Review Article:
Nonsteroidal Anti-Inflammatory Drugs; Expanding Indications for the Treatment of Retinal Diseases

SHERIF M. HEGAZY, M.Sc.*; MOHAMED A. EL SADA, M.D.**; MOHAMED EL MALT, M.D.* and MOHAMED EL AGHA, M.D.**

The Department of Retina, Research Institute of Ophthalmology, Giza* and Ophthalmology Department, Faculty of Medicine, Cairo University

Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) formulations use and indications in ophthalmology are evolving at a high rate. NSAIDs use in anterior segment disease and their ability to decrease postoperative inflammation is well documented. Recently, new topical formulation that allow higher intraocular penetration facilitate topical NSAIDs use in posterior segment disorders. The use of topical NSAIDs as a primary or an adjunctive treatment modality in numerous disorders such as diabetic retinopathy, age-related macular degeneration, vein occlusion and inflammation has been studied. Also, intravitreal injection dosage, safety and efficacy have been studied. Recent advances related to the use of NSAIDs for the treatment of posterior segment disorders have been reviewed.


Introduction
NONSTEROIDAL anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medications worldwide. Topical NSAIDs indications and formulations in ophthalmology are expanding. They have proven useful in cataract surgery to enhance mydriasis, reduce postoperative inflammation, prevent and treat postoperative cystoid macular edema (CME) [1]. In addition, they can be used to decrease pain and photophobia after refractive surgery [2] and to alleviate itching associated with allergic conjunctivitis [3]. A growing body of scientific evidence suggests that NSAIDs may be beneficial in treating many retinal disorders including diabetic retinopathy, age-related macular degeneration, vein occlusions and uveitis [4].

Pharmacology:
NSAIDs inhibit all isoforms of cyclo-oxygenase (COX), an important enzyme in the inflammatory process, which accelerates the production of prostaglandins (PGs) from arachidonic acid. Two main isoforms of COX, COX-1 and COX-2, have been identified. A third isoform, COX-3 is less well understood. The ciliary body, iris and retinal pigment epithelium and specific cells in the retina all express COX enzymes and are possible sources of endogenous PGs production. COX-2 is the predominant isoform in human retinal pigment epithelium and is significantly upregulated in response to proinflammatory cytokines. COX-2 is also present in choroidal neovascularization (CNV) [5] as well as in other highly vascularized lesions, and its expression increases in diabetic retinopathy [6].

Prostaglandins exert diverse physiological and pathological functions within the eye. It is well established that they disrupt the blood-ocular barrier and increase vascular permeability. In addition, they promote leucocyte migration, interact with and amplify many other soluble mediators. They are also involved in the induction of VEGF, thereby stimulating angiogenesis [7].

In a rabbit model of endotoxin-induced ocular inflammation, topical NSAIDs were shown to reduce leucocyte release, PG production, and disruption of the blood-aqueous barrier [8]. Substantial evidence demonstrated that NSAIDS have both anti-proliferative and anti-angiogenic properties.
Evidence indicates that COX-2 acts as an inducer of angiogenesis [9].

However, NSAIDs do not inhibit lipoxygenase (LPO) and thus do not typically prevent generation of leukotrienes. This may explain in part their decreased anti-inflammatory effects compared to corticosteroids, which inhibit both LPO and COX. Diclofenac is a notable exception which inhibits LPO by direct and indirect means, respectively [10].

There are six major classes of NSAIDs, however the topical formulations of NSAIDs are limited to the relatively water soluble classes: Indole acetic, aryl acetic, and aryl propionic acids [11]. Both Ketorolac 0.5% (Allergan) and Diclofenac 0.1% (Novartis Ophthalmics) are aryl acetic acid derivatives. They are FDA-approved for post-cataract inflammation and ocular discomfort after refractive surgery. They are dosed four times daily following cataract surgery. To reduce the incidence of burning and stinging, a 0.4% concentration of ketorolac tromethamine was formulated and appears to have a similar therapeutic effect [12].

