REVIEW ARTICLE

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Topical Nonsteroidal Anti-Inflammatory Drugs for Ophthalmic Use

A Safety Review

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used agents that despite chemically heterogeneity, share similar therapeutic properties and adverse effects. Topical ophthalmic NSAIDs are limited to the relatively water soluble phenylacetic and phenylalkanoic acids as well as indole derivatives, which are more suitable for ophthalmic use. Topical ophthalmic NSAIDs are commonly used in the treatment of post-operative inflammation following cataract extraction and various surgical refractive procedures. They are also used in the prevention and treatment of cystoid macular oedema and for the treatment of allergic conjunctivitis. Absorption of topical ophthalmic NSAIDs through the nasal mucosa results in systemic exposure and the occurrence of adverse systemic events, including exacerbation of bronchial asthma. Local irritant effects of topical ophthalmic NSAIDs include conjunctival hyperaemia, burning, stinging and corneal anaesthesia. A more serious complication involves the association of topical ophthalmic NSAIDs with indolent corneal ulceration and full-thickness corneal melts. Analysis of NSAID-associated corneal events implicates the now defunct generic dicolfenac product, diclofenac sodium ophthalmic solution as the agent primarily responsible. However, these events generated a renewed interest in the safety of ophthalmic NSAIDs and a scrutiny of the pharmacology regarding

NSAID action in the eye. An elucidation of possible pharmacodynamic explanations of NSAID-induced corneal injury includes the role of epithelial hypoxia, which not only appears to aid in determining the metabolic destination of arachidonate, it may play a key role in orchestrating a novel inflammatory response unrelated to prostanoid formation. The use of NSAIDs under conditions of corneal hypoxia may therefore not only result in a disappointing therapeutic response, it may result in a paradoxical inflammatory exacerbation. Other potential mechanisms include the relationship between NSAIDs and corneal matrix metalloproteinase and direct toxicity due to cytotoxic excipients such as surfactants, solubilisers and preservatives found in topical NSAID ophthalmic preparations. In general, ophthalmic NSAIDs may be used safely with other ophthalmic pharmaceuticals; however, concurrent use of agents known to adversely effect the corneal epithelium, such as gentamicin, may lead to increased corneal penetration of the NSAID. The concurrent use of NSAIDs with topical corticosteorids in the face of significant pre-existing corneal inflammation has been identified as a risk factor in precipitating corneal erosions and melts and should be undertaken with caution. Until clinical evidence dictates otherwise, data supporting theories of potential pharmacodynamic mechanisms of NSAID injury do not alter the favorable benefit-risk ratio of ophthalmic NSAID use when employed in an appropriate and judicious manner.

Ocular inflammation is a circumstance of a complex cascade of events, triggered in response to either injury or endogenous influences of cellular or humoral origin secondary to autoimmune or infectious circumstances. While corticosteroids in general have historically held a prominent role in the treatment of ocular inflammation, the development of topical anti-inflammatory agents devoid of the anticipatory detrimental effects of corticosteroid therapy represented a significant advancement in the development of ocular pharmacotherapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds that have been in use for over a quarter of a century, which, except for aspirin (acetylsalicylic acid), exert anti-inflammatory activity primarily through the reversible inhibition of cyclo-oxygenase (COX) activity. COX is the main constituent of an enzyme system that acts on certain polyunsaturated fatty acids (primarily arachidonate) to produce the eicosanoids, namely, prostaglandins, prostacyclin and thromboxanes.[1,2]

1. Ophthalmic Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Mechanism of Action and Uses

NSAIDs characteristically may be differentiated chemically from classic steroidal anti-inflammatory agents by their lack of a cholesterol-derived sterol nucleus.[3] Historically, the term nonsteroidal agent has often been loosely used interchangeably with the term COX-inhibitor based on the mechanism of action. The pharmacological properties of NSAIDs differ from traditional steroidal anti-inflammatory agents based on their pharmacodynamic effect on the inflammatory cascade. Corticosteroid agents inhibit production of arachidonate indirectly through the induction of lipocortin synthesis which inhibits the phospholipase enzyme, therefore preventing production of all autocoids including leukotrienes, endoperoxides and prostaglandins.[1] Nonsteroidal agents act solely on the action of COX, inhibiting the formation of prostaglandin (PG) G_2, PGH_2 and the products thereof.[1] While corticosteroids and NSAIDs both inhibit prostaglandin formation, it should be noted that

corticosteroid agents exert additional anti-inflammatory actions including a reduction in migration of macrophages and neutrophils, decreasing vascular permeability and suppressing the action of various lymphokines.[1] Interestingly, NSAIDs have also been demonstrated to exert additional anti-inflammatory actions, other than COX-inhibition, by suppressing polymorphonuclear (PMN) cell locomotion and chemotaxis, probably through a direct effect on the PMNs.[4] NSAIDs have also been shown to decrease expression of inflammatory cytokines as well as mast cell degranulation in experimental models of ocular allergy.[5] There is also evidence that NSAID compounds may also exert an effect as free radical scavengers, which may further contribute to the anti-inflammatory response.[2] It is interesting to note that because NSAID compounds are organic acids, they have a tendency to accumulate at sites of inflammation, further benefiting their anti-inflammatory properties.[2]

The action of NSAIDs may be further described based on their activity toward various isoforms of the COX enzyme. Constitutive COX-1 enzymes are equally expressed upon the endoplasmic reticulum of all cells, including platelets, cellular elements of the small and large bowel mucosa, vascular endothelium, renal medullary collecting ducts, interstitium, pulmonary and hepatic sites as well as the spleen.[6-9] COX-2 enzymes have limited inducible expression, which is often a result of cytokines, growth factors and stress mediated mitogens.[9] Traditional NSAID agents inhibit both COX-1 and COX-2 in a nonselective manner. The recent introduction of selective COX-2 inhibitors may effectively target inducible COX-2 thereby inhibiting tissue specific prostaglandin mediated inflammation without blanket COX-inhibition.[8,9]

For the purposes of this discussion, all designation to NSAID in this discussion infers references to traditional COX-1/COX-2 nonselective COX-inhibitors.

