Redefining the Treatment Paradigm for Post-operative Inflammation Control – The Role of Topical Non-steroidal Anti-inflammatory Drugs

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Abstract

Topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) are used in the treatment of post-operative ocular inflammation and pain following cataract surgery and for some other clinical applications of ophthalmology, including cystoid macular oedema. Products vary by their pharmacological properties, clinical efficacy and tolerability, which affect their place in therapy for new agents in Europe. The pharmacological properties of topical ophthalmic NSAIDs and their place in current treatment of post-operative ocular inflammation are discussed in this article, focussing on bromfenac, which has been submitted for approval by the European Medicines Agency (EMEA).

Keywords

Post-operative cataract surgery, ocular inflammation, ocular pain, cystoid macular oedema, non-steroidal anti-inflammatory drugs, bromfenac ophthalmic solution, prostaglandin inhibition

Despite recent technical advances in cataract surgery, the physical trauma of ocular surgery is still enough to induce significant post-operative ocular inflammation. Inflammation is a major risk factor for complications after ocular surgery, including pain, visual fluctuation, delays in visual recovery and wound healing, elevated intraocular pressure (IOP) and cystoid macular oedema (CMO). The blood–aqueous barrier (BAB), consisting of the endothelium of iris blood vessels and non-pigmented ciliary epithelium, is particularly vulnerable to surgical trauma during cataract surgery. Damage caused to the BAB may resolve quickly or last for up to several months after surgery.

Current treatment options available (both topical corticosteroids and topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs)) aim to reduce prostaglandin (PG) production through inhibition of steps in the arachidonic cycle. PGs have multiple pharmacological effects, including the induction of miosis, increase in the permeability of the blood–ocular barriers, conjunctival hyperaemia and changes in IOP. PGs also have chemokinetic properties, mediate humoural and cellular phases of inflammatory responses and play a role in pain response and allergic reactions. Therefore, inhibition of their production using topical treatment, therefore, aims to reduce post-operative ocular inflammation and pain.

Topical corticosteroids have frequently been used for the treatment of inflammation post-ocular surgery; however, concerns over serious side effects with corticosteroids, including elevation of IOP, progression of cataracts, increased risk of infection and worsening of corneal stromal melting have contributed to increased use of topical ophthalmic NSAIDs. NSAIDs appear to offer an improved risk/benefit balance with at least similar efficacy to the corticosteroids, but without most of the side-effects associated with corticosteroids. This is because NSAIDs act at a later stage of the arachidonic acid cycle than do corticosteroids, resulting in more specific anti-inflammatory effects and fewer adverse events.

Cyclooxygenases (COX) are involved in the inflammatory process. They catalyse the biosynthesis of eicosanoids from arachidonic acid to produce PGs. Although both COX-1 and COX-2 synthesise PGs, COX-2 may have important therapeutic implications in retinal diseases since it is the predominant isoform in human retinal pigment epithelium cells and is upregulated in response to pro-inflammatory cytokines. The topical ophthalmic NSAIDs inhibit the COX-1 and/or COX-2 enzymes that catalyse the production of PGs; the more selective and potent the inhibition of COX-2, in particular, the lower the production of PGs, as well as the lower potential for side-effects. Since inhibition of COX occurs later in the arachidonic acid cycle, it is predicted to result in fewer adverse events with NSAIDs compared with corticosteroids.

Although refinement of surgical techniques has resulted in significantly shortened durations of post-operative flare, the presence of risk factors such as diabetes, uveitis or iris trauma may cause major disruption of the BAB after cataract surgery, prolonging patient rehabilitation. Aqueous flare tends to be highest on the first day.
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after surgery, significantly declines until day 2 and continues to decline over the following months until pre-operative values are restored.\textsuperscript{30} The protein content of the aqueous humour has been considered to arise mainly in the anterior chamber, leading to the hypothesis that dilution of aqueous in the anterior chamber may be the mechanism by which pupil dilation decreases aqueous flare.\textsuperscript{29}

