

The Considerable Conundrum of NSAID-induced Melt

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Over 20 years after the first description of NSAID-induced Corneal Melt (NICM), a rare but potentially devastating visual complication induced by a topically applied medication, the optimal prevention and treatment for this condition remain unknown creating a clinical conundrum for eye care professionals and challenge for eye researchers. Optimal patient care requires physicians have the clinically relevant facts about the pathologic conditions and integration of such information into their workflows and treatment algorithms.

Diseases with low prevalence and high morbidity often create a difficult situation for doctors: there simply may not be enough factual data to support well-informed therapeutic decisions. This information void can result in suboptimal patient outcomes with significant cost to patients, providers and health care systems.

In our recent review article, we examined all available literature on the clinical features, prevalence and pathogenesis of NICM [1]. 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. We suggested 5 measures to mitigate its impact on ocular health. The article highlighted the importance of NICM and areas of uncertainty regarding its management as well as aspects of the condition which make studies of its pathogenesis and prevalence difficult to perform.

NICM is the loss of corneal epithelium accompanied by stromal thinning that can result in ocular perforation and vision loss. Corneal melt is associated with various conditions such as infections, sterile inflammation and surgical or chemical injury to the cornea. Concern is warranted given that topical NSAIDs, routinely used

following cataract surgery, are important in the treatment of a wide range of ophthalmological conditions including allergic conjunctivitis, ocular inflammation, pain caused by ocular surgery and cystoid macula edema following cataract surgery [2]. The importance of NICM derives from its clinical consequences: it can cause permanent vision loss or ocular deformity, requiring treatments such as corneal transplantation that mandate life-long therapy.

The first reported description of NICM was in 1999, following a survey of members of the American Society of Cataract and Refractory Surgery [3]. Although controversial at first [4,5] multiple case reports and small case series have cemented its acceptance as a true ophthalmologic entity. Although infrequent, its negative impact on vision was so significant that its manufacturer voluntarily withdrew diclofenac, the offending topical NSAID, from the market [6]. Currently, all but one of the topical ophthalmic NSAIDs have been associated with this potentially blinding complication [6-18]. Our understanding of the pathophysiology of this process since the original description, although significantly expanded, is still incomplete. Its low incidence and complex physiology defy easy answers to the many questions surrounding this condition.

Several important questions regarding the prevalence and a potential dose-dependent effect of NSAIDs on NICM persist in the absence of dedicated studies. Although the highest reported incidence of NICM is 7.5%, this is likely an overestimation [5]. Most reports in the literature are from individual case reports or small case series because a properly powered prospective study to determine true incidence of NICM would require too large a sample size to be informative. Similarly, any prospective trial comparing NSAIDs to other therapies would be difficult

because conventional levels of statistical precision are likely unobtainable for such a rare disease. Unfortunately, this means that clinicians treating NICM must form their judgments solely on the basis of (potentially biased) observational studies, experience, and anecdote. Based on existing data, the incidence of NICM should be considered “fairly low” but nothing beyond that can be stated with certainty. A second equally important and unanswered question regards the effect of cumulative dose or duration of NSAID treatment critical for the induction of NICM. NICM is reported to occur as early as 3 days and as late as 17 months after the initiation of topical NSAID therapy and it remains unclear what causes such a wide variation.

The pathophysiological cascade that culminates in NICM remains ill defined. It is still unclear what initiates the cascade in those that are susceptible. In the current conceptualization, an additional ‘trigger’ is required for NICM to occur; both the ‘trigger’ and how it initiates the process have not been identified. Any procedure involving a corneal incision appears to predispose to NICM. Other corneal co-morbidities such as keratoconus and ocular surface diseases that compromise the corneal epithelium such as dry eye disease also may increase the risk for NICM. Dry eye disease is considered by many authorities to be a relative (if not absolute) contraindication to the administration of topical ophthalmic NSAIDs [19]. Systemic diseases may also increase the risk for NICM. Diabetes mellitus and immune diseases such as rheumatoid arthritis, Sjogren’s syndrome and rosacea have been associated with NICM although the mechanism by which they increase risk is not understood. Vitamin E, an excipient in the initial formulation of ocular NSAIDs, was once posited to be responsible for NICM; the inference was that the NSAID in those preparations was exonerated. However, numerous reports have subsequently confirmed that vitamin E does not cause corneal melt [20].