The currently available non-selective COX-inhibitors marketed commercially for ophthalmic use include indole as well as phenylacetic and phenylalkanoic acids (table I).[2,3] Other chemical classes of NSAID, such as salicylates, fenamates and pyrazolone derivatives are considered too toxic to be used in the eye.[2,3] The water soluble nature of the indole, phenylalkanoic and phenylacetic acids is desirable for formulation of the these compounds as eyedrops.[2,3] Indeed, some of the toxicity noted with the use of topical ophthalmic NSAIDs may be attributed to the vehicle, solubiliser and/or preservative found in the solution, rather than the active agent (table II).[10] Topical indomethacin for ophthalmic use is available commercially only outside of the US.

Ocular application of NSAIDs results in excellent absorption and penetration of the drug. For example, following topical application of a 50µl drop of flurbiprofen 0.03%, in the rabbit, all anterior segment structures were found to have drug levels sufficient to provide 50% inhibition of the COX enzyme.[11] Lower levels were found in the lens and vitreous; however, vitreous levels in-

Table I. Commercially available topical nonsteroidal anti-inflammatory drug (NSAID) agents in the US

Ophthalmic NSAID	Chemical class	Active ingredient concentration	Approved indication
Flurbiprofen	Phenylalkanoic acid	0.03%	Inhibition of intraoperative miosis
Diclofenac	Phenylacetic acid	0.1%	Treatment of postoperative inflammation in patients who have undergone cataract surgery and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
Ketorolac	Phenylalkanoic acid	0.5%	Treatment of ocular itching due to seasonal allergic conjunctivitis and postoperative inflammation following cataract surgery. Preservative free ketorolac is also indicated for the reduction of ocular pain and photophobia following corneal refractive surgery

Table II here

crease in aphakic eyes.[11] It has been further demonstrated that topical administration of ophthalmic NSAID compounds results it significant systemic absorption[12,13] Studies in rabbits have found that up to 74% of the administered topical dose reaches the systemic circulation through absorption by nasolacrimal drainage.[12,13] It would be prudent to believe, therefore, that systemic toxicity may be manifested by topical ophthalmic administration of NSAIDs, particularly on a long-term basis.

While the use of systemic NSAIDs has focused on primary inflammatory disorders, commonly rheumatoid arthritis or other types of rheumatic spondylosises, the indications for ophthalmic NSAID are more variable (table III). Typically used to treat post-operative inflammation following procedures such as cataract surgery, topical ophthalmic NSAIDs also have shown benefit by preventing miosis secondary to prostaglandin formation released during procedures such as cataract surgery which involves iris manipulation.[14] NSAIDs also are of value in both the short and long-term treatment of seasonal allergic conjunctivitis.[15] NSAIDs are effective in reducing pain and post-operative inflammation following cataract surgery which, if not adequately treated, may contribute to loss of vision due increased intraocular pressure, capsule opacification or iris adhesions to the angle or implant.[16-18]

Studies also have found value in the treatment of post-operative pain following various refractive procedures such as laser *in situ* keratomileusis (LASIK), treatment of pain associated with corneal abrasion, treatment of inflamed pterygium and pinguecula and treatment of inflammation associated with trabeculectomy.[19-23]

NSAIDs also have been effective for the treatment of vernal conjunctivitis.[24]

2. Adverse Effects of Topical Ophthalmic NSAIDs

2.1 Systemic

Systemic effects found with topical ophthalmic NSAID use are rare. However, systemic absorption

Table II. Chemical constituents of commercially available ophthalmic nonsteroidal anti-inflammatory agents

Tradename/ company	Active agent	Nonionic surfactant (solubiliser)	Buffer	Preservative	Chelator	pH adjuster	Tonicity agent	Vehicle	Viscosity polymer	Additional components
Diclofenac/Falcon Ophthalmics, Inc. (discontinued)	Diclofenac 0.1%	Tocophersolan	Boric acid	Polyquaternium 0.005%	None	NaOH or HCl	Mannitol	Purified water	None	
Voltaren®/CIBA Vision	Diclofenac 0.1%	Polyoxyl 35 – castor oil	Boric acid	Sorbic acid	EDTA	None	None	NaOH or HCl	None	Tromethamine
Acular®/Allergan	Ketorolac tromethamine (0.5%)	Octoxynol 40	None	Benzalkonium chloride 0.01%	EDTA	NaOH or HCl	None	Purified water	None	
Ocufen®/ Allergan	Flurbiprofen 0.3%	None	Sodium citrate	Thimersol 0.005%	EDTA	NaOH or HCl	None	Purified water	1.4% polyvinyl alcohol	
Flurbiprofen/Bausch and Lomb, Inc	Flurbiprofen 0.3%	None	Sodium citrate	Benzalkonium chloride 0.01%	EDTA	NaOH or HCl	KCl or NaCl	Purified water	1.4% polyvinyl alcohol	
Acular PF 0.5®/ Allergan	Ketorolac 0.5%	None	None	None	NaOH or HCl	None	Purified water	None	None	
Indocid®/Merck[a]	Indomethacin 1%	Polysorbate 80	None	Benzalkonium chloride	EDTA	None	NaCl	Purified water	Hydroxy-ethylcellulose	Sodium bisulfite, benzyl alcohol, phenylethyl alcohol, sorbitol

a Canada and Europe, not available in US.

EDTA = disodium edetate.

Table III. Common uses for topical ophthalmic various nonsteroidal anti-inflammatory drugs (NSAIDs)[a]

Indication	Commonly used NSAIDs
Postoperative inflammation	Diclofenac, ketorolac
Postoperative topical analgesia	Diclofenac, ketorolac
Postoperative pain following refractive surgery	Diclofenac, ketorolac
Prevention and treatment of cystoid macular oedema	Diclofenac, ketorolac, indomethacin
Prevention of intraoperative miosis	Flurbiprofen, ketorolac
Treatment of allergic conjunctivitis	Ketorolac

a Includes common 'off label' uses not approved in the US by the Food and Drug Administration.

of topical ophthalmic NSAIDs leading to exacerbation of bronchial asthma has been documented.[25-27] Since 1989 there have been at least three reported cases of bronchial asthma exacerbation following use of topical ophthalmic NSAIDs.[25-27] Two cases involved topical indomethacin,[26,27] one case involved the Voltaren®**1** formulation of topical diclofenac.[25] In all cases, symptoms of asthma developed temporally following initiation of topical NSAID therapy and promptly abated following NSAID discontinuation. Two of the patients had a previous history of mild-moderate asthma including one who had a history of moderate dry eye and nasal polyposis.[25] The latter patient experienced acute asthma attacks following each administration of diclofenac which was prescribed for control of ocular 'redness and pain' secondary to an upper respiratory infection. Following discontinuation of topical diclofenac, the asthma attacks ceased, only to be initiated again following re-challenge with topical diclofenac administration. Nasolacrimal occlusion prevented attacks with further diclofenac use.

