A review of the use of ketorolac tromethamine 0.4% in the treatment of post-surgical inflammation following cataract and refractive surgery

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Abstract: The non-steroidal anti-inflammatory drug (NSAID) ketorolac tromethamine 0.4% ophthalmic solution, a recent reformulation containing 20% less active ingredient that the original formulation, is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery. Clinical studies have shown ketorolac tromethamine 0.4% to be as effective as ketorolac tromethamine 0.5% to control inflammation after cataract surgery including prevention of cystoid macular edema (CME). Its efficacy to inhibit miosis during cataract surgery as well as its role in the treatment of dry eye has been reported. The purpose of this paper is to review the use of ketorolac tromethamine 0.4% in the treatment of post-surgical inflammation following cataract and refractive surgery.

Keywords: NSAIDs, anti-inflammatory, ketorolac, ocular, ophthalmic

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit production of prostaglandins (PG) by inhibiting cyclo-oxygenase (COX) which is the main enzyme to produce eicosanoids (ie PG and thromboxanes). Two isoforms of COX (COX-1 and COX-2) with different physiological properties have been described (Warner and Mitchell 2004). COX-1 seems to be responsible for the physiological production of prostanoids while COX-2 is associated to the pathological function and inflammation. COX-1 and COX-2 are very similar in its aminoacid composition as well as molecular mass, intracellular location and function. However, there are differences such as different gene location, COX-1 is located in chromosome 9 while COX-2 is situated in chromosome 1. Furthermore, the amino acid at positions 434 and 523 in COX-1 is isoleucine and in COX-2 is valine (Warner and Mitchell 2006). Systemically, COX-1 has been associated with gastrointestinal side effects whereas COX-2 produces less gastrointestinal adverse events (Warner and Mitchell 2004, 2006). However, COX-2 selective inhibitors have been shown to increase the risk of serious cardiovascular adverse events, primarily acute myocardial infarction (Furberg 2006).

The effect of COX-2 as a therapeutic target in inflammation, pain, cancer, and its effect on the central nervous system (CNS), kidney, reproductive, gastrointestinal, and respiratory tracts as well as in the pancreas and cardiovascular system have been reported (Warner and Mitchell 2004). A third COX isoform has been described (COX-3); however, this form does not have the COX activity, and therefore, it is unlikely to have an impact in the PG production (Warner and Mitchell 2004, 2006; Hersh et al 2005).

The eye, after chemical, mechanical and thermal stimuli, has a wide range of inflammatory responses, many of which involve PG formation from arachidonic acid.
The PG and leukotriene synthesis after surgical trauma has been described in detail in previous publications (Flach 1992; Nichols and Snyder 1998; Perry and Donnenfeld 2006). The PG formation leads to the blood aqueous barrier breakdown, decreases the pain threshold and increases photophobia. Other ocular inflammation signs include hyperemia, miosis, and decreased vision. The control of inflammation within the eye is mandatory to keep the ocular integrity and function. The inflammatory cascade can be blocked at different locations using different therapeutic agents (ie, the release of arachidonic acid can be impeded by blocking the phospholipase A₂ activity using corticosteroids, NSAIDs can interfere with the COX-1 and COX-2 activity). It has been shown that NSAIDs also suppress polymorphonuclear cell ability to move and chemotaxis; decrease expression of inflammatory cytokines and mast cell degranulation (Gaynes and Fiscella 2002).

In ophthalmology, NSAIDs are commonly used to prevent intraoperative miosis during cataract surgery, to reduce postoperative inflammation and to prevent cystoid macular edema (CME) following cataract extraction, relief of seasonal allergic conjunctivitis symptoms, reduction of ocular discomort (pain and photophobia) after refractive surgery, and to treat CME once it occurs.

The purpose of this paper is to review the use of ketorolac tromethamine 0.4% in the treatment of post-surgical inflammation following cataract and refractive surgery.

**Characteristics**

Ketorolac tromethamine 0.4% (Acular® LS, Allergan, Inc, Irvine, CA, USA) was introduced in the United States in 2003. It is a member of the pyrrolo-pyrrole group of NSAIDs used in ophthalmology. Its chemical name is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). It is a racemic mixture of R-(+) and S-(−)-ketorolac tromethamine, which exists in three crystal forms which are equally soluble in water. Other characteristics include a pH of 7.4 and an osmolality of 290 mOsm/kg, pKa is 3.5 and its molecular weight is 376.41. Ketorolac tromethamine 0.4% and ketorolac tromethamine 0.5%, the original formulation, (Acular, Allergan, Inc, Irvine, CA, USA), share the mentioned characteristics. Acular 0.4% contains 20% less active ingredient than the original formulation. Other differences among the 2 solutions include the preservative concentration, ketorolac 0.5% contains 0.01% benzalkonium chloride while ketorolac 0.4% contains 0.006%. The concentration of edetate disodium, an inactive ingredient, is 0.1% and 0.015% in ketorolac 0.5% and 0.4%, respectively.

