Nepafenac in the Prevention and Treatment of Ocular Inflammation and Pain Following Cataract Surgery and in the Prevention of Post-operative Macular Oedema in Diabetic Patients

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Abstract

Nepafenac ophthalmic suspension is a topical non-steroidal anti-inflammatory drug (NSAID) approved in the US and Europe for prevention and treatment of post-operative pain and inflammation associated with cataract surgery, and recently approved in Europe for reduction in risk of post-operative macular oedema associated with cataract surgery in diabetic patients. Unlike conventional NSAIDs, nepafenac is a prodrug that is uncharged and this results in great corneal permeability. Experimental studies on nepafenac demonstrated enhanced permeability compared with other NSAIDs, and rapid bioactivation to amfenac by intraocular hydrolases within ocular tissues including ciliary body epithelium, retina, choroid and cornea, which results in targeted delivery of active drug to anterior and posterior segments. Furthermore, these study results have been confirmed in clinical trials. Nepafenac may have prolonged activity in vascularised tissues of the eye because bioconversion is targeted to the iris/ciliary body, and to a greater extent the retina and choroid. Nepafenac and amfenac are potent inhibitors of cyclo-oxygenase (COX) enzyme isoforms, COX-1 and COX-2. Topical nepafenac penetrated into the posterior segment in a rabbit model of concanavalin-A induced retinal inflammation, where it diminished vitreous protein and prostaglandin E_2 concentrations and reduced breakdown of the blood–retinal barrier. Other NSAIDs, including ketorolac, failed to reduce the increase of these inflammatory markers in the same study. A randomised clinical study showed that based on retinal thickening and vision, treatment with nepafenac beginning pre-surgery and used for up to 90 days post-cataract surgery is effective in preventing macular oedema and associated loss of visual acuity in diabetic patients.

Keywords

Non-steroidal anti-inflammatory drugs (NSAIDs), cataract surgery, pain, inflammation, nepafenac, prodrug, permeability

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During ophthalmic surgery, surgical trauma causes activation of cyclo-oxygenase (COX) COX-1 and COX-2, which metabolise arachidonic acid to prostaglandins (PGs). PGs are mediators of the inflammatory response, and increased production of these molecules can result in discomfort, pain and ocular inflammation. As inhibitors of PGs, non-steroidal anti-inflammatory drugs (NSAIDs) are often employed by ophthalmic surgeons to provide anti-inflammatory control post-surgery and work synergistically with steroid therapy to minimise pain and inflammation following ocular surgery,[1,2] albeit by different mechanisms. NSAIDS primarily act on cyclo-oxygenase-1 (COX-1) and COX-2 to minimise PG formation,[3] and while steroids also reduce PG synthesis, this is due to the inhibition of phospholipase A2.[4]

Moreover, NSAID treatment has been demonstrated to have a beneficial effect on visual outcomes,[5] preventing macular oedema after cataract surgery, however, it is essential to attain therapeutic concentrations in the posterior chamber to obtain the effect of NSAID treatment on the target retina tissue. Thus, for maximum therapeutic benefit, the ideal NSAID is one that reaches therapeutic levels in both the aqueous humour and in the posterior segment tissues. Nepafenac is a NSAID with a unique prodrug structure that has superior corneal permeability to other currently available NSAIDs.[6] This review aims to consider the properties, existing efficacy and safety data, other possible indications of nepafenac in inflammation treatment and the advantages it provides over existing NSAIDs in cataract surgery.

Mode of Action of Nepafenac

Nepafenac has a unique prodrug structure and is converted to a potent cyclo-oxygenase inhibitor, amfenac, by intraocular hydrolases (see *Figure 1*).[6,7] Upon ocular dosing, nepafenac permeates the cornea, is metabolised by intraocular tissues[8] and is converted into amfenac for optimal efficacy. The prodrug mechanism of action maximises bioactivation to amfenac in the iris, ciliary body, retina, choroid and cornea to a lesser extent, making nepafenac a target-specific NSAID.[9] Experimental studies on nepafenac demonstrated properties of enhanced permeability and rapid bioactivation to amfenac, to inhibit PG synthesis in the anterior and posterior eye segments.[7] Furthermore, from a safety standpoint, preclinical studies have shown that the

prodrug structure minimises surface accumulation, as it is rapidly distributed to the anterior chamber and to posterior segment tissues. Thus, ocular surface complications associated with conventional NSAID treatments may be minimised.[9] Cornea, anterior and posterior segment safety were studied *in vivo* via slit lamp biomicroscopic examination in two long-term preclinical trials, with no ocular or systemic toxicity.[10,11]

