Nepafenac

Dr. Sonia Rani John DNB, Dr. Meena Chakrabarti MS, Dr. Arup Chakrabarti MS

Ocular inflammation is a common result of cataract surgery, producing pain and photophobia in many patients and potentially leading to serious complications including increased intraocular pressure, posterior capsule opacification, cystoid macular oedema and decreased visual acuity. Steroidal agents have been the standard treatment for ocular inflammation in the past while the use of topical NSAIDS has increased over the past two decades. Clinical evidence suggests that the combined use of NSAIDS and steroids is synergistic. In fact it has become the standard of care to use a regimen of NSAIDS and steroids before and after cataract surgery.

Prostaglandins are involved in human intraocular inflammation and released in response to ocular trauma, including surgery. When present following trauma, intraocular surgery, or in association with uveitis, they may contribute to disruption of blood – ocular barriers and the generation of macular edema. During cataract surgery, arachidonic acid is released from phospholipids of cell membranes to provide the precursor for prostaglandin synthesis. Corticosteroids affect the cascade by attenuating the expression of inflammatory mediators that initiate activation of phospholipase and the release of arachidonic acid thus limiting prostaglandin production. NSAIDS exert their effects further downstream of the cascade, directly inhibiting cyclo-oxygenase and the production of prostaglandins.

There are 2 main settings of ocular surgery in which ophthalmologists use topical NSAIDS. One is refractive surgery and the other is cataract or other intraocular surgeries. With refractive surgery, NSAID drops are particularly effective in reducing discomfort both during and after the procedure. To a lesser extent, they also reduce inflammation in the eye related to refractive surgery, particularly in the cornea and conjunctiva.

With cataract and intraocular surgery, topical NSAIDS offer several benefits. The goals of topical prophylactic nonsteroidal anti inflammatory drug treatment include the prevention of intraoperative miosis, management of postoperative inflammation, prevention or treatment of CME and reduction of ocular pain. They lessen the patient’s discomfort during the procedure, which is especially important when using topical anesthesia in cataract surgery. NSAID also help maintain pupillary dilation during cataract surgery, which has been shown to lower the rate of complications. They help in controlling inflammation in the first few days after surgery, as measured by the presence of cells and flare in the anterior chamber. Finally, NSAIDS inhibit the development of cystoid macular oedema (CME), which usually occurs 4 to 6 weeks after cataract surgery. Even after a perfect cataract surgery with the most modern techniques and the best instrumentation, as many as 12 % of patients may develop some CME and the use of an NSAID may significantly reduce this complication.

Four topical ocular NSAIDS are currently approved by the U.S Food and Drug Administration (FDA) for the treatment of postoperative inflammation after cataract surgery. They are Acular (ketorolac 0.5 %), Xibrom (brimonidine 0.09 %), Voltaren (diclofenac 0.1 %) and Nevanac (nepafenac 0.1 %).
Nepafenac (Nevanac, Alcon Laboratories) is a novel topical nonsteroidal anti-inflammatory drug, which is the only prodrug NSAID, having less anti-inflammatory activity without conversion to its more active state. Each ml of Nevanac (0.1 %) suspension contains 1 mg of nepafenac. Nepafenac is designated chemically as 2-amino 3-benzoylbenzene acetamide with an empirical formula of C\textsubscript{15}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}.

Nevanac Ophthalmic suspension is the first and only topical NSAID structured as a prodrug. This unique design allows for target specific activity, because its efficacy is maximized at the intraocular sites of most concern to ophthalmologists. Once Nevanac penetrates the eye, intraocular hydrolysis converts the nepafenac molecule into a potent cyclooxygenase inhibitor called amfenac, an active drug that has strong anti-inflammatory capabilities.

Unlike conventional NSAIDs, the active forms of which tend to accumulate on the ocular surface and decrease in activity and concentration as they penetrate the eye, Nevanac is specially designed to maximize intraocular efficacy. Its unique prodrug structure allows Nevanac to achieve optimal distribution through the cornea into the iris/ciliary body and retina/choroid, providing superior inflammation suppression. At the same time, this rapid and targeted distribution may minimize tolerability issues commonly noted with conventional NSAID therapies, because the drug doesn’t overload the ocular surface.

Nevanac uniformly inhibits all prostaglandins of the iris/ciliary body, retina, PGE\textsubscript{2} synthesis, and the breakdown of the blood–aqueous barrier. Compared with conventional NSAIDs such as diclofenac, nepafenac 0.1 % is superior in blocking the production of prostaglandins in an uniform manner. Studies show that nepafenac 0.1 % inhibits 95 % of prostaglandin formation in the iris/ciliary body within 80 minutes after topical dosing, compared with diclofenac’s 53 %. This fact has important clinical implications in terms of potential differences in efficacy between Nevanac and conventional NSAID therapies.