Cooled intraocular irrigation reduces post-operative BAB disturbance after cataract surgery, but this effect is short-lived and may even prolong disturbance of BAB at a low intensity.\textsuperscript{27} Various studies have reported reduction in aqueous flare following the application of tropicamide in normal patients, but only one study of the effect of mydriasis on aqueous flare in pseudophakic patients reported a decrease of 20\% after three hours with a tropicamide and phenylephrine solution.\textsuperscript{30} However, the relative reduction in flare after tropicamide pupil dilation in the pseudophakic eye has been shown to be similar to the reduction before surgery, making it unlikely that the decrease in flare after pupil dilation is a consequence of the dilution.\textsuperscript{30} Other possible explanations for the reduction in flare could be the decrease in background scatter from the iris as a result of dilation\textsuperscript{31} or even the direct pharmacological effect of tropicamide.\textsuperscript{32}

BAB disturbance within the first 48 hours after small-incision cataract surgery differs significantly among patients and, in fact, may not even be detected during this timeframe. Studies in the future may elucidate the clinical relevance of acute flares and determine whether they can predict long-term BAB disturbance.\textsuperscript{26}

Treatment regimens for post-operative ocular inflammation are diverse, mainly because of the lack of good evidence-based comparisons between corticosteroids and NSAIDs, as well as a lack of information concerning protocol issues such as ideal treatment duration. Physicians currently tend to adopt their own style of treatment regimens based on little more than their clinical experience.

Several factors contribute to the issues of treatment protocols for post-operative ocular inflammation. For example, cataract surgery is a procedure that occurs mostly in elderly patients, a population in which compliance to medication is known to be poor. A treatment with eye drops that have to be applied several times a day already presents a compliance problem, but can be particularly off-putting when associated with side effects such as stinging and burning, as is the case with eye drops for post-operative inflammation. A good rate of persistence and compliance to ophthalmic NSAID treatment is likely to result in improved efficacy. A faster recovery to pre-operative conditions would be expected to result in an improvement in the patient’s quality of life.

**Key Characteristics of an Ideal Topical Ophthalmic NSAID and Currently Approved NSAIDs**

Ophthalmic NSAIDs play several critical roles in cataract surgery. Through their inhibition of PGs, they prevent intra-operative miosis, manage post-operative inflammation, prevent and treat CME, as well as reduce pain and discomfort following surgery (see Figure 1).\textsuperscript{33}

For the treatment of post-ocular inflammation and pain following cataract surgery, an ideal topical ophthalmic NSAID should have several features. The NSAID should penetrate efficiently into all ocular tissues to allow rapid and sustained achievement of therapeutic levels, which may facilitate early and prolonged control of post-operative ocular inflammation and pain. It should possess high potency of COX inhibition to enable sustained control of pain and inflammation with a reduced risk of side effects. Unlike orally ingested forms, topically applied NSAIDs inhibit PG synthesis because they reach high enough levels in the ocular tissues.\textsuperscript{4}

Excessive intra-operative miosis is prevented by every commercially available topical NSAID,\textsuperscript{34,35} although the pharmacological effects on pupil size of these NSAIDs is varied, suggesting that PG-induced miosis and surgical technique are not the only contributory factors for surgically induced miosis.\textsuperscript{4} Since decrease in pupil size is a risk factor for vitreous loss and zonular breaks in intraocular lens implantation during cataract surgery, the ability to prevent intra-operative miosis is an important clinical benefit.\textsuperscript{4}

Post-operative ocular inflammation is partially caused by the release of PGs from uveal tissues, which may ultimately result in disruption of the blood–ocular barriers.\textsuperscript{4} Activation of phospholipase A2 after tissue injury causes the breakdown of cell membrane phospholipids to arachidonic acid, which is then converted to PGs by COX or to hydroxyl acids and leukotrienes by 5-lipoxygenase.\textsuperscript{36} This cascade of events affects multiple sites including the conjunctiva, sclera, cornea, aqueous humour, iris, ciliary body, choroids, retina, vitreous humour and optic nerve, which makes post-operative ocular inflammation a complex condition. Historically, prevention and treatment of ocular inflammation involved the use of topical corticosteroids due to their effect on COX and lipoxigenase pathways. However, more recently, the NSAIDs, bromfenac, diclofenac, ketorolac and nepafenac were approved by the FDA for the prevention and treatment of post-operative inflammation. Five topical ophthalmic NSAIDs (see Table 1), diclofenac, flurbiprofen, indomethacin, ketorolac and...
Surgery Post-operative