Intraocular Penetration of Nepafenac

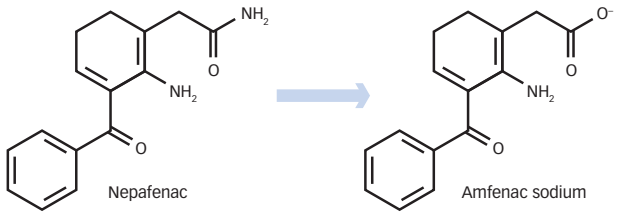
Compared with conventional NSAIDs, which are polar in structure, nepafenac has superior corneal permeability as it is uncharged. It permeates corneal barriers without delay as a neutral molecule and therefore has an advantage over classical acidic NSAIDs which have been demonstrated experimentally *in vivo* to show lag periods before crossing the cornea.[6] A non-clinical study evaluating the ocular distribution of nepafenac and amfenac following topical ocular administration of nepafenac demonstrated that following topical instillation, nepafenac and amfenac were readily available to all ocular tissues, including the posterior segment (see *Figure 2*).[12] Furthermore, high and sustained concentrations of the prodrug were observed in the conjunctiva, cornea and sclera, suggesting a depot for continued hydrolysis to amfenac. Low vitreous concentrations of both drugs indicated that posterior segment likely received the drug via trans-scleral penetration.[12] A multicentre investigative study evaluating the aqueous humour concentrations and COX inhibitory activities of nepafenac, amfenac, ketorolac and bromfenac following topical ocular administration in patients having cataract surgery, found that nepafenac had greater ocular bioavailability than any other drug tested (see *Figure 3*).[13] Nepafenac had the shortest time to peak concentration and greatest peak aqueous humour concentration. Additionally, both the C_{max} and the area under the curve (AUC) of nepafenac were significantly larger than the other drugs tested ($P<0.05$).

Anterior Segment Efficacy

Nepafenac is indicated for prevention of pain and inflammation in the anterior segment following cataract surgery with intraocular lens (IOL) implantation. A randomised double-blind vehicle-controlled trial was designed to examine whether nepafenac, as a sole treatment, decreases the incidence and severity of pain and inflammation following cataract surgery with IOL implantation.[14] A total of 476 patients were included in the study, and a much higher percentage of patients (83.1–93.0 %) in the nepafenac group (n=243) were pain-free at all visits as compared with vehicle-treated patients (41.6–46.4 %) (n=233). A greater number of patients in the nepafenac group were cured at day 14 (see *Figure 4*). Additionally, the nepafenac treated patient group had lower signs of inflammation (aqueous cells scores, mean aqueous flare scores and mean aqueous cells plus flare scores) supporting that nepafenac is effective in preventing inflammation (see *Figure 5*).

Similar results were observed in a multicentre, randomised, double-masked clinical study, comparing nepafenac, ketorolac and placebo.[15] A total of 227 patients undergoing cataract surgery were randomised to receive nepafenac (n=77), ketorolac (n=73), or placebo (n=77), one day pre-operatively and for 21 days post-operatively. When compared with placebo, nepafenac produced significantly more cures at day 14, more clinical successes from day 7 onward, and more pain-free patients from day three onward. Nepafenac was also superior to ketorolac in terms of clinical success at day 14 and in percentage of pain-free patients at day three. Compared with ketorolac, nepafenac showed less discomfort upon instillation.

Figure 1: The Molecular Structure of Nepafenac and its Active Metabolite, Amfenac



Posterior Segment Efficacy – Results from Preclinical Studies

To evaluate efficacy of nepafenac in the posterior chamber of the eye, a preclinical study was performed using a rabbit model of inflammation-mediated retinal oedema.[16] Pan-retinal inflammation was induced using intravitreal injection of the mitogen concanavalin A, and oedema and inflammation assessed by measuring retina PGE_2 synthesis, retinal thickness and protein leakage in the vitreous humour. As compared with control, topical application of nepafenac resulted in a significant reduction in retinal oedema (65 %) and inhibition of the breakdown of the blood–retinal barrier (62 %) and the blood-aqueous barrier (78 %). In addition, nepafenac significantly inhibited PGE_2 synthesis. The efficacy of nepafenac was compared with ketorolac, with the latter ineffective in reducing inflammation in the posterior segment as determined by vitreal accumulation of markers.[16] This non-clinical study demonstrated that nepafenac exhibited superior pharmacodynamic properties in the posterior segment following ocular dosing, indicating a unique therapeutic potential for various conditions associated with retinal oedema.