Two other aryl acetic acid derivatives, Nepafenac and Bromofenac which are FDA-approved for treatment of pain and post-cataract surgery inflammation can be dosed less frequently. A prodrug Nepafenac 0.1% (Alcon Laboratories) is rapidly converted to the more potent NSAID Amfenac after passage through the cornea by intraocular hydrolases. It is dosed three times daily and is the only suspension among the topical NSAIDs. Because Nepafenac is noncharged, it may have greater corneal permeability than other NSAIDs which have more polar acidic structures. Vitro studies have shown a six-fold greater corneal penetration of nepafenac compared to diclofenac [6].

Bromofenac 0.09% (ISTA Pharmaceuticals) dosed twice daily is structurally identical to Amfenac with the exception of a bromine atom at the C4 position. This key alteration may increase its penetration into ocular tissue, extend its duration and enhance its inhibitory effect on COX-2. Ketorolac is reported to be the most potent inhibitor of COX-1, while Bromofenac and Amfenac are the most potent inhibitors of COX-2. However, the relative importance of COX-1 versus COX-2 inhibition in ocular disease remains unproven [13].

Drug delivery routes:

Topical:

Although topical administration of classic NSAIDs provides aqueous humor levels adequate to suppress PG synthesis in the iris and ciliary body, their ability to suppress PG synthesis in the retina and choroid is less certain. In animal models, ketorolac 0.5% could not be detected in the vitreous after topical administration. Also, 0.1% diclofenac appeared to produce minimal inhibition of prostaglandin synthesis in the retina and choroid. However, both newer NSAIDs, 0.1% nepafenac and 0.09% bromofenac, have been detected in the rabbit retina after topical administration, and in one study nepafenac inhibited 55% of retinal PG synthesis [14].

A study measured vitreous drug levels in patients who received ketorolac 0.4% four times daily, bromofenac 0.09% two times daily, or nepafenac 0.1% three times daily for three days before vitrectomy surgery. Vitreous levels of ketorolac, bromofenac, and nepafenac were reported as 2.8ng/mL, 0.96ng/mL, and 1.1ng/mL respectively, but only ketorolac resulted in significantly lower vitreous PGE2 levels compared to placebo. Aqueous and vitreous concentrations of NSAID would likely have a direct effect on anterior (ciliary body and iris) and posterior (retina and choroid) PG production, respectively [15].

Periocular:

In an animal model of experimental uveitis, periocular injection of ketorolac produced higher concentrations in the vitreous than either topical or systemic administration [16]. Similarly, periocular injection of celecoxib resulted in a 54-fold higher concentration in the retina than systemic administration and effectively reduced PGE-2 secretion, VEGF production, and BRB leakage in an animal model of diabetes [17].

Intravitreal:

Intraocular injection of NSAIDs may provide drug levels to the posterior segment many times greater than can be obtained via topical or oral routes. Non-toxic intraocular doses for ketorolac and diclofenac have been established by Margalit [18] and Kim [19]. In another study designed to assess the intraocular efficacy for reducing inflammation in an animal, the safety of these agents was further assessed. The intraocular pharmacokinetics of both NSAIDs and their penetration into the retina was also evaluated. The study showed that a single intravitreal injection of either effectively reduces intraocular inflammation caused by lipopolysaccharide in an animal model [20].

Each of the NSAIDS reduced PG production dramatically and attenuated leucocyte recruitment, as reflected in the aqueous cell concentration.
While the magnitude of the anti-inflammatory effect was significant for both NSAIDs, it was less than that of triamcinolone. Although this finding can be explained by the broader anti-inflammatory actions of corticosteroids, the study suggests that diclofenac and ketorolac’s efficacy may have been limited by their short half-lives. The study also demonstrated substantial concentrations of both drugs in the retina not obtained with topical use. At these higher drug concentrations, greater therapeutic effects on retinal disease may be expected [20].

Diclofenac is a drug with a small molecule (318.13 Daltons) and has a short half-life in the vitreous (2.87 hours). Rapid elimination of diclofenac sodium from the vitreous necessitates several intravitreal injections which may be associated with complications such as retinal detachment and endophthalmitis. Methods of increasing the half-life of diclofenac in the vitreous should focus on its pharmacokinetic model and lipophilicity, as well as the delivery system. An animal study revealed that a less soluble form of the drug, such as diclofenac acid rather than diclofenac sodium salt, will remain in the vitreous cavity for up to 24 days, potentially resulting in therapeutic levels in posterior segment tissues for a few months [21].

