New Look at Ocular Inflammation Control – Powerful and Fast-acting Twice-daily Bromfenac for a Novel Standard in the Treatment of Inflammation

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Abstract

Inflammation in the eye arising from various factors – including allergy, infection, injury and surgery – can have serious consequences, and can continue long after the cause is removed, resulting in permanently damaged vision. The treatment of ophthalmic inflammation after surgery has traditionally consisted of topical corticosteroids, but adverse events such as delayed healing, rise in intraocular pressure and increased susceptibility to microbial infections have driven the search for alternative treatments. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used as alternatives to steroid treatments but also have limitations and cause adverse events. Bromfenac has emerged as a potent and safe treatment for inflammation after cataract surgery. Its unique chemical structure makes it a highly lipophilic molecule that penetrates all major ocular tissues in a rapid and sustained manner. It is also a potent inhibitor of the enzyme cyclo-oxygenase-2, which is believed to be the primary mediator of ocular inflammation. These properties permit less frequent dosing (twice-daily [BID]) and greater patient tolerability. A body of efficacy and safety data support use of bromfenac in this indication and it compares favourably with other NSAIDs and steroids in limiting post-operative inflammation. NSAIDs and corticosteroids have different, potentially synergistic effects. However, benefits specific to NSAIDs include lowering prostaglandin E-induced intraocular pressure elevation, no increased risk of secondary infections and stabilisation of the blood–aqueous barrier. With increasing demand for ophthalmic surgery, bromfenac and other treatments are likely to be important components in the treatment of inflammatory conditions after cataract surgery, decreasing pain and contributing to favourable visual outcomes.

Keywords

Bromfenac, ophthalmic non-steroidal anti-inflammatory drugs, ocular inflammation, cystoid macular oedema, ocular pain

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Ocular Inflammation and Cataract Surgery

Ocular inflammation – characterised by redness, swelling, and/or pain – may occur as a result of irritation or trauma to the eye.[1] It is an important concern following cataract surgery because it may lead to complications that ultimately can compromise visual outcome.

Surgical trauma initiates the arachidonic acid cascade, in which arachidonic acid is released from membrane phospholipids by the action of phospholipase A_2. A family of chemically distinct prostaglandins (PGs) and leukotrienes are produced from the arachidonic acid. PGs are produced by activation of cyclo-oxygenase (COX) enzymes, and the COX-2 isoform is believed to be the primary mediator of ocular inflammation. PGs are important in the development of post-operative complications, with associated clinical symptoms including hyperaemia, miosis, impaired vision, pain and diminished visual acuity secondary to cystoid macular oedema (CME).[1]

Treatments for Ocular Inflammation

The two main treatments for ocular inflammation are topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids interfere with the activity of phospholipase A_2, thereby inhibiting the release of arachidonic acid metabolites, including PGs.[2] By contrast, NSAIDs non-specifically and irreversibly inhibit the synthesis of PGs by directly interfering with the activity of COX-1 and COX-2 (see *Figure 1*).[2]

Corticosteroids

The corticosteroids, which are considered the gold standard for the treatment of ocular inflammation, are associated with an increased incidence of adverse events that warrant their judicious use.[3] These adverse events include a rise in intraocular pressure (IOP), increased susceptibility to microbial infections due to a suppressed host immune response and retardation in corneal epithelial and stromal wound healing. Steroids may not be safe for extended periods because their prolonged use is associated with the development of glaucoma, visual acuity defects, loss of visual field and posterior subcapsular cataract formation.[3] Cataract surgeons have therefore been interested in alternative treatments for post-operative pain and inflammation, with effectiveness equivalent to that of steroids but with fewer complications.

Non-steroidal Anti-inflammatory Drugs

The NSAIDs are safer alternatives to corticosteroids for the treatment of ocular inflammation. They comprise several chemically heterogeneous classes of drugs that possess potent COX inhibitory activity.[1]

Topical NSAIDs are classified into six groups based on their chemical composition: indoles, phenyl acetic acids, phenylalkanoic acids, salicylates, fenamates and pyrazolones. Salicylates, fenamates and pyrazolones are considered too toxic to be used in the eye.[4,5]

Most NSAIDs are weakly acidic drugs that ionise at the pH of lacrimal fluid, thus limiting their permeability through the ionic cornea, which has an isoelectric point (pI) of 3.2.[6] Reducing the pH of the formulation increases the un-ionised fraction of the drug, enhancing permeation. Being acidic, NSAIDs are inherently irritant, and reducing the pH of the formulation further increases their irritation potential, and also decreases their aqueous solubility.[7] In addition, the anionic nature of NSAIDs leads to the formation of insoluble complexes with cationic quaternary ammonium preservatives, such as benzalkonium chloride.[8,9] Thus, it has proved difficult to formulate NSAID formulations that are comfortable when applied topically to the eye.

