Ophthalmic NSAIDs Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
bromfenac 0.09% solution (Xibrom™)	Ista	• Post-operative inflammation secondary to cataract extraction • Ocular pain in patients who have undergone cataract surgery
diclofenac 0.1% solution (Voltaren®)	generic	• Post-operative inflammation secondary to cataract extraction • Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
flurbiprofen sodium 0.03% solution (Ocufen®)	generic	• Inhibition of intraoperative miosis
ketorolac tromethamine 0.5% solution (Acular®)	Allergan	• Temporary relief from ocular itching related to seasonal allergic conjunctivitis • Treatment of post-operative inflammation in patients who have undergone cataract extraction
ketorolac tromethamine 0.4% solution (Acular LS®)	Allergan	• Reduction of ocular pain, burning, and stinging after corneal refractive surgery
ketorolac tromethamine 0.5% solution (Acular PF®)	Allergan	• Reduction of ocular pain and photophobia associated with incisional refractive surgery
nepafenac 0.1% suspension (Nevanac™)	Alcon	• Treatment of pain and inflammation associated with cataract surgery

Overview

A wide variety of conditions can cause ocular inflammation. Inflammation of the eye may arise as a result of trauma, surgery. or infection. Local application of anti-inflammatory medications can decrease inflammation with minimal systemic adverse effects.

The main use of ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) is for ophthalmic surgery.[1] With refractive surgery, ophthalmic NSAIDs are effective at reducing pain both during and after the procedure. Ophthalmic NSAIDs also reduce inflammation in the cornea and conjunctiva in refractive surgery. During cataract surgery, ophthalmic NSAIDs are utilized to control pain, but more importantly, ophthalmic NSAIDs help maintain papillary dilatation during cataract surgery. Ophthalmic NSAIDs also control inflammation during the first few days following the procedure. Inflammation is measured by the presence of cells and flare within the anterior chamber.

Pharmacology[2,3]

Ophthalmic NSAIDs have analgesic and anti-inflammatory activity. The mechanism of action is thought to be through the inhibition of cyclooxygenase enzymes, essential in prostaglandin production. Prostaglandins disrupt the blood-aqueous humor barrier, produce vasodilation, and increase vascular permeability, leukocytosis, and intraocular pressure (IOP).

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. These agents inhibit the miosis induced during the course of cataract surgery and have no significant effect on IOP.

Pharmacokinetics

Due to the topical nature of this drug class, systemic absorption is minimal. Ketorolac (Acular, Acular LS, Acular PF) does achieve measurable systemic levels.[4,5,6] Nepafenac (Nevanac) is a prodrug that is metabolized via hydrolases to the active NSAID, amfenac.[7] Low systemic levels of nepafenac and amfenac have been observed after topical administration to the eye. Nepafenac has been shown to penetrate the cornea more rapidly and provides more complete (80 percent versus 50 percent) and longer lasting inhibition of prostaglandin synthesis (greater than six hours versus three hours) and vascular permeability (eight hours versus four hours) than diclofenac.[8,9] After topical instillation, systemic levels of bromfenac (Xibrom) and diclofenac (Voltaren) remain below the level of detection.[10,11]

Contraindications/Warnings

Bromfenac (Xibrom) contains sodium sulfite and is contraindicated in patients with sulfite hypersensitivity.[12]

As with all the NSAIDs, cross-hypersensitivity in patients with aspirin and other NSAID-hypersensitivities is possible; caution should be used in such patients.[13,14,15,16,17,18,19]

Refractive stability undergoing corneal refractive procedures and diclofenac (Voltaren) usage has not been well established. Monitoring of visual acuity is recommended.[20]

Precautions

NSAIDs may cause keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation.[21] These events may be sight-threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored. Patients who might be at risk for complications include those with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time. Using ophthalmic NSAIDs beyond the 14 days of recommended use may increase a patient's risk of severe corneal adverse events.