Exacerbation of asthmatic symptoms subsequent to use of topical ophthalmic NSAIDs highlights the dangers of potential systemic absorption following application of topical ophthalmic NSAIDs. The marked effect of punctal occlusion in eliminating symptoms of topical NSAID-induced asthma illustrates the extreme sensitivity some patients may exhibit to NSAID-induced asthma. While NSAID-induced asthma is most commonly associated with aspirin based products, any non-selective COX-inhibitor may be at fault. Intolerance to aspirin among patients with asthma is not uncommon, it is estimated that between 10 to 30% of patients with asthma will develop exacerbation of asthma symptoms following ingestion of aspirin or other NSAID products.[28,29] The influence of the NSAID in causing bronchoconstriction appears to be related to their potency as COX-inhibitors (table IV).[29] In addition, NSAIDs from all chemical classes may precipitate asthma attacks. Sensitivity often develops after the third decade of life and is frequently associated with chronic rhinitis, sinusitis and nasal polyposis.[29] NSAID-sensitive patients are typically nonatopic and often have a history of mild-moderate persistent asthma.[29] NSAID intolerance is often demonstrated clinically by the development of bronchospasm, rhinitis, conjunctivitis, urticaria, angio-oedema and anaphylaxis.[28,29] The aetiology of NSAID-induced asthma attacks is considered to be linked to COX-inhibition within the respiratory tract in sensitive patients. It appears shunting of arachidonate from the COX to the lipoxygenase pathway within the respiratory tract leads to the production to various leukotrienes (LTs), including

Table IV. *In vitro* cyclo-oxygenase inhibitory potential of various nonsteroidal anti-inflammatory drug formulations[30]

Drug	PG synthesis bovine seminal vesicles IC_{50} (μmol/L)
Indomethacin	0.07-20
Ibuprofen	3.7-6.2
Naproxen	0.8-1.8
Ketorolac	a
Flurbiprofen	3.9-7.0
Flufenamate	0.8-30
Aspirin (acetylsalicylic acid)	60-1500
Phenylbutazone	20-5000

a Ketorolac is approximately 100 times more potent than aspirin as a cyclo-oxygenase inhibitor.

IC_{50} = concentration required to inhibit 50%; **PG** = prostaglandin.

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

LTD_4 and LTE_4, both of which are potent spasmogens for nonvascular smooth muscle.[1]

Prevention of NSAID-induced asthma includes careful history taking which may clue clinicians to a history of nasal polyposis or previous bouts of NSAID-induced asthma exacerbation, perhaps with the use of various over-the-counter aspirin containing products. While sensitivity to oral NSAID agents may be lessened by NSAID titration, it is unclear if this technique is applicable to topical ophthalmic NSAID administration. Other, potential systemic effects related to topical ophthalmic NSAID administration include gastrointestinal (GI) irritation and ulceration, inhibition of platelet function and renal disease.[1]

Although GI erosions and ulceration associated with NSAID use may be related to local irritation, systemic absorption of NSAIDs leads to COX-inhibition within gastric and intestinal mucosa reducing biosynthesis of protective prostaglandins, particularly prostacyclin (PGI_2) and PGE_2.[1] Geriatric patients appear to be at increased risk for developing GI ulceration and bleeding due to NSAID use along with tobacco users and those who abuse alcohol.[31,32] Female gender and those with a history of antacid or proton pump inhibitor use, or those with a history of systemic corticosteroid or anti-coagulant therapy are also at risk for NSAID-induced GI complications.[31] Additional and noteworthy NSAID-related systemic effects include alteration of platelet and renal function. Platelet function is altered by NSAIDs due to their disruption of thromboxane A_2 synthesis, a potent aggregating agent.[1] While all NSAIDs have a propensity to disrupt platelet function, aspirin has the most potent effect due to its irreversible action on COX-inhibition.[33] Patients receiving NSAIDs are also at risk for drug-induced renal complications. In some patients, vasodilatory renal prostaglandins have a supportive effect on renal blood flow, particularly those with extracellular fluid depletion due to diuretic use, congestive heart failure, hepatic cirrhosis with ascites or chronic renal disease.[34] Geriatric patients also may be prone to NSAID-induced renal complications.[34] Recovery of renal function often results following discontinuation of NSAID therapy.[34] Additional systemic effects of NSAID use include liver injury, cephalalgia, aseptic meningitis, urticaria, erythema multiforme and hypersensitivity reactions.[8] Inhibition of prostaglandin formation during pregnancy may result in prolongation of labour, increased risk of post-partum haemorrhage and intrauterine closure of the ductus arteriosus.[1]

The potential for systemic absorption of topical NSAIDs is evident based on the reported cases of asthma precipitated by topical ophthalmic NSAID use. Although in general the systemic absorption of topically applied ophthalmic preparations is considered to be minimal, idiosyncratic drug reactions may occur even at the exceedingly low serum concentrations seen with topical NSAID administration. In order to avoid systemic adverse responses due to topical NSAID use, it would be prudent to carefully obtain a thorough drug and medical history before initiating topical ophthalmic NSAID treatment and ascertain the potential for any possible drug-disease interactions. Close attention should be made to use anticoagulants or pre-existing systemic diseases that may predispose to NSAID precipitated injury, such as asthma, inflammatory conditions of the bowel or GI ulceration. Patients with pre-existing kidney or liver disease should also be monitored with particular attention to potential GI or renal injury. These cautions are particularly important in long-term topical NSAID use in susceptible individuals. While there have no reports of systemic adverse experiences with topical ophthalmic NSAID use other than asthma, there exists a pharmacologically sound basis for the their occurrence.