In the EU, several NSAIDs are approved for the treatment of post-operative inflammation after cataract surgery (see *Table 1*).[10–15] Bromfenac 1mg/ml eye drops (Yellox, Croma Pharmaceuticals) recently joined this list, when the Committee for Medicinal Products for Human Use (CHMP), part of the European Medicines Agency (EMA), adopted a positive opinion. CHMP recommended the granting of a marketing authorisation for bromfenac 1mg/ml, which is intended for the treatment of post-operative ocular inflammation, with a twice-daily dosing schedule. Yellox received the European Commission Marketing Authorization at the end of May 2011.[15] A similar once-daily formulation of bromfenac (Bromday, ISTA Pharmaceuticals) was also recently approved by the US Food and Drug Administration (FDA).[16]

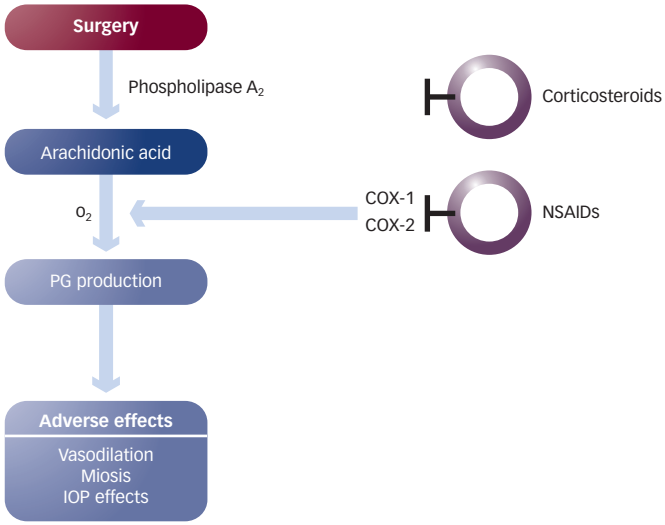
Ophthalmic NSAIDs currently play four principal roles in ophthalmic surgery. These include prevention of intra-operative miosis during cataract surgery, management of post-operative inflammation, reduction in pain and discomfort after cataract and refractive surgery and prevention and treatment of CME after cataract surgery.[17,18] One of the benefits of pre-operative NSAIDs, maintaining a dilated pupil, is often overlooked. A large pupil can be a good determinant of post-operative inflammation and recovery of visual acuity.

Studies comparing NSAIDs with corticosteroids have demonstrated no significant difference in results between these treatments.[4,19,20] However, NSAID treatment appears to be more effective than topical corticosteroids in re-establishing the blood–aqueous barrier.[20,21] Many studies that analysed the effects of NSAIDs on post-operative inflammation included the concurrent administration of corticosteroids, and these suggested that NSAIDs and corticosteroids have the potential for synergistic activities.[17,21,22] The beneficial effects of NSAIDs over corticosteroids include stabilisation of IOP, provision of analgesia and reduction in the risk of secondary infections.[23]

Introduction to Bromfenac

Bromfenac was initially approved in Japan for the treatment of post-operative inflammation, conjunctivitis, blepharitis and scleritis. The FDA approved bromfenac for the treatment of post-operative inflammation and pain following cataract surgery in 2005. Bromfenac

Figure 1: Mode of Action of Corticosteroids and Non-steroidal Anti-inflammatory Drugs



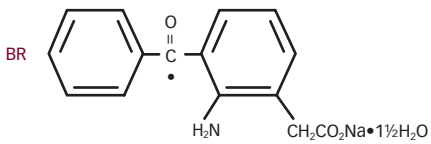
COX = cyclo-oxygenase; IOP = intraocular pressure; NSAIDs = non-steroidal anti-inflammatory drugs; PG = prostaglandin.

Table 1: Commercially Available Topical Non-steroidal Anti-inflammatory Drugs Indicated For Inflammation Associated with Cataract Surgery in Europe

Generic	Brand	Manufacturer	Formulation	Dosing
Ketorolac	Acular	Allergan	0.5% solution	TID
Diclofenac	Voltaren	Novartis	0.1% solution	QID
Nepafenac	Nevanac	Alcon	0.1% suspension	TID
Flurbiprofen	Ocufen	Allergan	0.03% solution	QID
Indomethacin	Indocollyre	Bausch & Lomb	0.1% solution	QID
Bromfenac	Yellox	Croma Pharmaceuticals	1mg/ml eye drop solution	BID

BID = twice daily; QID = four times daily; TID = three times daily.
Reproduced from package inserts.[10–15]

Figure 2: Chemical Structure of Bromfenac[24]



BR = bromfenac.