An effective slow-release delivery system for intravitreal diclofenac is a practical solution to achieve sustained therapeutic levels with the goal of providing prolonged clinical benefit. Many other drug delivery systems such as biodegradable and non-biodegradable implants may be future frontiers of diclofenac delivery to the posterior segment. The safety and efficacy of these techniques need to be verified [22]. Currently, there is no available study on implementation of these drug delivery strategies for intravitreal diclofenac.

Indications:

Diabetic macular edema:

Animal models of DR treated with NSAIDs showed prevention or delay in its progression [23]. Rheumatoid arthritis patients taking salicylates had a reduced incidence of DR. This observation was examined in two clinical trials. The early treatment of diabetic retinopathy study (ETDRS) which examined the effect of 650mg aspirin on advanced DR [24] showed no benefit. However, the Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) Study, which tested the impact of a higher dose on less severe cases [25], demonstrated delay of the development of retinal microvascular toxicity in early DR. This observation is explained by the use of a higher dose (990mg aspirin) in a less severe stage. This was further supported by a subsequent prospective, a randomized study where treatment with the NSAID Sulindac limited the development and progression of DR [26]. Another prospective is a controlled trial conducted by the National Eye Institute which demonstrated that oral celecoxib significantly reduced vascular leakage in patients with DR despite premature stoppage of treatment due to concerns regarding cardiovascular toxicity [27].

There are uncontrolled case reports reporting anatomical and visual improvement with topical NSAIDs for DME. Hariprasad described several patients with macular edema of various etiologies that were treated with nepafenac 0.1%. One patient underwent treatment for DME for six months with improved retinal thickness from 378 gm to 215 gm and a three-line visual gain [28]. Another study reported the treatment of DME in six eyes with nepafenac 0.1%. Both visual acuity and foveal thickness statistically improved over a mean duration of 210 days [29].

Soheilian investigated the safety and efficacy of a single intravitreal injection of diclofenac (500mcg/0.1mL) in five eyes with DME. The visual results were mixed. Two patients showed improvement, another two showed deterioration and only one showed stabilization. The mean CMT was actually worse than at baseline. However, this pilot study based on electroretinography measurements established no toxic effect of IVD on the retina [30]. Reis et al., injected intravitreal ketorolac (500mcg) unilaterally in twenty patients with bilateral refractory DME. The other eye served as a control. Although at one month, there was a significant improvement in VA in the treated eyes relative to controls, there was no change in foveal thickness [31]. Maldonado in 2011 used a larger dose of ketorolac (3000mcg) in 25 DME refractory to laser. Again visual improvement was recorded with no corresponding improvement in macular thickness [32]. Elbendary in 2012 compared intravitreal diclofenac (500mcg/0.1mL) to intravitreal triamcinolone (4mg/0.1mL) in the treatment of diffuse DME in a randomized study with a three month follow-up. CMT decreased in the diclofenac group from 419.8µm at baseline to 323.5µm at one month and 271.1µm in three months. IVD attained a similar efficacy on retinal thickness with significant reduction of IOP but the degree of visual improvement was slightly higher with triamcinolone [33].
Postoperative Cystoid Macular Edema (CME):

Accumulation of extracellular fluid in the retina due to leakage from vessels is not uncommon. Inflammation has been thought to play an important role in its development. NSAIDs have been used for the treatment and prophylaxis. Fluorescin angiography detected CME is much more common than clinically important CME [34]. Warren investigated the adjunctive use of nepafenac 0.1%, diclofenac 0.1%, ketorolac 0.4%, bromfenac 0.09% or placebo for 16 weeks in addition to intravitreal triamcinolone and bevacinumab for treatment of chronic CME. Both adjunctive use of nepafenac and bromfenac resulted in greater reduction of retinal thickness at 12 and 16 weeks. However, only nepafenac led to a significant improvement in vision [35]. Similarly, in a retrospective study, nepafenac improved retinal thickness and visual acuity in patients with chronic, recalcitrant CME [36]. Another study showed that prophylactic use of ketorolac 0.5% was effective in reducing angiographic CME in aphakic patients without the use of corticosteroids [37].