Ketorolac (Acular LS) and nepafenac (Nevanac) should not be administered while wearing contact lenses.[22,23]

Drug Interactions

Due to the topical nature of the products in this category, drug interaction studies have not been systematically performed. Nepafenac (Nevanac) has been investigated for potential impact on the cytochrome P450 system; no potential impact was identified.[24]

Ketorolac ophthalmic products (Acular, Acular LS, Acular PF) have been safely given with ophthalmic antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.[25,26,27]

Nepafenac ophthalmic suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.[28]

Adverse Effects

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
bromfenac 0.09% solution (Xibrom)[29]	2-7	2-7	nr	nr
diclofenac 0.1% solution (Voltaren)[30]	15	< 5	< 5	< 5
flurbiprofen sodium 0.03% solution (Ocufen)[31]	Reported	Reported	nr	nr
ketorolac tromethamine 0.5% solution (Acular)[32]	< 40	1-10	1-10	Reported rarely
ketorolac tromethamine 0.4% solution (Acular LS)[33]	20-40	1-10	1-5	nr
ketorolac tromethamine 0.5% PF solution (Acular PF)[34]	20	1-10	1 - 10	Reported
nepafenac 0.1% suspension (Nevanac)[35]	Reported	1-5	1-5	5-10

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative. nr = not reported.

Special Populations

Pediatrics

Safety and effectiveness in pediatric patients have not been established in children for bromfenac (Xibrom), diclofenac (Voltaren), and flurbiprofen sodium (Ocufen).[36,37,38] Nepafenac (Nevanac) has not been studied in children less than ten years of age.[39] Ketorolac products (Acular, Acular LS, Acular PF) have been approved for use in children age three years and older.[40,41,42]

Pregnancy

Agents in this class are Pregnancy Category C. Due to the known effects of NSAIDs and the prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system, including the closure of ductus arteriosus, the use of many of these ophthalmic NSAIDs during late pregnancy should be avoided.

Dosages

Drug	Dosage	Availability
bromfenac 0.09% solution (Xibrom)	Cataract surgery: One drop twice daily, starting 24 hours post-op for two weeks	2.5, 5 mL
diclofenac 0.1% solution (Voltaren)	Cataract surgery: One drop four times daily starting 24 hours post-op for two weeks Refractive surgery: One to two drops one hour prior to surgery, then one to two drops 15 minutes post-op, then one to two drops four times a day for up to three days	2.5, 5 mL
flurbiprofen sodium 0.03% solution (Ocufen)	Intraoperative use: Instill one drop every 30 minutes for a total of four drops over two hours pre-operatively.	2.5 mL
ketorolac tromethamine 0.5% solution (Acular)	Cataract surgery: One drop four times daily starting 24 hours post-op for two weeks Seasonal Allergic Conjunctivitis: One drop four times daily	3, 5, 10 mL
ketorolac tromethamine 0.4% solution (Acular LS)	Refractive surgery: One drop four times a day for up to four days as needed for burning or stinging following refractive surgery	5 mL
ketorolac tromethamine 0.5% PF solution (Acular PF)	Incisional refractive surgery: One drop four times a day for up to three days	0.4 mL single use vials – 12 in a package
nepafenac 0.1% suspension (Nevanac)	Cataract surgery: One drop three times daily beginning one day prior to surgery; continue on the day of surgery, and through the first two weeks post-op	3 mL

The following products contain the preservative benzalkonium chloride: Acular, Acular LS, Xibrom, and Nevanac.[43,44,45,46] Ocufen contains thimerosal.[47] Acular PF does not contain any preservative and is available in unit of use packages.[48]

Clinical Trials

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the ophthalmic use of all drugs in this class. Randomized controlled comparative trials for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Several studies were performed in the perioperative setting which is not applicable to the outpatient utilization. These studies were excluded from this review.

bromfenac (Xibrom)