Punctal occlusion techniques should be considered if concerns exist as to any possible systemic toxicity. One additional precaution involves NSAID use during pregnancy or breast feeding. Prostaglandins are known to play a crucial role in the inducement of labour and the use of NSAIDs during pregnancy has been shown to lengthen gestation in animal models.[35] NSAIDs are also known to have detrimental effects on the fetal cardiovas-

cular system (closure of ductus arterious); therefore, the use of NSAIDs during the third trimester of pregnancy should be particularly avoided.[35] Although these recommendations are based on the use of oral NSAIDs, it would be prudent to follow such cautions for the use of topical ophthalmic NSAIDs as well. In addition, it is of interest to note that most oral NSAIDs including diclofenac fall into pregnancy category risk B in regard to teratogenic potential. However, etodolac and ketorolac both fall into category C.[36] Therefore, topical ophthalmic diclofenac (Voltaren®) would be favoured as the topical NSAID of choice when an NSAID must be used during pregnancy. To minimise exposure to the nursing infant, a short half-life phenylalkanoic acid derivative with little biotransformation properties should be chosen. This includes drugs such as flurbiprofen and for oral use, ibuprofen.[37] Diclofenac, either orally or topical, also may be suitable.[37]

2.2 Local

The most common local adverse events occurring with topical ophthalmic NSAID use involves stinging and hyperaemia of the conjunctiva.[2,3] Most of the stinging, irritation and hyperaemia related to topical ophthalmic NSAID use is due to inherent properties of the free compounds which alone can be quite irritating to the unprotected mucous membrane.[10] For example, ketorolac is formulated as the tromethamine salt because the tromethamine moiety enhances the aqueous solubility resulting in a solution that has low potential for irritation.[10]

Additional local effects include post-cataract surgery atonic mydriasis.[38,39] Atonic mydriasis has been reported in some individuals who received topical NSAIDs prior to cataract surgery for preventing intra-operative miosis. Atonic mydriasis is characterised by an enlarged, unresponsive pupil that does not constrict with the application of pilocarpine, but does dilate following application of mydriatics.[38] The incidence reported from the literature is approximately 0.2%.[39] The aetiology of atonic mydriasis following routine cataract surgery is unknown; however, damage to the iris sphincter is suspected as the causative factor. Although topical NSAIDs have been associated with atonic mydriasis, there are many other additional factors, including surgical trauma, which may also play a role. Toxicity to various chemical protectants and pharmacologic agents administered intracamerally, such as viscoelastics and miotics have also been implicated as causative factors. Until further studies prove otherwise, the association of pre-operative ophthalmic NSAID use for preventing miosis and the occurrence atonic mydriasis is likely circumstantial at best.

Contact dermatitis has also been noted with use of topical NSAIDs.[40] Contact dermatitis is manifested by pruritus, erythema and oedema of the bulbar conjunctiva and eyelids following topical NSAID use. In sensitised individuals reactions may be immediate; however, reactions can appear weeks or months following use of the NSAID due to delayed hypersensitivity reactions.[40] A local anaesthetic effect also has been demonstrated by the NSAID diclofenac due to selective binding to inactive sodium channels within the corneal epithelium. It appears the arrangements of the two phenyl groups in the diclofenac molecule are oriented in such a fashion as to interact with key ligands within the sodium channels resulting in decreased in corneal sensitivity.[41] It should be noted that decreased corneal sensitivity due to long-term NSAID use may result in superficial punctate keratitis.[42]

Aragona et al.[43] reported on the effects of topical NSAIDs on the corneal epithelium and corneal sensitivity in healthy volunteers. Ninety subjects were divided into six groups receiving placebo, diclofenac 0.1%, indomethacin 0.1%, flurbiprofen 0.03%, ketorolac 0.5% and oxybuprocaine 0.4%, a local anaesthetic. One eye received placebo and one eye a study drug instilled four times at 5-minute intervals. The corneal epithelium was assessed, subjective burning was noted, and corneal sensitivity was assessed by the Cochet-Bonnet method. No drug produced epithelial damage except oxybuprocaine. All medica-

tions caused burning with the exception of placebo. Diclofenac produced a significant decrease in sensitivity, similar to the topical anaesthetic, starting 15 minutes after instillation and lasting until the end of the study. None of the other tested NSAIDs produced any significant changes in regards to corneal sensitivity.

The use of the Voltaren® formulation of diclofenac has been associated with keratitis that appears to be reversible with discontinuation of the drug.[42] Gills[42] has reported a series of 12 cases of diclofenac induced keratitis associated with treatment of cystoid macular oedema following cataract surgery. In the series reported by Gills,[42] it appeared that susceptible patients often had underlying pre-existing corneal or conjunctival disease. Gills[42] noted the prevalence of diclofenac-induced keratitis to be approximately 1%. It is important to note that drug-induced keratitis due to NSAID treatment may compound loss of visual acuity due to CME and limit attempts to further manage the CME with topical NSAID therapy. Development of epithelial defects has also been reported following use of the Voltaren® formulation of diclofenac for post-operative inflammation due to penetrating keratoplasty.[44] Lacrimal canalicular obstruction, although rare, has been reported in associated with use of topical indomethacin.[45]

A further, more serious problem with NSAID use involves corneal 'melts'.[46] Reports of severe corneal melts in regard to ophthalmic NSAID use were uncommon until the introduction of a generic version of Voltaren® (CIBA Vision, Novartis) termed diclofenac sodium ophthalmic solution (DSOS) manufactured by Falcon Laboratories. The dramatic increase in reports of severe corneal injury apparently related to use of DSOS ultimately resulted in the removal of this product from the market.[46,47] It is important to note, however, that reports of corneal melts and keratitis have been associated with the use of other ophthalmic NSAID products aside from the DSOS, albeit with much lower frequency.[47-50] A database to record NSAID-related ocular adverse effects was established in November 1997. Until March of 1999, no adverse events were reported with ophthalmic diclofenac use. Up until August 1998 the only diclofenac product available was Voltaren®. The generic version of diclofenac, DSOS, was introduced in the US in August 1998. Beginning in March 1999, the first corneal erosion related to the new DSOS formulation was received by the US Food and Drug Administration (FDA). By July 1999 10 more reports of corneal erosions or melts were received by MedWatch.[51] It was becoming increasingly obvious the new diclofenac formulation, was involved in an unacceptable number of significant adverse corneal events. Despite discontinuation of generic diclofenac in September 1999, 17 more reports of corneal melts associated with generic diclofenac use were reported by October 1999.[51] A summary of the events leading to the withdrawal and discontinuation of the DSOS product is shown in table V. From a mechanistic perspective it is of interest to note that peripheral corneal infiltrates have been related to the use of systemic diclofenac for the treatment of backache.[52] This finding suggests the observed negative effects of topical DSOS on the cornea are not entirely circumstances of local administration, but rather implicates the active drug alone in mediating the negative response.