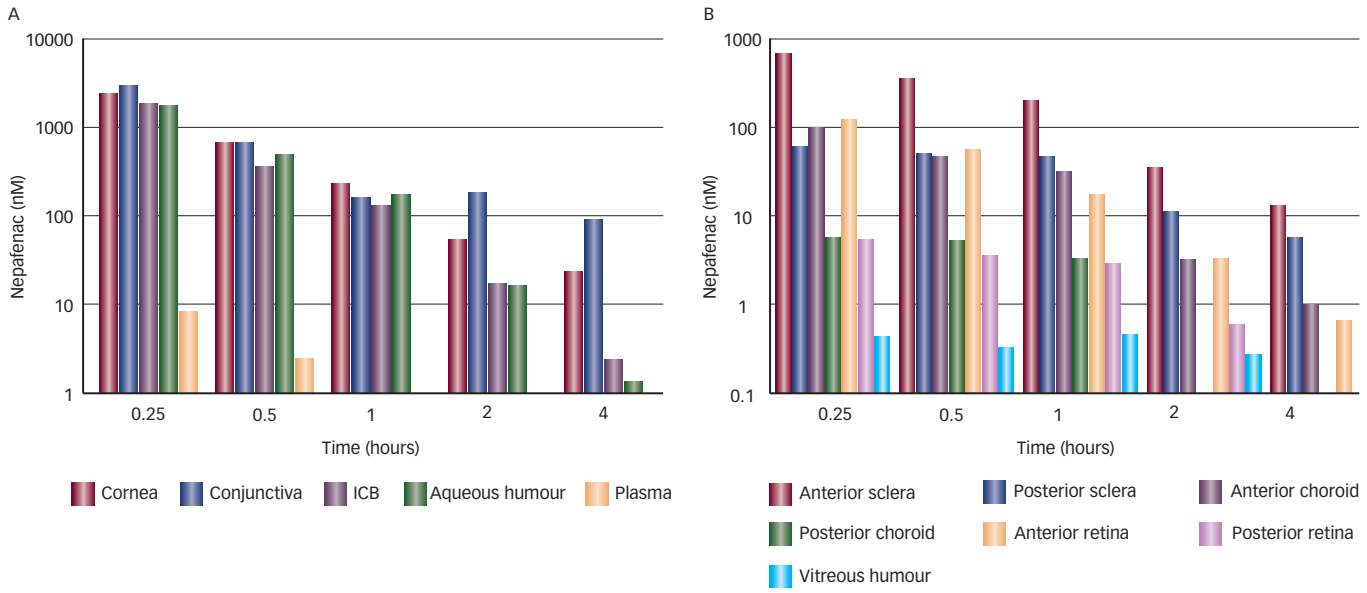
Prevention of Macular Oedema in Diabetic Patients after Cataract Surgery

In diabetic patients, macular oedema (MO) is a frequent cause of unfavourable visual outcome following cataract surgery.[17] Estimates of the rate of MO in diabetic patients following cataract surgery are variable and range from 31 to 81 % at assorted time-points post-surgery.[18–20] Chronic hyperglycaemia, chronic subclinical inflammation and blood–retinal barrier dysfunction are important factors in the pathogenesis of diabetic MO, and post-surgical inflammation is believed to be a major factor in the development of MO following cataract surgery. Nepafenac was recently approved in the EU for prophylactic use in the reduction in the risk of post-operative MO associated with cataract surgery in diabetic patients, following the publication of results from a randomised, double-masked, vehicle-controlled clinical trial.[21] In this study, 251 patients with diabetic retinopathy were treated with nepafenac (n=125) or vehicle (n=126), one day prior to cataract surgery and continued for 90 days post-surgery. Results from the study showed that a significantly larger percentage of patients in the vehicle group developed MO (16.7 %) compared with those treated with nepafenac (3.2 %) ($p<0.001$). Additionally, patients in the nepafenac group maintained better visual acuity and a larger percentage of patients in the vehicle treatment group experienced a decrease of >5 letters in best corrected visual acuity (BCVA) from day seven to day 90 (11.5 % as compared with 5.6 % of patients receiving nepafenac). Pre- and post-cataract treatment with nepafenac resulted in a lower incidence of MO and supports the efficacy of nepafenac in preventing MO in patients with diabetes undergoing cataract surgery.