It is believed that CME is caused by surgically induced prostaglandin formation in the aqueous and vitreous and/or by the breakdown of the blood–aqueous and blood–retinal barriers. Even mild CME damages the retinal pigment epithelium. Such damage is irreversible, because these cells do not regenerate. Therefore, any retinal swelling can have a lasting negative impact on a patient’s vision.

Due to their mechanism of action, NSAIDs have been shown to be a good line of defense against CME. Obviously, it is key that the NSAID selected reaches the target tissues to provide therapeutic anti-inflammatory activity and thus prevent the processes described.

The target-specific activity of Nevanac hold great potential for the superior prevention of post-cataract complication such as CME. Because the highest concentration of Amfenac occurs in the choroid and retina, the agent not only decreases inflammation in the anterior chamber, but should also lower the patient’s risk of developing CME. Studies have shown that nepafenac 0.1 % inhibits prostaglandin formation in the vitreous, whereas conventional NSAID such as diclofenac and ketorolac fail to do so. A study evaluating the suppression of prostaglandin synthesis of nepafenac 0.1 % versus diclofenac in the iris/ciliary body and the retina/choroid showed that a single topical dose of nepafenac 0.1 % significantly inhibited prostaglandin synthesis in the iris/ciliary body and retina choroid. Efficacy was sustained for 6 hours in the iris/ciliary body and for 4 hours in the retina/choroids. In contrast, for diclofenac peak suppression of prostaglandin activity in the iris/ciliary body was sustained for 20 minutes, with only minimal inhibition of prostaglandin synthesis observed with diclofenac in the retina/choroid.

Because nepafenac is a neutral molecule, it has been hypothesized to have greater corneal permeability than other NSAIDS which have acidic structures. In a vitro study of rabbit tissue, nepafenac had 6 fold greater corneal penetration than diclofenac as well as faster rate of penetration. Similarly in another study, nepafenac aqueous humor C\textsubscript{max} values were 3.6 fold higher than those of ketorolac despite having a starting concentration 4-fold (0.1 % versus 0.4 %). Nepafenac C\textsubscript{max} values were more than 8 fold higher than those of bromfenac, despite having similar starting concentrations (0.1 % versus 0.09 %). Thus the results in various studies support the fact that the prodrug nepafenac has faster corneal penetration rate than other conventional NSAIDs.
Intraocular drug concentrations are expected to correspond with the anti-inflammatory efficacy of a drug. The near-maximum concentrations of amfenac is maintained longer than those of Ketorolac suggesting that Nevanac may have a prolonged duration of action relative to other drugs in this class. This may be due to nepafenac prodrug structure which allows it to rapidly traverse the cornea, reaching C_{max} in the aqueous humor within 30 minutes.

Nepafenac is a non-steroidal anti-inflammatory pro-drug that potentially inhibits Cox-1 and Cox-2 activity ex vivo following topical ocular administration. Nepafenac demonstrates low intrinsic cyclo-oxygenase inhibitory activity in vitro, yet exhibits in vivo efficacy equal to that of diclofenac in models of anterior segment ocular inflammation. In addition to its anterior segment efficacy, nepafenac exceeds diclofenac in its ability to reduce posterior segment ocular inflammation.

Nevanac has been tested in various concentrations (upto 15 times its commercial concentration) and in short – as well as – long term settings and it was found to be safe and well tolerated^{15,16}. Nepafenac penetrates the target intraocular tissues faster than any other topical NSAID, thus providing greater efficacy on a clinical basis. Once inside, it has rapid conversion and therapeutic onset and a very high level of tissue concentration. Studies show that its rate of systemic absorption in approximately 1700 times less than that of an oral dose.

Nevanac hold the promise of fast, pain-free visual recovery without the potential common side effects noted with conventional NSAID therapies. As mentioned previously, its unique prodrug formulation ensures optimal intraocular distribution^{17} with superior inflammation suppression. The superior bioavailability of Nevanac to the retina / choroid also ensures an unsurpassed potential for preventing CME after cataract surgery.

Nevanac suspension, which was filed with the FDA for the treatment of inflammation following cataract surgery, will provide a novel, target-specific structure that optimizes penetration throughout the relevant ocular tissues to deliver enhanced, longer-lasting anti-inflammatory efficacy all the way to the retina / choroid which is of particular relevance to ophthalmic surgeons.

**References**

11. Walker LM, Rice RL, Heaton JD, et al. Ocular effects of Nepafenac ophthalmic suspension following three months of topical ocular suspension to cynomolgus monkeys. Paper presented at: The ARVO annual meeting; May 03, 2005; Fort Lauderdale, FL.

