2 potencies of ocular NSAIDs are emphasized. On the other hand, ketorolac is an approximately 5–50 times more potent inhibitor of COX-1 than diclofenac, bromfenac, and amfenac. The ability to inhibit both isoforms of COX for short periods of time may be advantageous in allowing more rapid and complete inhibition of prostaglandin production, but long-term inhibition of COX-1 may not be desirable because it is involved in normal physiologic function.

NSAIDs and corticosteroids

The combination use of topical NSAIDs and corticosteroids is sometimes referred to as "synergistic" in the literature. This clinical impression of synergy remains unproven and would seem unlikely, given the fact that both drug classes inhibit prostaglandin production (Figure 1). Synergy is defined, in general, as two or more agents working in combination to produce an effect that could not be obtained by each agent independently. A classic example of synergy involves penicillin and aminoglycoside antibiotics where use of both antibiotics in combination significantly lowers the IC_{50} of each antibiotic for a given organism. Although a large, randomized, prospective study demonstrated that ketorolac 0.5% was more effective than dexamethasone sodium phosphate 0.1%
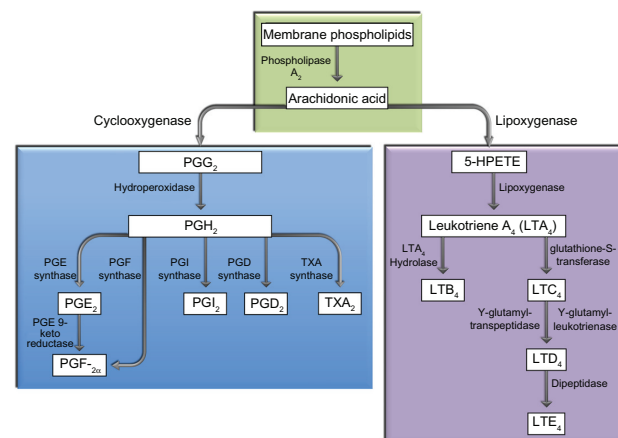

Figure 1 Corticosteroids inhibit phospholipase A_2 while nonsteroidal anti-inflammatory drugs act more downstream and directly inhibit cyclo-oxygenase.

solution in facilitating re-establishment of the blood–aqueous barrier after surgery, differences in drug formulation and intraocular concentration preclude any conclusions about synergy.[34–36] Furthermore, although many prospective studies have confirmed that the combination use of an NSAID and corticosteroid is superior to a corticosteroid alone for pain, inflammation, CME, and visual improvement after intraocular surgery, these findings can be explained by an additive effect of a second anti-inflammatory agent.[1,17,37] The distinction between a synergistic effect and an additive effect has important implications because synergy implies that an NSAID used in combination with a corticosteroid provides a therapeutic effect that cannot be replicated by simply increasing the dosing regimen of the corticosteroid.

Ketorolac and posterior segment disease

Although topical administration of NSAIDs provides aqueous humor levels adequate to suppress prostaglandin synthesis in the iris and ciliary body, the ability to suppress prostaglandin synthesis in the retina/choroid is less certain. In an animal model, ketorolac 0.5% could not be detected in the vitreous after topical administration, but in a small prospective comparative study of patients undergoing vitrectomy, ketorolac 0.4% could be detected in the vitreous (2.8 ng/mL) and reduced vitreous prostaglandin E_2 levels.[38,39] This observed reduction was presumably from inhibition of iris and ciliary body prostaglandin E_2 production because the measured vitreous concentration of ketorolac was considerably less than the IC_{50} for both COX-1 and COX-2 inhibition, and therefore unlikely to have inhibited COX activity in retinal cells.

Accumulating evidence indicates that COX-2 has important implications for retinal disease.[1,40] COX-2 is the predominant isoform in human retinal pigment epithelial cells and is significantly upregulated in response to proinflammatory cytokines.[41] COX-2 is also present in choroidal neovascularization, as well as in other highly vascularized lesions, and its expression increases in diabetic retinopathy.[1,42] In a variety of experimental systems, COX-2 inhibition suppresses angiogenesis.[43] In this regard, both nepafenac 0.1% and bromfenac 0.09% could be detected in the rabbit retina after topical administration, and in one study nepafenac inhibited 55% of retinal prostaglandin synthesis.[31,44] In another study, topical ketorolac 0.4% inhibited experimentally induced choroidal neovascularization and reduced both retinal prostaglandin E_2 and vascular endothelial growth factor levels by >30%.[45] While interesting, these results were obtained in animal models and cannot be directly extrapolated to humans. Given the favorable pharmacokinetics of Acuvail versus Acular LS, it is worth speculating that clinically meaningful retinal COX inhibition may now be achievable.