Safety and Tolerability

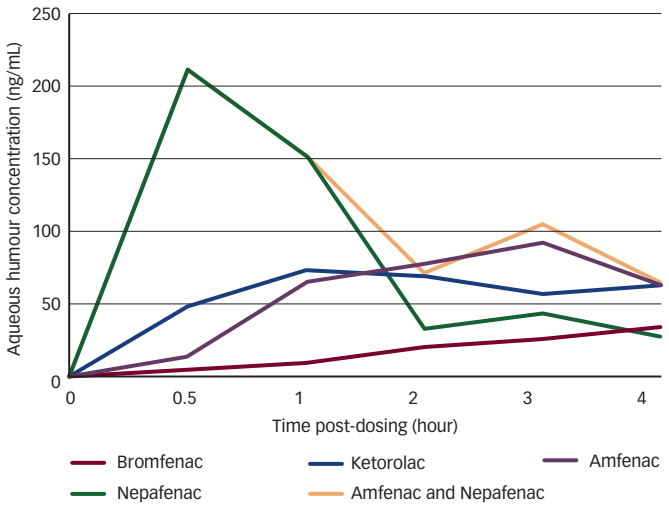
Although corneal complications following NSAID use are uncommon,[22] NSAIDs have been associated with corneal effects, such as keratitis and

Figure 2: Preclinical Studies of Nepafenac Concentration in the Anterior (A) and Posterior (B) Segment of the Eye



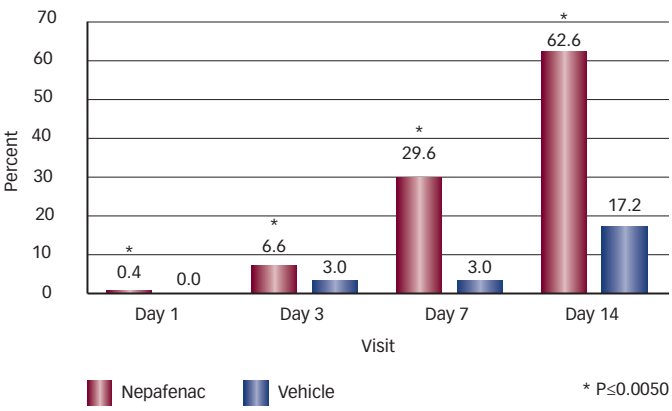
ICB = iris-ciliary body. Source: Hariprasad, et al., 2009.[12]

Figure 3: Aqueous Humour Drug Concentration Over Time



Source: adapted from Walters, et al., 2007.[13]

Figure 4: Cumulative Percentage Cures by Visit



Source: adapted from Lane, et al., 2007.[14]

delayed wound healing, and in some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation.[23] When tested and compared with placebo in animal models, nepafenac was proven safe and well-tolerated throughout ocular tissues with no delays in wound healing.[10,11,24] In the multicentre, randomised, double-masked clinical study comparing nepafenac, ketorolac and placebo, adverse events in the total safety population were mainly mild or moderate in intensity and usually did not disrupt patient continuation in the trial. No clinically significant differences were observed between the therapy groups in the total safety population. No safety issues were detected for intraocular pressure, visual acuity, ocular signs or dilated fundus parameters based on a study of changes from baseline.[15]

The ocular safety of nepafenac has been confirmed in preclinical studies in concentrations up to 1.5 % (15-times commercial concentration) and in treatment durations up to six months. During a Phase III trial of nepafenac, safety analysis demonstrated no ocular adverse events related to therapy, and there were no clinically relevant treatment-related changes from baseline in visual acuity, ocular signs, intraocular pressure or dilated fundus parameters.[14] In the recent clinical trial evaluating nepafenac in the prevention of MO in diabetic patients, no related serious adverse events or targeted adverse events were identified.[21] Approximately 3 % of patients (of a total of 800) involved in clinical studies experienced adverse reactions when receiving nepafenac, leading to discontinuation in 0.6 % of patients.[23] This was less, however, than the discontinuation of patients receiving placebo (1.3 %). No serious adverse events were reported in these studies. In the multicentre, randomised, double-masked clinical study comparing nepafenac, ketorolac and placebo, at the day 7 visit only, mean ocular discomfort was significantly lower for nepafenac 0.1 % compared with ketorolac 0.5 % (p=0.0158) and lower but not significantly in respect to placebo (see *Figure 6*).[15]

Discussion

Nepafenac ophthalmic suspension is a topical NSAID approved for the treatment of post-operative pain and inflammation after cataract