Table 1: Dosing Schedules of Topical Ophthalmic Non-steroidal Anti-inflammatory Drugs Approved in Europe for the Treatment of Post-operative Ocular Inflammation and/or Pain

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosing Schedule</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>One drop 4–6 times per day 24 hours before surgery, 24 hours post-operatively until resolution of the symptoms</td>
<td>Gaynes et al., 2008.13</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>One drop TID 24 hours before surgery, up to 3 weeks post-operatively</td>
<td></td>
</tr>
<tr>
<td>Nepafenac</td>
<td>One drop TID 30–120 minutes before surgery, first 2 weeks post-operatively, extended up to 3 weeks, as directed by the clinician</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>One drop QID Up to 28 days post-operatively</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>One drop QID Up to 28 days post-operatively</td>
<td></td>
</tr>
</tbody>
</table>

All the above-listed non-steroidal anti-inflammatory drugs are approved in Europe for the treatment of post-operative pain and inflammation, except flurbiprofen, which is not approved for post-operative use. "QID = four-times daily; TID = three-times daily."

Table 2: Proportion of Subjects with a Summed Ocular Inflammation Score Equal to Zero at Each Study Visit While on Monotherapy with Bromfenac

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Bromfenac</th>
<th>Placebo</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30 (8.4%)</td>
<td>2 (1.2%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>8</td>
<td>124 (34.8%)</td>
<td>23 (13.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>15</td>
<td>211 (59.3%)</td>
<td>46 (26.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>22</td>
<td>234 (65.7%)</td>
<td>67 (39.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>29</td>
<td>285 (80.1%)</td>
<td>85 (49.7%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Subjects who received a rescue medication are censored at the time of receipt of medication. The subject’s last score before receipt of the medication is used for analysis. *For bromfenac versus placebo and from the Cochran-Mantel-Haenszel test. Source: Donnenfeld et al., 2007.26

nepafenac, are approved in Europe for the management of post-operative inflammation, pain or both.

Although they are approved specifically for post-operative use, topical NSAIDs are also routinely used pre-operatively to better reduce inflammation as well as to prevent miosis during operative procedures, and this practice is supported by results from clinical studies.4,6 Furthermore, although studies have found no significant differences between the efficacy of NSAIDs and corticosteroids, NSAIDs do appear to be more effective at rebuilding the BAB.10,36 Diclofenac, ketorolac and nepafenac are indicated for the reduction of ocular pain following corneal refractive surgery and some physicians also use topically applied NSAIDs to reduce pain after corneal abrasions.

The efficacy and safety of topical ophthalmic NSAIDs in the control of ocular inflammation and pain are well known,11,13,16,22 however, two common local and transient adverse events following NSAID application are burning and stinging.2,3 For example, ketorolac and diclofenac cause transient burning and stinging in 40 and 15% of patients, respectively.8 These adverse events may affect the patient’s ocular comfort, compliance and persistence to treatment.

Although CMO is not a disease in itself, it is the most common cause of decline in vision following cataract surgery and is caused by the accumulation of fluid in the central retina. Approximately 20–30% of patients who undergo uncomplicated surgery develop angiographically proven CMO.19 However, a clinically significant decrease in visual acuity is seen only in approximately 1–2% of patients.20 If cataract extraction is complicated by posterior capsule rupture and vitreous loss, severe iris trauma or vitreous traction at the wound, there is a significantly higher incidence of up to 20% of clinically apparent CMO.20 Inflammation due to trauma from surgery and the destruction of the BAB are thought to be part of the pathogenesis of CMO, but the exact causes are unknown.29 Symptoms include blurry or reduced central vision and painless retinal inflammation or swelling, but CMO is predominantly asymptomatic. Permanent loss of vision from CME is rare.24 However, in high-risk patients routine measure of CMO by optical coherence tomography should be conducted following cataract surgery as part of the follow-up schedule.25 There is no approved therapy for prevention of CMO despite the evidence supporting the potential benefits of NSAIDs for the treatment of this condition.21,22 Studies to date have investigated the use of NSAIDs in conjunction with corticosteroids. Since the two have somewhat different mechanisms of action, their combination may offer synergistic activity to minimise post-operative ocular inflammation.2,23

PGs are first-line therapy for the treatment of glaucoma and ocular hypertension and are used by a significant number of patients admitted for cataract surgery. However, PGs are released naturally from the iris and ciliary body during cataract surgery and migrate to the retina. Additional PG therapy is thought to contribute to the onset of post-surgery CMO. Therefore, it has been advocated to discontinue the use of PGs up to two weeks before surgery and replace with an alternative form of therapy.26

Future Treatment Options – Can Less Frequent Dosing Improve Compliance with Ophthalmic Therapy?