Despite the reported link between DSOS and corneal erosions and melts, additional reports have suggested a link between other ophthalmic NSAID products and corneal erosions as well.[48-50] Mah

Table V. Timetable of diclofenac sodium ophthalmic solution (DSOS) introduction and discontinuation

Date	Event
August 1998	Generic diclofenac introduced (DSOS)
March 1999	First adverse event regarding generic DSOS reported to the FDA
June 1999	Ten cases of corneal complications associated with generic DSOS reported to the FDA
July 1999	Eight cases of corneal complications with generic DSOS reported to the FDA
September 1999	Generic DSOS is removed for distribution and use

FDA = US Food and Drug Administration.

et al.[50] discussed the occurrence of corneal erosions and melting with ophthalmic ketorolac as well as both Voltaren® and generic diclofenac. Mah et al.[50] reported that scleral wound melting can occur with any ophthalmic NSAID and not only generic diclofenac in patients who have undergone cataract surgery.The occurrence of marginal corneal ulcers following photorefractive keratectomy have also been associated with use of the brand products Voltaren® and Acular®.[53] Guidera[49] also reports the occurrence of corneal ulceration and erosion associated with the use of generic diclofenac, Voltaren® and preservative free ketorolac. While the majority of corneal insults following NSAID use have occurred post-operatively following cataract surgery, there has been a report of corneal melt associated with both DSOS and Voltaren® use following refractive surgery.[48] Three cases of corneal melts following LASIK were described after administration of DSOS or Voltaren® following surgery.[48] Two cases developed perforations and one case resulted in a descemetocele. Histopathology of the amputated LASIK flap at day 3 of an involved eye suggested frank direct corneal injury with a total epithelial defect, keratolysis, loss of corneal lamellae and little inflammatory cellular response. Amputation of the LASIK flap in an involved eye from a different patient revealed a more typical inflammatory scenario with extensive influx of inflammatory cells, loss of lamellae and necrosis near the perforation site. No organisms were found in either case. Reviewing the reports of NSAID-related corneal injury, it appears most have occurred with DSOS for post-operative inflammation following cataract surgery, which incidentally was the only FDA approved use of DSOS. However, it is also apparent that other types of NSAID agents may also induce corneal injury subsequent to other invasive corneal procedures, including refractive surgery.

A report by Lin et al.,[46] describes five cases of corneal melting associated with the use of topical NSAIDs after ocular surgery. The cases involved three women and two men between the ages of 66 to 79 years. Three patients had received DSOS and two patients received the branded product, Voltaren®. The duration of therapy ranged from 10 to 29 days with all patients using the medication four times daily. Four patients were using the products post-operatively following cataract extraction and one was using NSAIDs following argon laser trabeculoplasty. Only one patient was receiving concurrent corticosteroid eyedrops. All cases occurred within a four-month period, with four cases progressing to corneal perforation. Three eyes required tissue adhesive, with one requiring a patch graft and the other a penetrating keratoplasty. One eye required a patch graft and the other eye antibiotics and lubrication. Decreased corneal sensation from diclofenac use was confirmed in two patients, while the others were not tested. It was believed that decreased corneal sensation was one reason the patients may have not sought immediate help.

An epidemiological study of 129 individuals (140 eyes) examining potential trends between ophthalmic NSAID use and adverse corneal events has found a definitive association between DSOS-use and the occurrence of 'severe' corneal events.[54] Severe events were characterised by corneal wound leak, descemetocele, corneal perforation, use of tissue adhesive, tectonic graft, penetrating keratoplasty, keratoprosthesis or enucleation. However, cases of NSAID-induced corneal injury which were classified as severe were associated with branded products such as Voltaren® and Acular® as well, albeit to a much lower extent.[54] Most of the cases involving branded products Acular® and Voltaren® appear to be associated with increased administration and the presence of various concurrent ocular disease states.[54] The presence of diabetes mellitus was significantly higher in those individuals who experienced severe corneal events, whether it be DSOS or branded products.[54] Interestingly, neither autoimmune disease such as rheumatoid arthritis or 'dry eye' was associated with any particular type of outcome.[54]

3. Ophthalmic NSAIDs and Corneal Injury: Potential Mechanisms

3.1 Pathways of Corneal Inflammation

The development of serious corneal complications following use of various topical NSAID ophthalmic products prompts evaluation of possible pharmacodynamic explanations of potential NSAID-related corneal injury. An understanding of the pathways of arachidonate metabolism within the corneal epithelium may lend insight to potential mechanisms of NSAID-induced corneal events. Corneal epithelium from rabbit, porcine and bovine sources has been shown to have the capacity to metabolise arachidonic acid by three alternative routes.[55] These include the COX, lipoxygenase and cytochrome P450 (CYP) pathways.

Typically, the COX pathway of arachidonate metabolism within the corneal epithelium leads to the production of PGs and thromboxanes (TX).[56,57] PGE_1, PGE_2, PGF_{2a} and PGD_2 have been isolated from ocular tissue as well as aqueous humour.[57] PGE_2 is a pro-inflammatory autocoid that has been associated with vasodilatation, inhibition of platelet aggregation and macrophage spreading.[57]

PGE_2 has also been identified as a primary mediator of ocular inflammation, a finding supported by the partial effectiveness of NSAID agents in alleviating ocular inflammation.[56] TXA_2, a potent vasoconstrictor and platelet aggregator, is also produced as a result of COX-related arachidonate metabolism.[57]

Products of lipoxygenase activity in corneal epithelium include LTC_4, LTD_4, and LTE_4.[57] LTB_4 appears to be the most potent arachidonate metabolite found within the eye that acts synergistically with PGE_2 and PGD_2 to enhance vascular permeability, oedema and neutrophil infiltration.[57] LTB_4 is also a potent leucocyte aggregator.[57]

The lipoxygenase pathway within the corneal epithelium also acts on arachidonate to produce 12(S)-hydroxy-5,8,11,14-eicosatetraenoic (HETE).[56,58] 12(S)-HETE has several actions including inhibition of adenyl cyclase, enhancement of leucocyte aggregation, stimulation of endothelial cell mitogenesis as well as serving as a substrate for 12(R)-hydroxy-5,8,14-eicosatrienoic acid (HETrE) synthesis, which also carries potent pro-inflammatory properties.[59,60]