**Mechanism of action**

Systemically, ketorolac tromethamine has shown anti-inflammatory, analgesic and antipyretic action (Litvak and McEvoy 1990). Many of these activities appear to be associated mainly with the inhibition of PG biosynthesis by inhibiting the COX enzymatic system (Litvak and McEvoy 1990; Jay 1991). The effect of ketorolac ophthalmic solution is thought to be due to the inhibition of ocular PG synthesis (Litvak and McEvoy 1990).

Waterbury and Flach (Waterbury and Flach 2006) using a rabbit model of ocular inflammation induced by injecting a lipopolysaccharide endotoxin isolated from *Salmonella enterica* intravenously investigated the anti-inflammatory activity of ketorolac 0.4% and other NSAIDs. They reported a nearly complete inhibition of PG synthesis in the aqueous humor compared with vehicle.

In a similar animal model, Waterbury et al (2004) evaluating the COX activity and anti-inflammatory effect of ketorolac 0.4% found that ketorolac 0.4% is a relatively COX-1 selective NSAID with potent ocular anti-inflammatory action producing almost complete inhibition of PG synthesis in aqueous humor in the treated eyes. These findings are similar to previous studies conducted in rats (Pallapies et al 1995; Jett et al 1999) which have shown than ketorolac tromethamine is a potent inhibitor of COX-1 and 2.

**Pharmacokinetics**

In rabbit eyes, ketorolac 0.5% is distributed throughout all the ocular tissues (Ling and Combs 1987; Litvak and McEvoy 1990). After topical application of ketorolac 0.5%, peak plasma levels of approximately 0.2 µg/mL within 15 minutes after application were detected (Ling and Combs 1987). In the US Food and Drug Administration (FDA), safety sheet data, it is reported that 5 out of 26 normal patients, after application of one drop of ketorolac 0.5% 3 time a day for 10 days, showed ketorolac plasma levels between 10.7 and 22.5 ng/mL at day 10.

**Indications**

One drop of ketorolac tromethamine 0.5% 4 times a day is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis, and one drop 4 times a day starting 24 hours after the procedure and continuing for 2 weeks for the treatment of postoperative inflammation following cataract surgery.

Ketorolac tromethamine 0.4% is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery. The recommended dosage is one drop
4 times a day in the operated eye as needed for up to 4 days following corneal refractive surgery.

**Adverse effects**

Keratitis, corneal subepithelial infiltrates, ulceration, and corneal melt are adverse events that have been associated with the use of NSAIDs (Teal et al 1995; Guidera et al 2001; Solomon et al 2001). Transient stinging and burning on instillation of ketorolac tromethamine 0.5% was reported by 40% of subjects participating in clinical trials (FDA safety sheet data). The reduction in the concentration of ketorolac would decrease patient complaints of stinging and burning after its instillation (Solomon et al 2004; Sandoval et al 2006).

**Clinical studies evaluating ketorolac tromethamine 0.4%**

**Ketorolac tromethamine 0.4% post photorefractive keratectomy (PRK)**

A few studies have been published in the peer reviewed literature regarding the use of ketorolac tromethamine 0.4%. Solomon et al (2004) in a large, two multi-center, randomized, double-masked vehicle controlled study involving 313 eyes of 313 subjects evaluated the safety and analgesic efficacy of ketorolac 0.4% after PRK. In this trial, patients were treated with one drop of either ketorolac 0.4% (n = 156) or its vehicle (n = 157), 4 times a day for up to 4 days. Measured outcomes included pain intensity, pain relief, use of escape medication, and severity of ocular symptoms. The results of this study showed that compared with the vehicle patients, ketorolac 0.4% was associated with significantly reduced ocular symptoms (burning/stinging, 25.0% vs 47.8%; foreign body sensation, 36.5% vs 58.9%; photophobia, 49.4% vs 71.3%; and tearing, 49.4% vs 71.3%). During the first 12 hours after surgery, fewer patients in the ketorolac 0.4% group had severe to intolerable pain (41.6% vs 84.4%) and required less escape oral pain medication (45.5% vs 90.4%). These results were statistically significant. There were no significant differences among the two groups for any reported adverse events.

**Ketorolac tromethamine 0.4% and cataract surgery**

A prospective, double-masked study including 40 eyes of 40 patients to compare the effectiveness and patient tolerance of ketorolac 0.4% (n = 20) compared with ketorolac 0.5% (n = 20) after routine phacoemulsification and lens implantation was conducted by Sandoval et al (Sandoval et al 2006). The assigned treatment was started 15 minutes prior to surgery and subjects were instructed to continue using it 4 times a day after surgery for 1 week and twice a day for the following 3 weeks. Assessments included best-corrected visual acuity (BCVA), slit-lamp (SL) cell evaluation, intraocular pressure (IOP), laser cell and flare measurements, and subjective patient tolerance. The authors found that at day 1 after surgery, 70% of patients in the ketorolac 0.5% group reported more symptoms mainly foreign body sensation and stinging/burning compared with 40% in the ketorolac group. No significant differences were found in BCVA, SL cell evaluation, IOP, and laser cell and flare measurements. The authors concluded that ketorolac 0.4% has the same effectiveness to reduce anterior segment inflammation after routine cataract surgery than ketorolac 0.5% with less patient discomfort.