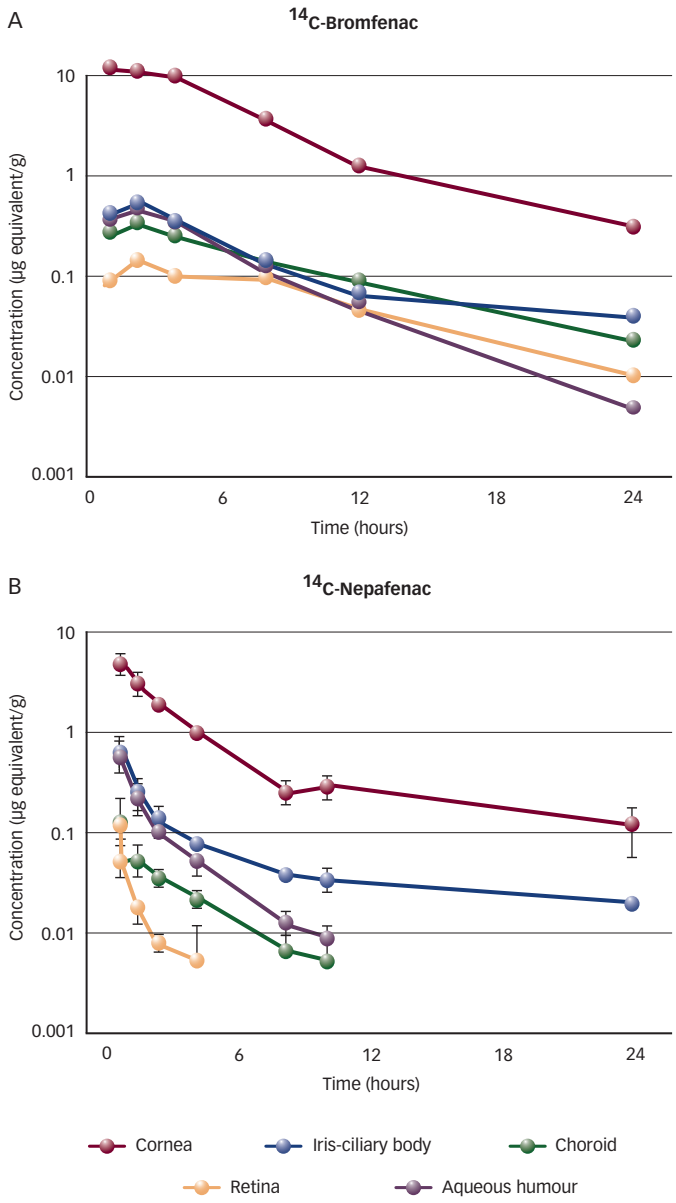
1mg/ml eye drop solution (Yellox, Croma Pharmaceuticals) was submitted to the EMA for centralised approval in 2009 throughout the EU. Approval has now been granted, and Yellox is the first ocular NSAID dosed two times per day for use by patients in Europe.

Molecular Structure and Properties

Bromfenac sodium is chemically designated as sodium 2-amino-3-(4-bromobenzoyl) phenyl acetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1½ \cdot H_2O$. The structural formula for bromfenac is shown in *Figure 2*.

Amfenac is a highly potent inhibitor of both COX-1 and COX-2, but is unable to penetrate the corneal epithelium.[25] Two NSAIDs have been developed to exploit the anti-inflammatory potency of amfenac within the eye: nepafenac and bromfenac.

Figure 3: Two Separate Animal Studies, Conducted under a Common Protocol Demonstrating Ocular-tissue Concentrations of ^{14}C-bromfenac (A) or ^{14}C-nepafenac (B) following a Single Topical Dose (Three Times the Commercial Strength) to Rabbits



A: Detectable levels in all ocular tissues through the 24-hour time-point; B: Retina not detectable at six hours and aqueous humour and choroid not detectable at 12 hours. Reproduced from Baklayan et al., 2008.[24]

Nepafenac is an inactive precursor of amfenac, which can penetrate the corneal epithelium. Nepafenac must then be converted to the active amfenac within the eye before it can have any anti-inflammatory effect.[25] However, there is evidence that a substantial proportion of nepafenac is not converted to amfenac within the eye, leading to reduced PG inhibition.[26]