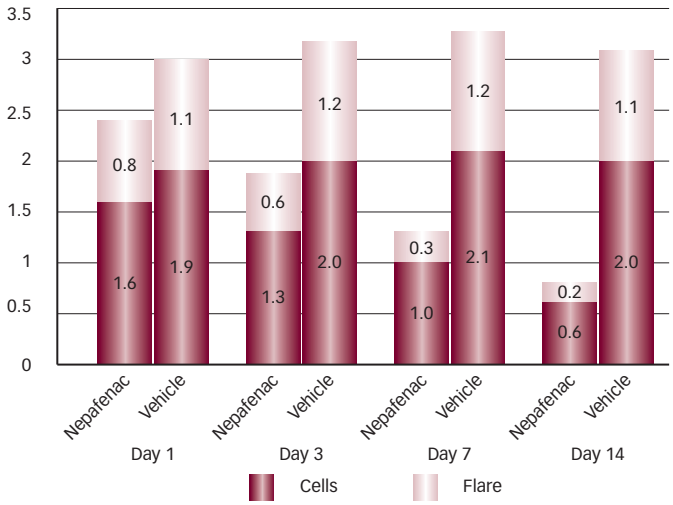
surgery, and for reduction in risk of post-operative MO associated with cataract surgery in diabetic patients. Nepafenac has corneal permeability properties and is targeted as it converts to its active metabolite amfenac, a potent anti-inflammatory in the iris, ciliary body, retina and choroid due to greater hydrolase activity in these sites. Amfenac effectively inhibits PG synthesis and protein extravasation, thus stabilising the blood–retinal and blood–aqueous barriers. Trials have demonstrated that nepafenac has proven safe and well-tolerated, similar to or better than older NSAID formulations. Since the breakdown of the blood–retinal barrier has been found to be associated with the development of cystoid macular oedema, nepafenac may play a part in the prevention of macular oedema in high-risk patients such as those with diabetes. Approval has recently been given in the EU for the prophylactic use of nepafenac for the prevention of macular oedema in diabetic patients undergoing cataract surgery.

Future Developments

Topical anaesthesia for ocular surgeries and advances in ophthalmic technologies has significantly enhanced patients' expectations and confidence in ophthalmic surgery especially with multifocal IOLs. Also a subtle MO may be highly distressing for the patient. Moreover, patients no longer tolerate pain during and after ocular surgery and this requirement will doubtlessly increase in future years. Unfortunately, most refractive procedures often cause post-operative pain and discomfort. In the near future, we will continue to see an increasing number of ocular medications to improve comfort, optimise compliance and minimise adverse reactions with maximal benefit.

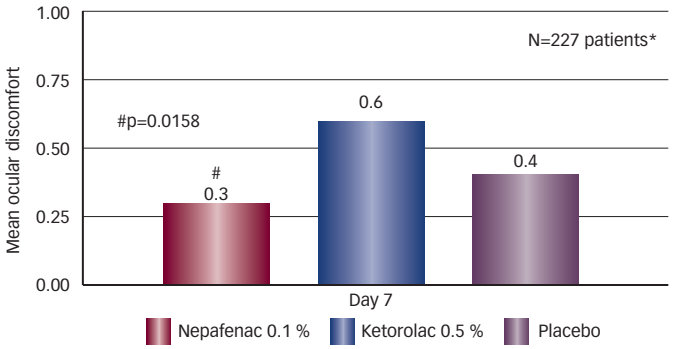
Nepafenac is a non-steroidal prodrug, with high conversion rates in posterior sites of the eye, and these properties may prompt future trials to determine efficacy in treating or preventing various conditions related to retinal oedema, such as diabetic macular oedema, MO in venous obstruction, vitreoretinal surgery and teleangiectasia. A Phase II trial is currently ongoing, investigating the use of nepafenac in the treatment of non-central involved diabetic MO (DMO).[25] The primary outcome of the study is the effects of nepafenac on macular retinal volume, however, central subfield thickness and progression of non-central DMO to central DMO will also be assessed. As DMO is predicted to affect 235,602 diabetic patients in the UK by the year 2020,[26] results of the trial will be watched with great interest by the ophthalmic community. New indications in different types of conditions associated with retinal oedema may be indicated for future nepafenac monotherapy or as concomitant treatments. ■

Figure 5: Cell Scores and Flare Scores by Treatment



Source: adapted from Lane, et al., 2007.[14]

Figure 6: Mean Ocular Discomfort of Eye Drops at Day 7



Source: Nardi, et al., 2007.[15]

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