The currently available topical ophthalmic NSAIDs have frequent dosing schedules (three- or four-times daily). There is evidence from several clinical studies, mainly in glaucoma patients, suggesting that improvements in patient compliance can be associated with less frequent dosing.14,27 Therefore, it may be predicted that an NSAID with a less frequent dosing schedule could potentially offer improved patient compliance and persistence to treatment. It has also been suggested that reduced dosing schedules may reduce corneal epithelial toxicity since the patient’s exposure to the drug and to potentially toxic preservatives would be reduced.28

The twice-daily topical ophthalmic NSAID, bromfenac, is approved in Japan and the US (in 2000 and 2005, respectively), for the treatment of post-operative inflammation and/or ocular pain after cataract surgery, and is currently undergoing European regulatory review. It may, therefore, become another treatment option in this market.

The Pharmacokinetic Profile of the Bromfenac Ophthalmic Solution

Bromfenac is a derivative of amfenac that includes an additional bromonion ion. This enhances the lipophilicity of bromfenac, which in turn may facilitate penetration of the compound into all ocular tissues and thereby enhance the drug’s potency.29,30,31 This pharmacokinetic profile will likely be the major contributing factor to the molecules’ deep tissue penetration, early and sustained drug levels demonstrated in
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in vitro studies have shown that bromfenac consistently provides highly potent inhibition of COX-2 relative to other NSAIDs. Invariably, these studies have shown that the inhibition of prostaglandin synthesis with bromfenac, and hence in vitro potency, as measured by its high COX-1/COX-2 IC50 ratio, was preferentially through COX-2 inhibition, resulting in greater inhibitory effect than most other available NSAIDs. As these are in vitro studies that had different designs and used different laboratory technologies, it is difficult to translate these results into clinical practice. Penetration of ocular tissues is also thought to be an important determinant of the efficacy of ophthalmic NSAIDs. Studies on bromfenac have demonstrated that the drug penetrates rapidly and deeply throughout the ocular tissues, which makes twice-daily dosing sufficient.

Clinical Efficacy and Safety of the Bromfenac Ophthalmic Solution

One of the first in vivo studies demonstrating the efficacy of topical bromfenac on ocular inflammation, performed in Japan, showed that bromfenac was almost 11 times more potent than pranoprofen on ocular inflammation, performed in Japan, showed that bromfenac was almost 11 times more potent than pranoprofen.

In clinical practice, an optimal ophthalmic NSAID therapy will have highly effective anti-inflammatory activity, a rapid onset of action that produces sustained relief of inflammation, a formulation that is comfortable and well tolerated, and a convenient dosing regimen. Based upon its features, bromfenac seems to satisfy these parameters.
Twice-daily dosing with bromfenac ophthalmic solution is effective for treatment of ocular inflammation after cataract surgery without the need for pre-treatment. Moreover, twice-daily bromfenac demonstrates an early and sustained level of clinical action with little burning and stinging and minimal adverse events. The twice-daily dosing schedule makes bromfenac a more convenient treatment regimen for inflammation compared with other NSAIDs, potentially enhancing patient compliance and adherence to the recommended dosing schedule. Other factors such as less exposure to the preservative, benzalkonium chloride, in NSAID solutions due to less dosing frequency (twice daily) and no shaking required before administration make bromfenac an attractive option. A once-daily version of bromfenac will, potentially, further enhance patient compliance and adherence.
72. Flach AJ, Dolian BJ, Donahue ME, et al., Comparative effects of ketorolac 0.5% or diclofenac 0.1% ophthalmic solutions on inflammation after cataract surgery, Ophthalmology, 1999;106:1775–9.
77. Data on file, ISTA Pharmaceuticals, Inc.