In a study comparing topical diclofenac 0.1% versus fluorometholone (FML) 0.1% on prevention of post-cataract CME, angiographic CME was seen to occur ten times more common in FML-treated eyes. Because FML has limited intraocular penetration, these results may be interpreted to approximate the effectiveness of diclofenac as compared to placebo [38]. A more recent study comparing topical ketorolac 0.4% plus prednisolone versus prednisolone alone demonstrated a significantly reduced rate of CME with combination treatment in low-risk patients after cataract surgery. However, the results were not significant regarding incidence of true or probable CME or visual affection [39]. Studies investigating the effect of using topical NSAIDs to prevent or cure CME post-vitreoretinal surgery followed the same trend. Adding topical NSAIDs does decrease macular thickness but not to statistical levels [40].

Age-related Macular Degeneration (AMD):

VEGF is established as the principle mediator of CNV, the wet form of AMD. While VEGF inhibitors have revolutionized the treatment of neovascular AMD, they do not stop the underlying disease process. Therefore, multiple injections are needed, with the associated financial and medical burden. However, a growing body of evidence indicates that inflammation plays a central role in CNV development [41]. COX-2 has been detected in human choroidal neovascular membranes [8]. Also, considerable evidence indicates that COX is a promoter of angiogenesis [9]. In a number of experiments, inhibition of COX-2 suppressed angiogenesis [42]. Furthermore, the clinical observation that patients who regularly take NSAIDs have a 40-50% reduction in mortality from colorectal cancer, may be explained by the high expression of COX in colorectal tumors [43].

Kim demonstrated that both topical and intravitreal ketorolac significantly reduces angiographic leakage and retinal levels of PGE2 and VEGF in an animal model of CNV [44]. Other investigators have also reported similar results with topical or oral NSAIDs [45,46]. Although a large retrospective study reported decreased rates of CNV among AMD patients taking aspirin, no association between systemic NSAIDs and five-year incidence of AMD was observed in the Blue Mountains Eye Study [47]. Studies investigating topical NSAIDs for exudative AMD have also reported conflicting results. A number of studies showed no benefit with the addition of topical bromfenac [48] or nepafenac [49] to intravitreal anti-VEGF agents in patients with persistently active exudative AMD. In contrast, two prospective, randomized, controlled clinical studies reported favorable effects of topical bromfenac with respect to retinal thickness and reduced number of anti-VEGF treatments. Flaxel investigated combination treatment with topical bromfenac 0.09% for new or recurrent exudative AMD [50]. Although, there was no observed difference in regards to vision or number of injections between groups, there was a significant difference in favor of combination treatment in reduction of CMT. In a further study by Gomi et al., combination treatment with bromfenac 0.1% and IVR significantly reduced the number of anti-VEGF injections needed compared to IVR monotherapy [51].

Uveitis:

Intravitreal diclofenac (IVD) injection for the treatment of refractory uveitic CME was evaluated in a series of eight cases. Although, BCVA and CMT showed improvement at follow-up for 36 weeks, these changes failed to reach statistical significance [52]. Kim studied the use of intravitreal ketorolac in steroid resistant cases with chronic inflammation. Although there were some positive results the main outcome was the establishment of the drug safety [53].

BRVO:

In a study by Shimura bromfenac was given to patients with branch vein occlusion to assess for a synergistic effect with intravitreal bevacizumab (IVB). Although it did not increase the reduction effect by IVB, it did prolong its effect thereby
reducing the frequency of IVB over a 1-year follow-up. A limitation in this study was that bromfenac use was initiated only after the confirmation of recurrence of ME at month 3. Perhaps, longer application may bring more prominent results. It is not surprising that this combination therapy has a beneficial effect for ME secondary to BRVO. The anti-VEGF drug bevacizumab suppressed hypervascular permeability, while a topical NSAID of bromfenac suppressed inflammatory conditions [54].

Conclusion:

The recent advances in the understanding of the molecular interactions responsible for development of retinal disease, allowed the development of various new targets for pharmacological treatment. NSAIDs have shown great promise as an anti-inflammatory agent, in addition to its effect on angiogenesis. The development of new topical agents capable of reaching the posterior segment allows their use as primary or adjuvant treatment for retinal disease. Higher concentrations of NSAIDs needed in more severe scenarios can be achieved by means of intravitreal injections which have been proven safe and effective. The future of NSAIDs in the treatment of posterior segment disorders shows great promise.

References


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