CYP mono-oxygenases represents the third major pathway of arachidonate metabolism within the corneal epithelium. CYP pathway comprises an enzyme system consisting of CYP as the hemoprotein, a flavoprotein identified as the NADPH-dependent CYP-reductase and phosphatidylcholine which facilitates electron transfer in the microsomal system.[55] In the corneal epithelium, arachidonic acid metabolised via CYP results in two biologically active species. Both species, 12(R)-hydroxy-5,8,10,14-eicosatetraenoic acid [12(R)-HETE] and 12(R)-hydoxy-5,8,14-eicosatrienoic acid [12(R)-HETrE] are endogenously formed within the cornea epithelium and are effective mediators of ocular inflammation.[61,62] 12(R)-HETE is a potent inhibitor of Na^+-K^+ adenosine triphosphatase enzyme (ATPase) as well as an aggregate for PMN leucocytes.[61-63] 12(R)-HETE also serves as a substrate for 12(R)-HETrE synthesis catalysed by CYP mono-oxygenases. 12(R)-HETrE has been shown to mediate limbal microvessel endothelial cell proliferation and angiogenesis.[64]12(R)-HETrE also has been demonstrated to educe conjunctival vasodilation, increase permeability of the blood-aqueous barrier and act as an aggregate for PMN leucocytes (figure 1).[59,61] The CYP system also leads to the production of 12(S)-HETE and 12 (S)-HETrE.[65] However, the inflammatory role of the (S)-enantiomers is not as clearly defined as the (R)-forms.[65]

3.2 The Importance of Hypoxia in NSAID-Induced Corneal Injury

The relationship between the COX, lipoxygenase and CYP pathways of arachidonate metabolism within corneal epithelium is subject to various pathophysiologic influences, which may induce or inhibit each pathway as a consequences of events such as trauma, hormonal stimulation or hypoxia. While trauma, infection or autoimmune processes

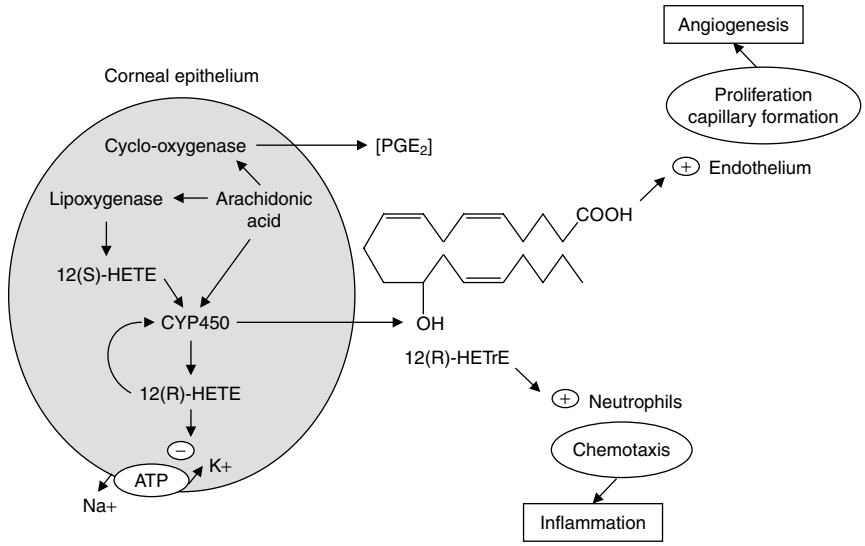

Fig. 1. Pathways of arachidonate metabolism in the eye (from Mieyal et al.,[56] with permission). **CYP450** = cytochrome P450; **12(R)-HETE** = 12(R)-hydroxy-5,8,11,14-eicosatetraenoic acid; **12(R)-HETrE** = 12(R)-hydroxy-5,8,14-eicosatrienoic acid; **PG** = prostaglandin.

are well identified causes of ocular inflammation, the presence of hypoxia, appears to be an important, yet perhaps overlooked, adjunct to the occurrence of ocular inflammation with important ramifications in topical NSAID use. For example prolonged hypoxia due to conditions such as contact lens wear can disrupt cellular homeostasis and result in angiogenesis and corneal neovascularisation.[66] Hypoxia appears to suppress COX activity whereas corneal CYP and lipoxygenase pathways are enhanced.[55] It has been shown that rabbit cornea demonstrates a profound decrease in synthesis of epithelial PGE_2 following as little as 24 hours of hypoxia.[56] Although COX-1 activity decreased with hypoxia, COX-1 protein levels remain unchanged suggesting the oxygen dependent nature of COX-1 activity.[56] Decreased oxygen tension also appears to induce the corneal CYP isoform 4B1, which is responsible for 12-hydroxyeicosanoid production.[67,68] Phenobarbital (phenobarbitone), an inducer of hepatic CYP4B1 also has been demonstrate to induce rabbit corneal 12-HETE and 12-HETrE synthesis as well.[67]

Various NSAIDs have themselves been shown to induce both COX as well as CYP enzymes. Factors that appear to play a role in COX-2 as well as CYP induction due to NSAID use relate to their role as peroxisome proliferators and their activity at the peroxisome receptor.[69] Peroxisomes are subcellular organelles that perform an array of functions including oxidation of fatty acids and cholesterol metabolism.[70] Peroxisome proliferators (PPs) may be classified as dissimilar compounds which include both industrial and pharmaceutical chemicals. PPs act by binding to the peroximase proliferator-activated receptor (PPARs) which results in the expression of genes involved in lipid metabolism, cell growth and peroxisome proliferation.[70] PPARs appear to play a role in the transcriptional regulation of COX-2 activity as well.[68] Flurbiprofen as well as indomethacin have been shown to induce COX-2 as well as CYP4B1 activity in rabbit corneal epithelial cells apparently

through a mechanism that involves activation of peroxisome proliferator receptors.[69] Additional studies have also shown that high doses of diclofenac induce a novel form of COX-2 perhaps through a PPAR mechanism.[71] The diclofenac-induced COX-2 is unique in that it appears to be sensitive to paracetamol (acetaminophen) with decreased sensitivity to other types of NSAIDs. NSAID-induced increase in COX-2 activity, whether secondary to hypoxia or NSAID treatment, appears not to occur in concert with a corresponding increase in PGE_2 accumulation.[69,71]