Bromfenac is structurally identical to amfenac, with the key exception of a bromine atom at the fourth carbon atom of the phenyl ring.[27] The addition of the bromine atom imparts important characteristics to the bromfenac molecule that distinguish it from other NSAIDs.[28] First, bromine enhances the lipophilicity of the molecule and facilitates its penetration through the cell membrane of various tissues, including ocular tissues. Second, bromination at the fourth position of the phenyl ring increases the duration of analgesic and anti-inflammatory activity.[1]

Penetration of Ocular Tissues

The unique bromination of amfenac can increase lipophilicity, resulting in enhanced penetration of bromfenac through the cornea and other ocular tissues. Baklayan et al. presented data from two separate but similar studies in which bromfenac and nepafenac were administered at three times the commercial dose in an animal model.[24] Bromfenac achieved measurable levels in all major ocular tissues that were detectable at 24 hours, but no significant levels of nepafenac/amfenac were detected in the aqueous humour and choroid after 12 hours and in the retina after six hours (see *Figure 3*). In the same report, Baklayan et al. presented data from a similar study in which bromfenac was instilled at normal commercial strength, with similar results; peak concentrations of bromfenac were observed at or before two hours, with measurable levels in all major ophthalmic tissues over 24 hours.

Sustained Therapeutic Activity

In humans, absorption of bromfenac occurs within 15 minutes, with peak aqueous humour concentration at 150–180 minutes (see *Figure 4*).[24,29] These early peak concentrations in aqueous humour remain above the concentration required to inhibit COX-2 by 50% (IC_{50}) for more than 12 hours, suggesting that BID dosing is sufficient to maintain anti-inflammatory activity.

Cyclo-oxygenase Inhibition

NSAIDs vary in their relative potency against COX-1 and COX-2. In the post-cataract surgery setting, COX-2-specific activity is important because it is this form of the enzyme that is believed to be the primary mediator of ocular inflammation.[1] Although the exact plasma concentration of bromfenac following ocular administration is unknown, the relative potency is assessed by determining the concentration of drug required to inhibit COX enzyme activity by 50% (IC_{50}). A smaller IC_{50} value signifies greater inhibition of the enzyme.[29]

A number of *in vitro* studies have been conducted. Such studies have shown that the inhibitory effects of bromfenac on COX-2 are 3.7 times greater than those of diclofenac,[30] 6.5 times greater than those of amfenac[31] and 18 times greater than those of ketorolac.[32] In another study, Kida et al. compared the ophthalmic NSAIDs, diclofenac, ketorolac, nepafenac and bromfenac, and found that bromfenac was approximately three to four times more potent than the other three formulations in inhibiting the COX-2 enzyme (see *Table 2*).[33] It should be noted that the study designs and technologies used in *in vitro* studies differ, making interpretation of the clinical impact difficult. However, these studies have invariably shown that the inhibition of PG synthesis with bromfenac – and hence *in vitro* potency, as measured by its high COX-1/COX-2 IC_{50} ratio – was preferentially through COX-2 inhibition, resulting in greater inhibitory effect than most other available NSAIDs;[1,10,15,29] therefore, bromfenac is a unique and highly potent NSAID.

Clinical Efficacy

Two phase III, double-masked, placebo-controlled clinical trials were performed in the US to evaluate the efficacy, safety and tolerability of bromfenac ophthalmic 1mg/ml eye drop solution in treating post-operative inflammation and pain after cataract surgery. The subjects were randomly assigned to either bromfenac twice daily for

14 days (n=356) or placebo (n=171). The primary end-point of the trial was the proportion of patients achieving summed ocular inflammation score (SOIS) = 0 at 15 days (14 days of treatment), although SOIS was additionally evaluated before and after day 15.[34]

A pooled intent-to-treat (ITT) analysis of these two studies was conducted, including all 527 patients. It revealed that significantly more bromfenac-treated (64% [228/356]) than placebo patients (43.3% [74/171]; p<0.0001) had achieved SOIS = 0 on day 15. It should be noted that the ITT analysis included all patients in their assigned group, regardless of whether they actually received the assigned treatment. Also, the results include the effects of any alternative anti-inflammatory regimens administered after the start of the trial (given, for instance, because of adverse effects or lack of efficacy).[34]

A separate analysis of the data while patients were on their assigned treatment only, excluding the effects on any rescue medication, was conducted ('last observation carried forward' in those patients requiring a change in regimen). This analysis demonstrated a rapid effect of bromfenac. In all, 8.4% (30/356) of patients in the active treatment group achieved clearance of ocular inflammation (SOIS = 0) by day three compared with 1.2% (2/171) in the placebo group (p=0.0012). At day 15, 59.3% (211/356) of patients in the bromfenac group had a SOIS = 0 versus 26.9% (46/171) with placebo (p<0.0001) (see *Figure 5*).[34]

