Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for decades to relieve pain and fever. These agents block the cyclo-oxygenase pathway which converts arachidonic acid into endogenous prostaglandins, which are the most potent mediator of inflammation. Hence if prostaglandin production is inhibited, there is less inflammation. Unlike steroids, NSAIDs do not have a cyclopentanoperhydro phenanthrene skeleton.

Non-steroidal anti-inflammatory drugs have been used in ophthalmology as a topical agent for more than three decades. Topical Indomethacin was first used as a pre-operative drug to decrease post-operative inflammation after cataract surgery. It was formulated as a sesame seed oil solution, but due to local irritation and low efficacy its use was discontinued. Newer drugs which had increased penetration into the anterior chamber and more efficacy, slowly replaced the old ones. There are presently four classes of topical NSAIDs – indoles, phenylacetic acids, phenylalkanoic acids and arylacetic acids. Indomethacin is an indole, Diclofenac and Bromfenac are phenylacetic acids; Flurbiprofen, Suprofen and Ketorolac are phenylalkanoic acids and Nepafenac is a pro-drug arylacetic acid. On topical application, the NSAIDs penetrate the eye and have an aqueous humor level adequate to inhibit prostaglandin synthesis. Topical NSAIDs are commonly used in the management and prevention of ocular inflammation and cystoid macular edema related to intraocular surgery. Other common uses are maintenance of mydriasis during cataract surgery, reduction of discomfort after surgery and laser or in allergic conjunctivitis. Many clinical studies have also suggested a role of topical NSAIDs for the treatment of inflamed pinguecula, pterygia, strabismus, glaucoma, refractive errors and corneal abrasions.

Persistent inflammation in the anterior chamber leads to cystoids macular edema (CME), which is the most common cause of decrease in visual acuity after uncomplicated cataract surgery. Topical NSAID decrease the incidence of CME by decreasing the postoperative inflammation. Concurrent administration of corticosteroids and NSAIDs may prove a synergistic activity resulting in more rapid resolution of symptomatic CME. In patients with established CME, NSAIDs are more effective than steroids alone. It is evident that corticosteroids have a greater anti-inflammatory effect in suppressing AC cells and flare following cataract surgery. However the complementary role of NSAIDs in preventing CME has become increasingly clear from published studies and clinical practice. A recent study even showed improvement in quality of vision after concomitant NSAID application.

The issue of preventing rather than treating CME is much more important. Some of the risk factors for the development of CME can be classified as follows:

A) Preoperative: diabetes, uveitis, prior history of CME, retinal vein occlusion (branch vein occlusion, central retinal vein occlusion, diabetic macular edema, macular degeneration)

B) Intra-operative: iris trauma, retained lens material, posterior capsule rupture, vitreous loss, sulcus and anterior chamber IOL implantation
C) Post-operative: sudden discontinuation of medication, idiopathic increased intraocular inflammation, trauma.

D) Other conditions: epiretinal membrane, retinitis pigmentosa, use of prostaglandin analogues just before surgery etc.

There are various reports of CME associated with latanoprost after uncomplicated cataract surgery.\(^{16,17}\) It is therefore not advisable to use latanoprost during pre and postoperative periods. If at all, they must be well covered with the judicious use of NSAIDs.

Diclofenac and Ketorolac are primarily used to decrease the pain and inflammation after ocular surgery, while Flurbiprofen and Suprofen are primarily used to inhibit postoperative miosis. Ketorolac also decreases itching caused by seasonal allergic conjunctivitis. It is the only NSAID which is available as a preservative free solution.

Bromfenac\(^{18}\) and Nepafenac are the recent NSAIDs. Bromfenac is much more active against COX-2 than COX-1 unlike Ketorolac\(^{19}\).

A study was conducted to measure the relative potency of different NSAIDs with regards to the different molecules of cyclo-oxygenase enzyme i.e. COX-1 and COX-2. This is measured by IC50, which is the drug concentration required to inhibit the enzyme by 50%.

As the IC50 decreases, the potency of the drug increases. Inhibition of COX-2 is responsible for the anti-inflammatory action of these agents.

<table>
<thead>
<tr>
<th></th>
<th>IC50 COX-1</th>
<th>IC50 COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>0.53uM</td>
<td>0.023uM</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.95uM</td>
<td>0.085uM</td>
</tr>
<tr>
<td>Amfenac</td>
<td>0.25uM</td>
<td>0.150uM</td>
</tr>
</tbody>
</table>

Nepafenac is hydrolysed to form Amfenac. Bromfenac is 3.7 times more potent than Diclofenac and 6.5 times than Amfenac. Hence it is a stronger inhibitor of COX-2 enzyme as compared to other ocular NSAIDs.