In rabbit cornea, both PPAR inducible CYP4B1 and COX-2 mRNAs were increased by conditions of hypoxia.[69] However, a parallel increase in PGE_2 was not found secondary to COX-2 induction due to hypoxia.[69] These findings suggest that under certain conditions of stress, particularly hypoxic inflammation, the inflammatory response is not prostaglandin mediated, but rather due to alternative mechanisms, such as accumulation of CYP-derived eicosanoids. It is therefore understandable that in various clinical circumstances, the therapeutic utility of NSAIDs would be diminished due to the occurrence of non-prostanoid mediated inflammatory responses.[72] Moreover, it is feasible that NSAIDs may in fact exacerbate the inflammatory response by induction of CYP4B1 resulting in increased production of the pro-inflammatory epithelial eicosansoids 12-HETE and 12-HETrE.[72,73] Although studies examining expression of epithelial eicosanoid production have primarily involved rabbit, bovine and porcine cornea, recent studies have found that pro-inflammatory eicosanoids such as 12-HETrE are indeed present in human tears as well and are expressed up to 40-fold in inflamed human eyes.[74] It is of interest to note that ocular surface disease conditions may contribute to chronic epithelial hypoxia due to prolonged qualitative and/or quantitative tear deficiencies or metabolic abnormalities within the epithelium.[75]

While previous studies have failed to find a relationship between dry eye and the occurrence of adverse corneal events associated with NSAID use, studies have demonstrated that diabetes mellitus is a risk factor for severe adverse corneal events with topical NSAID use.[54] Diabetes mellitus has been shown to be associated with keratoconjunctivitis sicca as well as various levels of neurotrophic involvement typified by a decrease in corneal sensation.[76,77] Studies have shown that following treatment with aldose reductase inhibitors, those with diabetes mellitus showed a significant improvement in rose bengal and fluorescein staining as well as tear break-up time.[76] It is apparent that diabetes reversibly alters tear film physiology leading to signs of keratoconjunctivitis sicca despite a lack of symptoms, perhaps due to concurrent decreased corneal sensitivity.[54] Based on the theoretical premise that corneal hypoxia is a risk factor for NSAID induced injury, it would be of interest to re-examine the potential relationship between chronic tear deficiency or other causes of altered corneal epithelial morphology such as long term contact lens wear and the occurrence of adverse corneal events in those who require NSAID use.[68]

3.3 The Role of Matrix Metalloproteinases in NSAID-Induced Corneal Injury

The relationship between matrix metalloproteinases (MMPs) and corneal injury is also of interest as a potential mechanism of NSAID induced corneal injury. Garrana et al.[78] examined epithelia from patients with recurrent corneal erosion to assay for the presence of MMPs in comparison to epithelia from healthy individuals. Twelve of 13 erosion specimens demonstrated MMP-2 activity, 1 of the 12 also showed MMP-9 activity. All normal corneas were devoid of MMP activity. Additional studies regarding corneal MMPs corroborate the hypothesis that MMPs have a role in corneal re-epithelialisation failure.[79] These studies become more curious when one considers the findings of Ito et al.[80] who have demonstrated that both diclofenac as well as indomethacin augment production of proMMP-9 in rabbit articular chondrocytes. Ito et al.[80] have also shown that COX-derived PGE_2 down regulates the production the proMMP-9. It appears that COX-inhibitors

may enhance degradation of proteoglycans by limiting PGE formation and that both PGE_1 as well as PGE_2 play an important role in limiting inflammatory destruction of articular cartilage.[80] Based on these findings and the determination of the presence of MMP-9 activity in the human corneal epithelium, it may be possible that topical NSAIDs exert deleterious effects on the corneal epithelium as well as the collagen rich stroma by promoting MMPs activity through inhibition of PGE production. Indeed, studies by Hargrave et al. have described a case of corneal decompensation subsequent to the use of DSOS which, on further examination, demonstrated a strong presence of MMP-9 activity. It is unclear, however, if the presence of MMP-9 was a secondary finding due to the pathology of enzymatic contributions of tissue destruction or was a product of interaction with DSOS.[81]

3.4 Direct Mechanisms of NSAID-Induced Corneal Injury

In addition to indirect mechanisms for NSAID-induced corneal toxicity, other potential direct mechanisms for NSAID toxicity are of interest. Studies utilising scanning electron microscopy have concluded that various NSAID solutions do indeed cause alterations in epithelial cell membranes and surface microvilli when used over a 5-day period on intact rabbit corneal epithelium.[82] The extent of cell damage appeared to be related to the pH of the solution, preservative and type of NSAID.[83] In addition, stromal swelling in the rabbit cornea has been correlated directly to NSAID administration as well as the integrity of the corneal epithelium.[83] Rabbit studies have also demonstrated that topical diclofenac 0.1% and flurbiprofen 0.03% significantly retard re-epithelialisation of iatrogenic corneal epithelial abrasions; however, no significant differences in stromal oedema, corneal haze or conjunctival hyperaemia among the control and treatment groups were found.[84] Contrary to the previous rabbit studies, however, indomethacin or flurbiprofen were shown to have little effect in the re-epithelialisation of cultured rat corneas following a 3mm abrasion while lipoxygenase inhibitors were shown to markedly slow corneal re-epithelialisation.[85] Additional human studies examining the effects of diclofenac 0.1% on corneal epithelial structure and function following small incision cataract surgery have found no ill effects of the drug following three times a day use for 2 months post-operatively.[86] Test parameters included vital staining tear function, corneal sensitivity, endothelial and epithelial specular microscopy, pachymetry, anterior fluorometry and cell/flare assessment both before and after diclofenac use. However, it should be noted that study participants were excluded if there was evidence of diabetes mellitus, autoimmune disease, a history of chronic corneal and conjunctival disease or contact lens wear.[86] It is remarkable to note that while the therapeutic entity found in DSOS and Voltaren® are the same, the various buffers, preservative and surfactants were distinctly different between the two diclofenac products.