The phase III placebo-controlled clinical trials employed stringent entry criteria, including no pre-dosing or concomitant steroids. Furthermore, all of the patients had moderate to severe ocular inflammation (mean baseline SOIS of 3.7) after cataract surgery.[34]

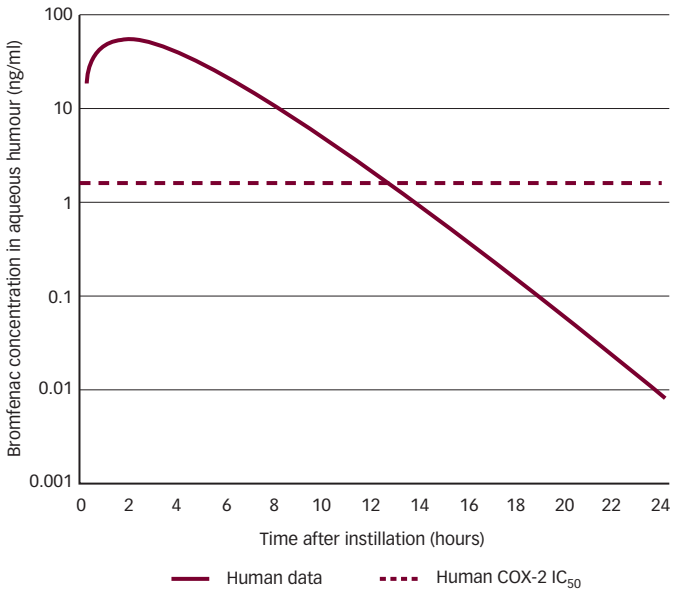
Miyanaga et al. prospectively randomised 72 patients who underwent cataract surgery to treatment with one of three regimens: 0.1% bromfenac, 0.1% betamethasone for one month and then fluorometholone for one month, or both agents. The patients were followed throughout the first two post-operative months. The group found no significant difference in best corrected visual acuity, IOP, aqueous flare or corneal thickness, showing that bromfenac was as effective as the steroid regimen after cataract surgery.[35] Another multicentre, open-label, clinical study divided 111 subjects into two treatment groups, each of which received two drops of bromfenac or diclofenac pre-operatively and then bromfenac twice-daily or diclofenac three times daily with concomitant ophthalmic steroid and anti-infective for four weeks, beginning the day after surgery. Anterior chamber cells and flare and corneal epithelial disorder in the two groups showed no statistically significant difference after day 7.[36]

Adverse Event Profile

In the safety evaluation in the two phase III clinical trials described above, bromfenac treatment was not associated with treatment-related systemic adverse effects. Overall, the incidence of adverse events was lower in the bromfenac treatment group than in the placebo group (33.7 versus 47.4%; p=0.0027). Iritis (7.0 versus 18.1%; p=0.0001) and eye pain (4.2 versus 11.7%) – among the most common ocular adverse events – were half as frequent with bromfenac as with placebo.[29,34] In separate pooled phase III data from the US and Japan (n=973), bromfenac was generally well tolerated, with only 3.4% of patients experiencing one or more adverse events.[37]

It should be noted that more than 20 million patients have been treated with bromfenac worldwide over the past nine years, which

Figure 4: Projection Showing that Concentrations of Bromfenac Sodium Hydrate Ophthalmic Solution 0.1% in the Aqueous Humour Remain above the IC_{50} (1.5ng/ml) for COX-2 in Humans for 12 hours after Instillation of a Single Drop



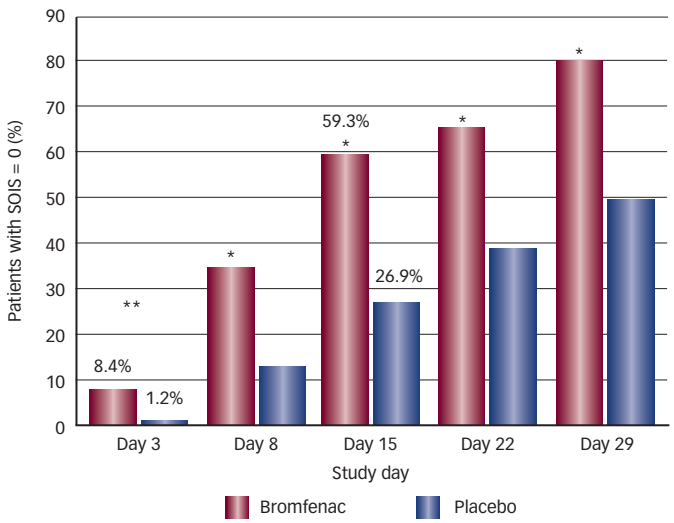
Bromfenac sodium hydrate ophthalmic solution 0.1% is equivalent to bromfenac ophthalmic 1mg/ml eye drop solution. Reproduced from Donnenfeld et al., 2006.[29] COX = cyclo-oxygenase.