A study conducted to measure the penetration of NSAIDs in ocular tissues detected the presence of Bromfenac even after 24 hours. The Bromfenac ocular concentrations were present for longest time period in comparison to Nepafenac. This accounts for the bid dosing of Bromfenac and possibly the earlier efficacy seen in reduction of pain.

The resolution of pain after cataract surgery was rapid in patients that received Bromfenac therapy. This was demonstrated by 2 US clinical trials where 93.3% of the patients receiving Bromfenac treatment were pain free as opposed to 63.7% of the patients receiving placebo treatment.

Less than 2% adverse effects are seen with Bromfenac.\(^{14}\)% of the patients who received this drug developed CME, while 4.7% in the placebo group developed CME.\(^{20}\)

Bromfenac also has a potential use in the management of allergic conjunctivitis.\(^{21}\) It is comparable to Pemirolast when used for allergic conjunctivitis.\(^{22}\)

Nepafenac is a new topical NSAID pro-drug which is hydrolysed by intraocular tissue to Amfenac, which is a potent anti-inflammatory agent. It has been approved by the US Food and Drug Administration (FDA) for the treatment of pain and inflammation after cataract surgery. It is the only NSAID which can reach the posterior segment and inhibit prostaglandin synthesis.\(^{23}\) Therefore this drug appears promising in reducing prostaglandin mediated vascular leakage such as cystoid macular edema. Nepafenac also has anti-VEGF properties and decreases neovascularisation.\(^{24}\) Kern et al. demonstrated that topical application of this drug may inhibit progression of diabetic retinopathy.\(^{25}\)

The dosing schedule of Bromfenac is twice daily; Nepafenac is thrice daily and for all other NSAIDs is four times a day. There is a general consensus among ophthalmologists that NSAIDs should be started 1-3 days before surgery to decrease postoperative inflammation and the incidence of CME. Post-operatively it should be continued for about 4-6 weeks. For high risk patients it should be continued for three months or more. Common side effects include transient burning, stinging and hyperemia of the conjunctiva. Corneal complications like superficial punctuate keratitis, sub epithelial infiltrates, stromal infiltrates and persistent epithelial defects after topical NSAID use are uncommon.\(^{26}\) There have been few reports of corneal melt with topical Bromfenac, Diclofenac and Ketorolac drops.\(^{27,28,29}\) In addition, allergies and hypersensitivity reactions have been reported with all the NSAIDs.

Ophthalmologists must be aware of the conditions which predispose to corneal melting. Some of these are severe keratoconjunctivitis sicca, persistent
epithelial defect, and neuropathic keratopathy. Ocular cicatrical pemphigoid, Steven Johnson Syndrome and chemical burns. The mechanism of melting is unclear, probably multifocal. Recent studies have further defined the role of matrix metalloproteinases (MMPs) in the pathogenesis of corneal ulcerative keratolysis associated with the topical use of Diclofenac. Histopathologic examination of the corneal button which was perforated by the use of topical NSAIDs showed an increased level of MMP-8 in the corneal epithelium. Corneal melt may also occur as a result of increased amounts of precursor metabolized by the lipo-oxygenase pathway, resulting in an increased amount of lipo-oxygenase products, like leukotriene B4. Also, frequent instillation of Ketorolac and Diclofenac leads to significantly decrease in normal corneal sensation which resembles neurotrophic keratitis and therefore may trigger corneal melting.

Today, several NSAIDs are commercially available: Diclofenac, Flurbiprofen, Ketorolac, Bromfenac and Nepafenac. At present the ophthalmologists have to make a decision between the more efficacious topical NSAID, Nepafenac. At present the ophthalmologists have to make a decision between the more efficacious topical NSAID, Nepafenac. Today, several NSAIDs are commercially available: Diclofenac, Flurbiprofen, Ketorolac, Bromfenac and Nepafenac. At present the ophthalmologists have to make a decision between the more efficacious topical NSAID, Nepafenac.

Reference

4. Solomon KD et al. Topical 0.5 % ketorolac vs 0.03 % flurbiprofen for inhibition of miosis during cataract surgery. Arch Ophthalmol 1997; 115:1119-22
21. Fujishima H, Tanaka M, Fukagawa K, et al. Comparison of the efficacy of NSAID (bromfenac sodium) and...