Interestingly, studies have demonstrated that NSAIDs, particularly indomethacin and to some extent diclofenac, produce apoptosis of cultured chicken embryo fibroblasts in a dose and time dependent manner.[87] Drugs that only weakly inhibit COX enzymes such as isoxicam and acetophenetidin, have little, if any, apoptotic effect, even at high doses.[87] The mechanism as to which NSAIDs lead to apoptosis remains unclear, and it is uncertain if the COX enzyme is directly involved. However, it does appear that COX activity and its products play a critical role in the maintenance of cell integrity.[87]

Furthermore, it is of interest to note that tocophersolan, the solubiliser present in DSOS is a tocopherol (vitamin E) compound that acts in concert with polyethylene glycol succinate to aid in the dissolution of the solute. In general, tocopherol derivatives are considered to exert beneficial effects on cellular health by exerting significant anti-oxidative properties. However, tocopherol has also been demonstrated to inhibit retinal pigment epithelial cell proliferation as well as inducing

apoptosis of mouse mammary cells. It is unclear if these findings have any relationship to the events seen with the use of DSOS; however, it is evident further studies on the toxicity of tocophersolan as an ophthalmic pharmaceutical solubiliser is warranted.[81]

4. Drug Interactions

Topical NSAIDs for ocular use are often used concurrently with other topical ophthalmics, such as antibiotics as well as corticosteroids for use following cataract surgery or other invasive procedures in which inflammation with or without an infectious aetiology co-exist.[88] A fixed dose combination product of diclofenac 0.1% and tobramycin 0.3% was found to be effective in reducing anterior chamber inflammation following cataract surgery with acceptable ocular tolerability and efficacy.[89] Further studies have shown that a combination of diclofenac with gentamicin results in a 2-fold increase in aqueous humour concentration of diclofenac 0.1% when diclofenac is used in combination with gentamicin compared with use of diclofenac alone.[90] These observations may be due to the known negative effects of gentamicin on corneal integrity allowing for increased corneal permeability and drug penetration. Topical ophthalmic NSAIDs such as ketorolac as well as diclofenac have also been shown to be effectively combined with the anti-viral drug cidofovir which has been used as an experimental drug for the topical treatment of corneal adenoviral disease.[91]

Ophthalmic NSAIDs are effectively combined with other classes of antibiotics such as the fluoroquinolones. In addition, use of topical β-blockers or prostanoid derivatives for the treatment of glaucoma may be safely used with topical NSAIDs; however, use of the these agents may result in loss of corneal epithelial integrity leading to greater penetration of the NSAID. This may be particular true with combined use of topical NSAIDs with topical carbonic anhydrase inhibitors due to the latter's demonstrated negative effect on corneal epithelial integrity.[92]

While corticosteroids have been used topically in conjunction with ophthalmic NSAIDs, the concurrent use of topical corticosteroids and NSAIDs has been identified as a risk factor for the development of corneal erosion and potential perforation.[88]

It is also of interest to note that co-administration of oral indomethacin with topical ophthalmic brimonidine 0.2% results in a significant loss of the ocular hypotensive response known to be induced by brimonidine for the treatment of elevated intraocular pressure.[93] It is unclear if other oral nonsteroidal agents exert similar effects, or if the use of topical ophthalmic NSAIDs results in a similar interaction.[93] However, intraocular pressure should be carefully monitored when co-administrating topical ophthalmic NSAIDs and α_2-agonists such as brimonidine.

5. Conclusion

The primary mechanism that NSAIDs are thought to act in the eye to decrease inflammation is by the reduction of prostaglandins produced by COX within target ocular tissue. The development of a safer alternative to corticosteroids in the treatment of ocular inflammatory disease, such as NSAIDs, was considered to be a significant advance in ocular pharmacotherapy. Indeed, from a historical standpoint, the issue of significant complications following NSAID use remained isolated until the recent development of corneal melts associated with the use of DSOS.

The occurrence of corneal melts associated with DSOS prompted concerns regarding the safety of topical ophthalmic NSAIDs in general, as well as specific clinical circumstances that may predispose to NSAID-induced ocular injury. The corneal melts that have been reported with NSAID use also prompts a re-examination of the clinical pharmacology of topical NSAIDs as a class and their ramifications in ophthalmic use. How NSAIDs modify the metabolic balance between alternative pathways of arachidonate metabolism within the corneal epithelium may be a key factor in the development of therapeutic failures and drug toxicity.

The lack of PGE_2 accumulation in the face of increased COX-2 activity subsequent to hypoxia challenges the role of COX-derived prostaglandins in mediating ocular surface inflammation and provides at least a partial explanation as to why NSAIDs are often partially effective in quieting significant inflammatory disease.[55,69,94,95] The use of NSAIDs in various patient specific circumstances such as diabetes mellitus may exacerbate pre-existing conditions such as an inflammatory keratitis leading to more serious corneal injury.[86,96] The role of preservatives and surfactants found in ophthalmic NSAIDs as precipitating factors in corneal injury must also be considered, particularly when the agent is used on a long-term basis.[94,96] Further research utilising animal models may help delineate if corneal hypoxia plays a role in NSAID induced corneal injury and if administration and pharmacokinetic factors are considerations in NSAID-induced corneal injury.[97] In addition, the known effect of NSAIDs on decreasing corneal sensitivity may interrupt the relationship between the corneal surface and lacrimal gland secretion leading to altered tear physiology and subsequent corneal hypoxia. This effect may be exacerbated by the neuropathic effect on corneal sensitivity noted with diabetes mellitus.[54,98] Evidence also exists that diclofenac decreases substance P content of human tears.[99] Substance P is a neuropeptide that appears to promote migration and proliferation of corneal epithelial cells and may be of interest to future research concerning the detrimental effects of NSAIDs on the corneal epithelium as well.[99] The development and use of topical ophthalmic COX-2 specific inhibitors will also be of considerable clinical as well as research interest.

Until clinical evidence dictates otherwise, the data supporting theories of potential mechanisms of NSAID-induced corneal injury, while of interest, do not significantly alter the current favourable clinical risk-benefit assessment of topical ophthalmic NSAID use. However, the broad range of indications for which ophthalmic NSAIDs are used requires attention to possible drug-induced reactions that may masquerade as disease progression. Lack of a clinical response also requires consideration of alternative therapeutic approaches, rather than merely switching NSAID classes. Unlike corticosteroids, increasing the frequency of administration will not enhance or modify the anti-inflammatory action of NSAIDs although similar to corticosteroids, tapering NSAIDs may help avoid inflammatory rebound. Like corticosteroids, NSAIDs are replete with their own set of potential hazards, which may be a direct effect of the NSAID itself, or in some cases, an indirect circumstance of the complex events associated with ocular inflammation, topical NSAID use, ophthalmic preservatives and surfactant combinations and concomitant ocular disease states. However, with appropriate administration, diligent monitoring as well as an understanding of the pharmacodynamics of NSAID action, non-selective topical ophthalmic NSAIDs can achieve therapeutic goals in a safe and uneventful manner.

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