Table 2: IC_{50} and Relative Potency (versus Bromfenac) for Four Commercially Available Ophthalmic Non-steroidal Anti-inflammatory Drugs

	IC_{50} (µmol/l)	Relative Potency (versus Bromfenac)
Bromfenac	0.0075	1.0
Amfenac	0.0204	0.37
Ketorolac	0.0279	0.27
Diclofenac	0.0307	0.25

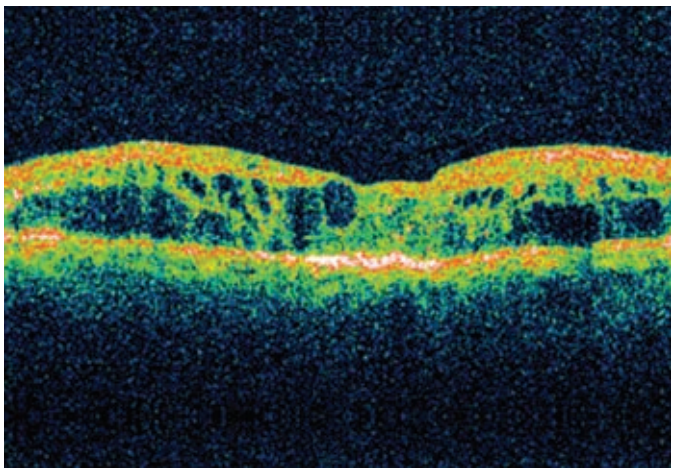
Reproduced from Kida et al., 2007.[33]

Figure 5: Proportion of Subjects with a Summed Ocular Inflammation Score Equal to Zero at Each Study Visit while on Assigned Treatment Only in the Two-phase III Clinical Trials



**p<0.0001 versus placebo; **p=0.0012; SOIS = summed ocular inflammation score.*

Figure 6: Optical Coherence Tomography Shows Intra-retinal Cystic Spaces Consistent with Cystoid Macular Oedema



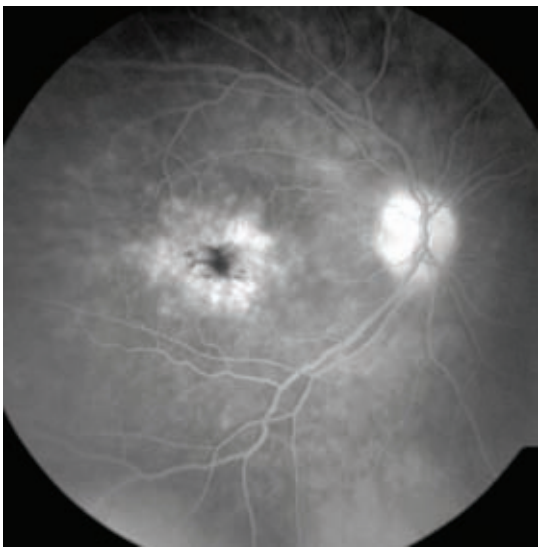
Reproduced from Cho et al., 2009.[56]

Table 3: Pathological Conditions Causing Cystoid Macular Oedema

Inflammatory disorders: intraocular surgery, uveitic syndromes, laser procedures
Retinal vascular disease: diabetic retinopathy, retinal vein occlusion, hypertensive retinopathy
Choroidal vascular disease: choroidal neovascularisation
Tractional maculopathies: epiretinal membrane, vitreomacular traction syndromes
Drug reactions: epinephrine, prostaglandin analogues, nicotinic acid, tamoxifen, glitazones
Inherited retinal dystrophies: retinitis pigmentosa
Retinal detachment: exudative, rhegmatogenous
Intraocular tumours: choroidal melanoma
Optic nerve head abnormalities: diabetic/hypertensive papillopathy, neuro-retinitis, optic nerve pits/colobomas
Idiopathic

Reproduced from Cho et al., 2009.[56]

Figure 7: Fluorescein Angiography (Right Eye)