Two Phase III, randomized, double-blind studies evaluated bromfenac 0.09% in the treatment of post-operative inflammation and reduction of ocular pain in patients undergoing cataract surgery.[49] Bromfenac 0.09% (n=356) or vehicle (n=171) was instilled twice daily for 14 days followed by a 14-day evaluation period. The primary endpoint was cleared ocular inflammation as measured by the summed ocular inflammation score (SOIS), defined as less than five cells and absence of flare after 14 days of treatment. Bromfenac 0.09% was superior to vehicle in reducing ocular inflammation after cataract surgery at day 15 (64 percent versus 43.3 percent; $p<0.0001$). The effect of bromfenac on clearance of ocular inflammation was observed as early as day three after initiation of treatment (8.4 percent versus 1.2 percent for placebo, $p=0.0012$). Bromfenac 0.09% reduced median time to resolution of ocular pain to two days, compared with five days for vehicle ($p<0.0001$). Most commonly reported adverse effects included eye irritation, burning and stinging, and photophobia; all of these adverse effects were reported more frequently with placebo. No clinically significant systemic adverse events or changes in liver enzymes were reported with bromfenac.[50]

diclofenac (Voltaren) versus flurbiprofen (Ocufen)

In a double-blind trial, 43 patients undergoing cataract extraction were randomized to diclofenac sodium 0.1% or flurbiprofen 0.03%.[51] The assigned medication was instilled every six hours for three doses prior to surgery, then four drops over 90 minutes just prior to surgery. After surgery, patients administered the assigned medication four times daily for three to six weeks. Patients were examined one, three, and six weeks post-operatively. There were no statistically significant differences between the treatment groups for conjunctival hyperemia, corneal surface changes, IOP, or anterior chamber inflammation.

diclofenac (Voltaren) versus ketorolac (Acular)

In a double-masked, randomized trial during the post-operative period of cataract extraction and implantation of an intraocular lens, a total of 120 patients were treated with either diclofenac 0.1% solution or ketorolac tromethamine 0.5% solution four times daily for 30 days.[52] Treatment began the first post-operative day after surgery. Objective measurements of inflammation and toxicity were made at three post-operative visits. The anti-inflammatory effects were similar at all three post-operative visits. Both treatments were equally tolerated.

In a long-term follow-up to the above study, the primary endpoint was to evaluate the incidence of post-operative posterior opacification.[53] Patients were followed for three years and received yttrium-aluminum-garnet (YAG) laser capsulotomies and were evaluated for any existing post-operative posterior opacification. The incidence of post-operative posterior opacification and YAG capsulotomies were similar (12 percent in each treatment group). Adverse effects from therapy were also similar in both groups.

In a double-blind, randomized study, diclofenac 0.1% solution and ketorolac 0.5% solution were compared in 30 patients for efficacy in relieving corneal pain after refractive surgery.[54] Patients underwent radial keratotomy and were monitored for post-operative pain and instillation comfort. Both diclofenac and ketorolac were similarly effective in reducing ocular pain and had similar comfort on instillation ($p=0.29$).

diclofenac (Voltaren) versus nepafenac 0.1% (Nevanac) versus nepafenac 0.03%

In a randomized, double-blind, parallel-group trial, nepafenac 0.03% and 0.1% ophthalmic suspensions and diclofenac 0.1% were compared in 60 patients undergoing excimer photoreactive keratectomy (PRK).[55] On surgery day, two drops were given one hour prior to surgery, two drops within one hour after surgery, then one drop four and eight hours after the post-operative dose. The day after surgery, patients instilled one drop of the assigned medication four times daily, then therapy was discontinued. Patients recorded pain (0 to 9 on visual analog scale) and photophobia (0=none and 3=severe). On surgery day, there were no significant differences between groups except that, at three hours, the nepafenac 0.03% group had significantly higher pain scores than the nepafenac 0.1% group (mean score, 4.0 versus 3.0; $p<0.038$). On day two, the nepafenac 0.1% group had less pain at bedtime compared to the diclofenac group (1.9 versus 3.1; $p<0.024$). Less morning photophobia was recorded in the nepafenac 0.1% group compared to the diclofenac group (1.2 versus 1.8; $p<0.023$). No significant differences in the rate of corneal re-epithelialization existed among the three groups. Adverse events were infrequently reported. Nepafenac is not indicated for the treatment of pain and inflammation following PRK.

ketorolac 0.4% (Acular LS) versus nepafenac 0.1% (Nevanac)