Price and Price (2004) studied the efficacy of ketorolac 0.4% to control pain and discomfort associated with cataract surgery. In this single-center, double-masked, randomized, fellow-eye placebo-controlled trial, they included 25 subjects undergoing bilateral cataract extraction. The treatment (ketorolac 0.4% or artificial tears) was randomized to the first eye undergoing surgery and the second eye received the alternate treatment. Patients were instructed to use the assigned treatment four times a day starting 3 days prior to and 1 day after surgery. Patient cooperation and ocular pain or discomfort during surgery was evaluated by the surgeon while patients rated ocular pain and discomfort immediately and 24 hours postoperatively. The results showed that patients in the ketorolac 0.4% reported significantly less ocular pain during the 24 hours after the procedure than the control group (4% vs 39%). No significant differences among the groups were detected in patient cooperation, ocular pain and discomfort during or immediately after surgery. No adverse events occurred during this trial.

An assessment of the clinical benefit, relative efficacy, and pharmacokinetic-response curve of preoperative and postoperative ketorolac tromethamine 0.4% to improve outcomes during and after cataract surgery was performed by Donnenfeld et al (2006). In this prospective, double-masked study, patients were randomized to 1 of 4 groups of 25 subjects each. Group 1 received ketorolac 0.4% 4 times a day for 3 days and 3 times every 15 minutes in the hour before surgery; group 2, ketorolac 0.4% 4 times a day for 1 day prior to surgery and 3 times every 15 minutes in the hour before surgery; group 3, ketorolac 0.4% every 15 minutes in the hour before surgery; and group 4, had no predosing schedule and received vehicle only every 15 minutes in the
hour before surgery. Postoperatively, all subjects in the 4 treatment groups received ketorolac 0.4% for 3 weeks; the placebo group received vehicle. Preservation of preoperative mydriasis, phacoemulsification time and energy, operative time, corneal clarity, endothelial cell counts, postoperative inflammation, intraoperative and postoperative discomfort, complications, and incidence of clinically significant CME were evaluated. The authors reported that pupil size was maintained significantly better in groups 1 and 2 than in groups 3 and 4. The use of ketorolac 0.4% 1 and 3 days before surgery decreased surgical time, phacoemulsification time and energy, and endothelial cell loss; it improved visual acuity outcomes. CME was observed in 4% and 12% in groups 3 and 4, respectively while none of the patients is

Ketorolac tromethamine 0.4% and dry eye
A clinical study was conducted to determine the role of ketorolac 0.4% as adjuvant in the induction phase of chronic dry eye treatment when combined with cyclosporine-A. In this single-center, randomized, open labeled trial patients received either cyclosporine-A combined with artificial tears (n = 27) or with ketorolac 0.4% twice a day (n = 25). Corneal staining, Schirmer’s test (with anesthesia), tear break-up time (TBUT), ocular comfort, and an ocular surface index (OSDI) were assessed. The combined treatment with ketorolac provided significant greater improvement in ocular comfort at 2 weeks compared with the control group. Mean reduction in corneal staining as well as mean OSDI scores were greater in the cyclosporine-A + ketorolac 0.4% group at 2 and 6 weeks. No differences in mean change in Schirmer’s test and TBUT were observed. No corneal adverse events were noted (Schechter 2006).

Summary
Ketorolac tromethamine, a NSAID, has been widely used in ophthalmology. In reported clinical trials, it has been shown to be highly effective in relieving pain after radial keratotomy (RK) (Yee 1998; McDonald et al 1999), photorefractive keratectomy (PRK) (Rajpal and Cooperman 1999), laser in situ keratomileusis (LASIK) (Kosirukvongs et al 2001); and to treat allergic conjunctivitis (Yaylali et al 2003). Its efficacy to reduce inflammation after cataract surgery has been shown (Solomon et al 2001) and it has been compared with the efficacy of topical steroids after extra-capsular cataract extraction (Flach et al 1987; Simone et al 1999) and phacoemulsification (Solomon et al 2001; Holzer et al 2002).

The effectiveness of ketorolac 0.5% in the treatment of aphakic and pseudophakic macular edema has been also described (Flach 1987).

The relative new reformulation of ketorolac tromethamine 0.4% containing 20% less active ingredient indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery has been proven in different studies to be as effective as the original formulation to reduce anterior segment inflammation as well as to prevent CME after routine cataract extraction. Reduction in patient complaints, intraoperative maintenance of pupil size, improvement of visual outcomes, and it use as adjuvant in the initial treatment phase of chronic dry eyes has been also shown.

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References
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