The recirculation phase of the angiogram demonstrates a classic 'petalloid' appearance consistent with cystoid macular oedema. Reproduced from Cho et al., 2009.[56]

has allowed a substantial amount of post-marketing and surveillance data to be collected.[38] A post-market surveillance survey in Japan compiled treatment data from 3,425 patients treated with bromfenac 0.1%. There were 56 cases (incidence of 1.64%) of adverse events reported.[39] In addition to the post-market surveillance survey, data from spontaneous adverse events reporting in Japan was collected between 15 January 2000 and 14 January 2006. During this time, approximately 7.8 million patients were treated with bromfenac ophthalmic solution (0.1%), with over 10 million vials distributed. In the literature so far, a total of 16 serious ocular adverse events were spontaneously reported (0.0002%).[29]

Convenience, Tolerability and Compliance

Bromfenac ophthalmic 1mg/ml is the first and only twice-daily topical ocular NSAID indicated in Europe for the treatment of post-operative inflammation in patients who have undergone cataract extraction. The twice-daily dosing schedule is convenient for the post-cataract surgery patient population and may enhance patient compliance and adherence to the recommended dosage schedule. Multiple clinical studies have shown that patient compliance in administering medications, especially in older subjects, improve with less frequent dosing.[40,41]

A further convenience factor for bromfenac in comparison with other NSAIDs is that bromfenac ophthalmic solution does not require shaking before administration. Also, less frequent dosing means reduced exposure to the preservative benzalkonium chloride.[34] Higher levels of benzalkonium chloride have been associated with corneal epithelial dysfunction.[42] However, the level of benzalkonium chloride in bromfenac is 0.005%, which is as low as or lower than that in any commercially available preserved NSAID.

Cystoid Macular Oedema

CME is a painless disorder that affects the central retina or macula. Since its first recognition and description in 1974,[43] CME has been recognised as the most common cause of decreased vision post-operatively in uneventful cataract surgery.[44] CME is caused by cystic accumulation of intra-retinal fluid in the outer plexiform and inner nuclear layers of the retina, as a result of the breakdown of the blood-retinal barrier (see *Figure 6*).[45] CME can be a serious consequence of numerous ocular procedures and conditions, including cataract surgery, ocular inflammatory disease, retinal vascular diseases and tractional disorders (see *Table 3*).[46] It is not a disease itself; rather, it is the end-point of a variety of processes that lead to the accumulation of fluid in the central retina.[47]

Clinical CME has historically been defined as a reduction in vision to 20/40 or less that is attributable to ophthalmoscopically or angiographically visible CME.[48] It can present with symptoms of blurred or decreased central vision, and painless retinal inflammation or swelling. In post-operative CME, vision loss is usually temporary, with infrequent incidences of permanent visual loss.[18] CME is often asymptomatic and may only be detected with optical coherence tomography (OCT) (see *Figure 6*) or fluorescein angiography (see *Figure 7*).[49]

Studies suggest that the rate of clinical CME is in the range of 1–2%,[50] whereas the incidence of angiographic CME may be as high as 9–19%.[51,52] OCT is another technology that can be used to evaluate macular thickness. It is more sensitive than other techniques and

can detect even modest changes in retinal thickness. Reported CME incidence rates with OCT include 4–10.9% (at four weeks after cataract surgery) and as high as 41%, although OCT-based definitions of CME differed in these studies.[53,54]

Post-operative increase in retinal thickness correlates with a decline in post-operative contrast sensitivity. It is believed that patients with even a subtle 10 micron change in retinal thickness (not frank CME) can experience changes in contrast sensitivity and might have an effect of visual acuity. NSAIDs may therefore be beneficial in reducing the risk of post-operative retinal thickening and of often subtle loss of contrast sensitivity.[55]

There are no properly designed clinical trials of corticosteroids in the prevention and treatment of CME.[54] Although very few ocular NSAIDs have been approved for the prevention and treatment of CME, topical NSAIDs have increasingly been used over the past two decades. NSAIDs, specifically indomethacin, first demonstrated efficacy for the prevention of pseudophakic CME in 1977,[57] and another recent study has also demonstrated that indomethacin is an effective drug for preventing and treating pseudophakic CME. Pre-dosing lowered the CME risk, and longer post-operative treatment up to four to six weeks also lowered the risk, particularly in inflammation-prone patients.[58] However, it was not until much later that ketorolac 0.5% and diclofenac 0.1% proved effective in treating this condition. Ketorolac 0.5% was efficacious in decreasing post-operative macular oedema when used prophylactically after cataract surgery,[59] while diclofenac 0.1% was more effective than betamethasone in preventing angiographic CME and blood–aqueous barrier disruption after small-incision cataract surgery.[60]