Ketorolac 0.4% ophthalmic solution and nepafenac 0.1% ophthalmic suspension were compared in a randomized, double-blind study in 132 patients undergoing cataract extraction.[56] Patients were given ketorolac 0.4% or nepafenac 0.1% four times daily for two days before cataract extraction. The primary outcome measures in the study were the level of prostaglandin E(2) [PGE(2)] in the treated eyes and aqueous concentration of the active drug therapy in the treated eyes. Significantly more ketorolac eyes (61.9 percent) had PGE(2) levels below the level of detection than did the eyes receiving nepafenac (17.5 percent, $p<0.001$). Mean aqueous concentrations of active drug were significantly higher with ketorolac (1,079 ng/mL) than with amfenac (353 ng/mL), the active form of nepafenac. The mean level of inactive nepafenac was 588 ng/mL ($p<0.001$ versus ketorolac).

Nepafenac 0.1% and ketorolac 0.4% were compared for effects on corneal re-epithelialization and pain after PRK in 40 adults.[57] In the double-blind, randomized trial, nepafenac 0.1% and ketorolac 0.4% were administered in the contralateral eyes as one drop three times daily for three days after bandage contact lens insertion. Patients were evaluated on days one, three, four, five, and seven. Pain and comfort upon eyedrop instillation were assessed at each visit. The epithelial defect was assessed starting on day three and was found to be similar with both treatments at each post-operative visit ($p>0.05$). The average time of healing was 4.18 days with nepafenac and 4.0 days with ketorolac ($p=0.3134$). Mean post-operative pain scores were similar between the two drugs. Nepafenac patients had lower mean sensation scores for instillation pain ($p=0.009$), irritation ($p=0.0007$), and burning and stinging ($p=0.0003$) compared to ketorolac. Overall comfort score was also in favor of nepafenac (7.43 versus 6.41, $p<0.0001$). Nepafenac is not indicated for the treatment of pain and inflammation following PRK.

ketorolac 0.5% (Acular) versus ketorolac 0.4% (Acular LS)

The two formulations of ketorolac tromethamine 0.4% and 0.5% ophthalmic solutions were compared for effectiveness and patient tolerance in 40 patients undergoing phacoemulsification and lens implantation.[58] In a double-masked study, patients were randomized to receive one of the two strengths of ketorolac starting 15 minutes prior to surgery. After surgery, patients administered one drop four times daily for one week, then twice daily for three weeks. Patients were examined on day one, seven, and 30. On day one, more patients reported foreign body

sensation or stinging and burning in the ketorolac 0.5% group (70 percent) than the ketorolac 0.4% group (40 percent; p<0.05). There were no significant differences between the two groups for best-corrected visual acuity, IOP, slit-lamp assessment of cells, or cell/flare measured using the laser cell/flare meter.

In a pooled analysis of two multicenter, randomized, double-blind, vehicle-controlled studies, the safety and efficacy of ketorolac 0.4% in PRK were evaluated.[59] A total of 313 patients had unilateral PRK in the analysis. Patients were given one drop of ketorolac 0.4% or vehicle four times daily for four days post-operatively. Pain intensity was significantly less with the active treatment (p<0.001). Intolerable pain was significantly less with ketorolac 0.4% (41.6 percent versus 84.5 percent for the vehicle control). The median time to no pain was 30 hours with ketorolac and 54 hours with the vehicle (p<0.001). The ketorolac 0.4% provided pain relief during the study (p<0.001), and the active treatment group had significantly less use of rescue medication in the 48 hours after surgery (p≤0.008). Treatment related adverse effects were reported in higher frequency with the vehicle.

Summary

Corticosteroids are the first-line therapy for the treatment of ophthalmic inflammatory conditions, but corticosteroid use can lead to elevated IOP. The NSAIDs offer equivalent anti-inflammatory efficacy for post-operative inflammation without the typical corticosteroid adverse effects. The majority of the ophthalmic NSAIDs use is in the post-operative setting for a variety of procedures. The ophthalmic NSAIDs reduce inflammation as well as provide pain control.

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