Although the details regarding the pathophysiology of NICM are elusive, the current paradigm of NICM speculates that the process begins with a corneal epithelial defect, which, progresses in cases of non-resolution to loss of the stroma. The loss of corneal epithelial integrity is a key initiating factor in the progression of the process. Increased levels of various matrix metalloproteinases (MMPs), released by various inflammatory cells, result in hydrolysis of the corneal collagen (stromal fibers) which initially results in corneal thinning, descemetocoele formation, and finally, in the most severe cases, corneal perforation. Infiltrating inflammatory cells also contribute to the early corneal destruction, possibly in part through the release of MMP’s.

It is surmised that eicosanoids and MMPs are major effector molecules in corneal melt. Eicosanoids, such as PGE₂, are cytoprotective to the cornea [21]. Commercially

available topical NSAIDs nearly abolish the biosynthesis of eicosanoids and increase the propensity for corneal melt because of the inability to heal or maintain corneal epithelial integrity. Elevated corneal expression of MMPs -1 -2 -8 and -9 has also been implicated in corneal melt [5,22]. Increased MMP levels can cause digestion of the corneal extracellular matrix leading to progressive thinning of the stroma eventually culminating in a frank perforation if unchecked.

In our review, we proposed a two-stage mechanism of NICM that begins with an *epithelial stage*, followed by a *stromal stage*. The development of an epithelial defect in a cornea that is compromised by topical NSAID use, surgery or other local and systemic risk factors is the initiating event, or ‘trigger’. Topical NSAID administration also results in rapid reduction of cytoprotective PGE₂ levels preventing repair of the epithelial defect. Additional corneal damage ensues from infiltrating leucocytes that migrate to the area due to the chemoattractant effect of increased HETEs levels that are a byproduct of COX inhibition. These leucocytes release activated MMPs which disrupt tight junctions in corneal epithelial cells preventing healing of the epithelial defect and allowing the process to advance to the stromal stage. Once in the stromal stage, activated MMPs dominate the process hydrolyzing corneal collagen fibrils below a denuded epithelium. Unchecked, the progressive lysis of collagen can reach Descemet’s membrane and occasionally cause corneal perforation.

A recent report by our laboratory demonstrated that the modified NSAIDs (phosphosulindac being a prime example) are extremely unlikely to cause corneal melt as a side effect [23]. At least two sets of data strongly support this conclusion. First, unlike commercially available topical NSAIDs, phosphosulindac is not a cyclooxygenase inhibitor and does not completely abolish the levels of the cytoprotective PGE₂ in cornea. Second, both *in vitro* and *in vivo* experiments performed in our lab demonstrated that expression and activity of MMPs was inhibited by phosphosulindac. Combined these two effects protect the cornea. These properties starkly contrast the effects of two clinically used NSAIDs, diclofenac and ketorolac, both implicated in NICM. These conventional NSAIDs obliterated PGE₂ expression and had no effect on MMPs. Finally, as modified NSAIDs such as phosphosulindac do not inhibit the arachidonic acid pathway, shunting of metabolites towards the HETEs should not occur resulting in less leukocyte infiltration and MMP release.

Our review proposed the following five suggestions based on evidence-based information for clinicians to mitigate the risk of NICM:

1. Clinicians must remain cognizant of NICM as a distinct entity and of its severity.

2. Clinicians must consider both ocular and systemic risk factors when initiating therapy with topical ocular NSAIDs. Important risk factors to consider include ophthalmic surgery, ocular surface diseases that compromise the cornea such as dry eye disease and systemic conditions such as diabetes and systemic immune diseases.
3. When topical use of NSAIDs is required, the duration and frequency of administration should be kept to the minimum required. Open-ended administration of topical ocular NSAIDs should not be avoided.
4. All patients that require topical ophthalmic NSAIDs should be informed and monitored closely for the occurrence of NIDM.
5. If corneal melt is suspected, immediately discontinue NSAID eye drops and initiate aggressive and timely treatment.

In the year 2020, the cause and prevention of NICM still remain less than clear. The potentially devastating consequences of NICM provide two challenges 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. Solutions to these two challenges will not only result in better patient care and better outcomes but also higher clinical effectiveness, efficiency, and satisfaction. Until such time that answers to these questions are known, clinicians must decide how to manage this clinical conundrum using their best judgement with imperfect information. In order to answer some of these important questions, agencies will face a conundrum to fund either large prospective studies to assess this rare but occasionally dangerous complication, or funding basic research and translational studies that can help define corneal pathophysiology and advance novel therapeutic agents. We believe that the example of modified NSAIDs makes a strong argument for the latter. Regardless of the means, better understanding of this unique pathology should make NICM a thing of the past.

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