

## NSAID-induced corneal melt: Clinical importance, pathogenesis and risk mitigation.

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### Commentary

In the age of evidence-based medicine, non-steroidal anti-inflammatory drug (NSAID)-induced corneal melt (NICM) remains a standout in that its prevention, etiology and optimal management are still not guided by well-defined scientific data. NICM, the loss of corneal epithelium accompanied by stromal thinning that can result in ocular perforation and profound vision loss, remains a rare but well accepted entity. In our recent review, we examined the available literature on the clinical features and pathogenesis of NICM, and proposed measures to mitigate its impact on ocular health.

After its first description in 1999, following a survey of members of the American Society of Cataract and Refractory Surgery, multiple case reports and small series cemented this rare condition as a true ophthalmologic entity. Although infrequent, its negative impact on vision was so significant that Alcon voluntarily withdrew from the market the offending NSAID diclofenac. Since then, all but one of the topical ophthalmic NSAIDs have been associated with corneal melt. Our understanding about the pathophysiology of this process since the original description, although significantly expanded, remains incomplete.

Several important questions regarding NICM remain without definitive evidence for a best practice from existing literature. Perhaps the most important among them is the true incidence of NICM. Although the highest reported incidence is 7.5%, this is likely an overestimation. Because prospective studies to determine the true incidence would require an impractically large sample size (reflecting the infrequent occurrence of NICM), estimates of its incidence from isolated reports will remain the best indication of its true incidence. Currently, the incidence of NICM is “fairly low” but nothing beyond that can be stated with certainty. Equally unclear is the effect of dose and duration of NSAID treatment. NICM is reported to occur as early as 3 days [1] and as late as 17 months [2] after the initiation of topical NSAID therapy.

Another unresolved question regards how NICM begins. Although existing literature suggests an additional insult is required for NICM to occur, the exact ‘trigger’ and the means by which such a trigger initiates the process remain unclear. Apparently, any procedure involving a corneal incision can predispose to NICM. Keratoconus and ocular surface diseases that compromise the cornea such as dry eye disease are local conditions that may well predispose to NICM. Dry eye disease is considered by many authorities to be a relative (if not

absolute) contraindication to the administration of topical ophthalmic NSAIDs. Additional systemic risks for NICM include diabetes mellitus and immune diseases including rheumatoid arthritis, Sjogren’s syndrome and rosacea. Vitamin E, an excipient in the initial formulation of ocular NSAIDs, was once proposed to be responsible for inducing NICM; the inference was that the NSAID in those preparations was exonerated. However, numerous reports have since confirmed that vitamin E does not cause corneal melt.

The uncertainty created by these unanswered questions generates a conundrum for clinicians who must weigh the risk for the rare but potentially devastating complication of NICM to the clinical benefit NSAIDs provide for common ocular conditions such as postoperative cystoid macular edema, ocular inflammation and/or pain. Clinicians must always remain cognizant that the incidence of NICM is probably ‘fairly low’ but certainly a real possibility, especially in the right clinical setting.

When scientific data are lacking or incomplete, evidence-based approaches dictate that clinical management should be guided by logical conclusions and plans derived from available data. Our review proposed a mechanism for NICM, highlighted the potential benefits of a new class of drugs (phospho-modified NSAIDs), and proposed an algorithm to minimize the detrimental effects of NICM [3].

Current understanding of the pathogenesis of NICM suggests that corneal melt begins with a corneal epithelial defect, which, if not corrected, is followed by breakdown of the stroma. The loss of corneal epithelial integrity is a key factor in the progression of the process. Hydrolysis of corneal collagen (stromal fibers), mediated by various matrix metalloproteinases (MMPs), results in corneal thinning, followed by a descemetocoele and in the most severe cases, corneal perforation. Infiltrating inflammatory cells also contribute to the early corneal destruction.

Eicosanoids and MMPs are among the major players in corneal melt. Eicosanoids, such as PGE<sub>2</sub> are cytoprotective to the cornea. Commercially available topical NSAIDs, which inhibit the biosynthesis of eicosanoids, can accelerate corneal melting due to inability to heal or maintain an intact epithelial layer. Increased expression of MMPs -1 -2 -8 and -9 in the cornea has been implicated in corneal melt. The cumulative effect of increased MMP expression results in the degradation of the corneal extracellular matrix leading to progressive erosion of

the stroma that can result in desmatocele formation and frank perforation when prolonged.

We proposed a two-stage mechanism of NICM. It begins with the epithelial stage, followed by the stromal stage. The initiating event is the development of a corneal epithelial defect induced by NSAIDs in a cornea compromised by local or systemic risk factor(s). The rapid reduction of PGE<sub>2</sub> levels prevents the repair of the epithelial layer. The cornea is damaged by infiltrating leucocytes (perhaps attracted by increased levels of hydroperoxyeicosatetraenoic acid and leukotrienes resulting from COX inhibition) and activated MMPs, which disrupt the tight junctions of epithelial cells allowing the process to advance to the stromal stage. In the latter, the process is dominated by activated MMPs, which hydrolyze the collagen fibrils below the denuded epithelium. Unchecked, the progressive lysis of collagen can reach Descemet's membrane and occasionally cause corneal perforation.

A recent report by us indicated that the modified NSAIDs (phosphosulindac being a prime example) are extremely unlikely to have corneal melt as a side effect. At least two reasons strongly support this conclusion. First, phosphosulindac is not a COX inhibitor and does not adversely affect PGE<sub>2</sub> levels in the cornea. Second, phosphosulindac suppresses both the expression and activity of MMPs. Their combined effect protects the cornea. These properties are in stark contrast to those of diclofenac and ketorolac, which have been implicated in NICM. Both of these conventional NSAIDs suppress PGE<sub>2</sub> almost completely and have no effect on MMPs. Finally, modified NSAIDs such as phosphosulindac may be less likely to attract infiltrating leukocytes since they do not shunt metabolites of the arachidonic acid pathway toward hydroperoxyeicosatetraenoic acid and leukotrienes as occurs with conventional NSAID inhibition of the COX pathway.

The exemplary safety of phosphosulindac shown in preclinical models of dry eye [4] and other diseases [5-8], combined with its apparent efficacy stemming mainly from its anti-inflammatory properties make it a promising candidate drug for many eye conditions. There is ongoing work towards its clinical development.

### ***Our review formulated the following evidence-based suggestions to mitigate the risk of NICM.***

- Clinicians must remain cognizant of NICM as a distinct entity and of its severity.
- Ocular and systemic risk factors should inform the decision to prescribe ocular NSAIDs. Ophthalmic surgery is a risk factor. Ocular surface diseases that compromise the cornea such as dry eye disease are contraindications to the use of ocular NSAIDs. Diabetes, systemic immune diseases are also clear risk factors.
- Carte blanche and open-ended administration of topical ocular NSAIDs should not be done. Frequency and duration of use should be restricted to the minimum required.

- All patients, especially those post ocular surgery or with other risk factors for NICM that receive topical ophthalmic NSAIDs should be monitored closely.
- When corneal melt is diagnosed, immediately discontinue NSAID eye drops and initiate aggressive and timely treatment.

The potentially devastating consequences of NICM provide a challenge for ocular pharmacology: Either develop approaches that eliminate the occurrence of NICM, or develop novel therapeutics that control pain and inflammation but are free of this side effect. Clinicians will greatly benefit from resolution of this therapeutic conundrum. Until such time, an evidence-based approach mandates that sensible awareness of this entity will best serve our patients.

### **References**

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