While no randomised trials have yet been conducted to test the ability of the two new-generation topical NSAIDs – nepafenac and bromfenac – in treating CME, numerous reports suggest that these agents also have activity against this condition.[61] A study by Wolf et al. compared the incidence of visually significant pseudophakic macular oedema after uneventful phacoemulsification in patients treated post-operatively with topical prednisolone and those treated with topical prednisolone and nepafenac 0.1% suspension. They found that those treated with topical prednisolone alone had a significantly higher incidence of visually significant pseudophakic macular oedema.[22] Wittpenn et al. also corroborated the synergistic effect of prednisolone and NSAIDs, showing that adding perioperative ketorolac 0.4% to post-operative prednisolone significantly reduced the incidence of CME and macular thickening in cataract surgery patients already at low risk for this condition.[55] In that study, there was no statistically significant difference in contrast sensitivity between the two treatment groups. However, a subanalysis detected a statistically significant relationship between greater retinal thickening and decreased contrast sensitivity that warrants further study. If increasing retinal thickness leads to a decrease in contrast sensitivity, then it is possible that sublinical CME – or any other condition that leads to increased retinal thickness – may reduce quality of vision, even if it does not have a discernible effect on visual acuity.

Bromfenac has also shown some potential to reduce the risk of CME, with a reported 70% lower incidence of CME compared with placebo (1.4% in the bromfenac group versus 4.7% in the placebo group).[34] Less retinal thickening at four and six weeks has also been shown in another study, which compared bromfenac sodium ophthalmic solution versus a steroidal solution after cataract surgery in patients with non-proliferative diabetic retinopathy.[62] Rho et al. compared bromfenac ophthalmic 1mg/ml eye drop solution with diclofenac 0.1% and ketorolac 0.5% for the treatment of acute pseudophakic CME. Sixty-four eyes with documented CME after uncomplicated cataract surgery were randomised to receive bromfenac twice-daily, diclofenac four times daily, or ketorolac four times daily for three months. After the treatment period, all three treatment groups achieved statistically significant visual improvement, evaluated by the Early treatment diabetic retinopathy study letter gained over baseline. Although the difference between the groups were not significant, there was a trend towards greater improvement for the bromfenac group.[63] Rho et al. concluded that twice-daily bromfenac was as effective as diclofenac 0.1% or ketorolac 0.5% dosed four times daily.[63]

Conclusion

In an ageing population, ophthalmic surgery is likely to become more common. However, cataract surgery is not without risks, and inflammatory complications – as a result of PG production – can diminish visual outcome and increase costs. Therefore, the need for anti-inflammatory treatments will only increase.

Corticosteroids have been the standard treatment for ocular inflammation,[1] but NSAIDs are increasingly favoured because their side effects are generally less serious or frequent than those of corticosteroids.[1] The clinical effectiveness of NSAIDs in the treatment of CME remains to be completely elucidated. NSAIDs offer similar anti-inflammatory efficacy to corticosteroids and may reduce the risk of CME,[1,36] especially when the two classes are used in combination.[17] Most studies on CME compared a combination of NSAID plus steroid versus a steroid alone, and showed a lower incidence of CME with the combination therapy.[22,57–59,61] Additional benefits of NSAIDs include their mydriatic effects during surgery, reduced PG-induced elevation in IOP, no increase in risk of secondary infections and stabilisation of the blood–aqueous barrier.

The NSAID bromfenac – recently introduced to the European market – has important benefits in the management of ocular inflammation. The unique chemical structure of bromfenac makes it a highly lipophilic molecule that rapidly penetrates to produce early and sustained drug levels in all ocular tissues. Also, it potently inhibits COX-2, which is the key enzyme in producing PG-mediated complications. Bromfenac's potency and penetration allow twice-daily dosing. The efficacy and safety of bromfenac ophthalmic 1mg/ml eye drop solution have been demonstrated in two large, multicentre phase III trials and through extensive global experience. This convenient dosing schedule and comfortable solution may enhance patient compliance. Bromfenac can therefore be considered the new standard in NSAID efficacy, thanks to its ease of use and rapidity of action.

Further clinical investigations will explore the expanding use of bromfenac in a variety of other, already investigated clinical settings including (but not limited to) the management of ocular inflammation and pain following cataract surgery, acute and chronic pseudophakic CME, allergic conjunctivitis and anterior uveitis.

Stress of surgery on the visual system can compromise visual outcome and significantly reduce patient satisfaction. This drug holds great promise for all patients expecting enhanced quality of vision following cataract extraction. ■

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