Safety and tolerability

The overall incidence of treatment-related adverse events was significantly higher in the vehicle group (14%) than in the Acuvail group (6%).[21] The most common adverse events reported were increased intraocular pressure, conjunctival hyperemia, and/or hemorrhage, corneal edema, ocular pain, headache, tearing, and blurred vision. The most common adverse events reported at a higher frequency than vehicle included increased intraocular pressure (5.8% versus 1.8%), conjunctival hemorrhage (1.2% versus 0.6%), and blurred vision (1.2% versus 0.6%), and were generally considered by the clinical investigators to be a consequence of the cataract procedure. Adverse events of burning and stinging were low, with only 1.5% of patents in the Acuvail group and 0.6% in the vehicle group reporting such an occurrence.

When ketorolac 0.5% was topically applied in one eye three times daily, only five of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7–22.5 ng/mL) at day 10. In contrast, when ketorolac 10 mg was administered systemically every six hours, peak plasma levels were around 960 ng/mL. Given the possibility of systemic absorption after topical application, techniques such as lid closure and nasolacrimal occlusion may be used to decrease systemic exposure.

As with other NSAIDs, Acuvail may slow or delay healing, and in some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. There exists the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, and therefore caution should be used when treating individuals who have previously exhibited sensitivities to these drugs. NSAIDs interfere with thrombocyte aggregation and may prolong bleeding time. Therefore, it is recommended that topical NSAIDs be used with caution in patients with known bleeding tendencies or who are receiving anticoagulation.

There are no adequate well controlled studies of topical NSAIDs in pregnant woman and, as such, these medications are classified as Category C. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of topical NSAIDs should be avoided during late pregnancy.

Severe corneal toxicity has been reported with diclofenac 0.1%, ketorolac 0.5%, nepafenac 0.1%, and bromfenac 0.09%.[1] Although uncommon, these dramatic events are referred to as corneal melt. However, a definite link between NSAID use and corneal melt remains unproven, but it is still prudent to avoid NSAID use in patients with severe corneal surface disease.

Patient satisfaction

There are limited data on patient satisfaction with Acuvail. Older formulations of ketorolac had an incidence of transient burning and stinging on instillation of approximately 20%–40% for the 0.4% concentration and 40% for the 0.5% concentration.[22,23] In contrast, Acuvail was associated with substantially lower rates (1.5%) of burning and stinging.[21]

Most importantly, a significantly higher percentage of patients randomized to Acuvail had a 3-line or more improvement in vision from baseline compared with those treated with vehicle.[21] At least two previously published studies using ketorolac 0.4% demonstrated a similar beneficial effect upon visual acuity following cataract and vitreoretinal surgery.[17,37] In patients undergoing routine vitreoretinal surgery, patients randomized to ketorolac 0.4% experienced an average 4.3-line improvement from baseline compared with a 2.5-line improvement with placebo.[37] This greater improvement in vision in the ketorolac group was observed despite concomitant corticosteroid use in both groups.

Conclusion

Excessive postoperative inflammation and pain after cataract surgery can delay visual recovery and affect long-term outcomes. There is substantial evidence from well designed studies with sufficient numbers of patients that ketorolac formulations 0.4% and 0.5% effectively treat both inflammation and pain after cataract surgery. Recent evidence indicates that Acuvail possesses similar therapeutic benefit. Given the favorable pharmacokinetics, better tolerance, and reduced dosing requirement of Acuvail, additional clinical studies comparing Acuvail with other NSAIDs for the treatment of inflammation and pain after cataract surgery are indicated to confirm these promising results.

Acknowledgment

Disclosure

SJK is a consultant for Ophthotech. RR declares no conflicts of interest in this work.

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