



Commentary

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Commentary: NSAID-Induced Corneal Melt: Clinical Importance, Pathogenesis and Risk Mitigation

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Corneal melt, the loss of corneal epithelium accompanied by thinning or even perforation of the corneal stroma, is a potentially serious eye condition. The association of corneal melt with topical use of non-steroidal anti-inflammation drugs (NSAIDs) has received recent attention not only because of its clinical importance, but also because of its impact on the therapeutic use of NSAIDs in the eye. NSAIDs are used frequently to treat ocular inflammation and/or pain¹.

In our publication², we evaluated the literature on NSAID-induced corneal melt (NICM), assessed NICM as a clinical entity (its association with NSAIDs was initially doubted), examined its pathogenesis and recommended measures to mitigate its impact on ocular health.

The first description of NICM was reported in 1999 based on a survey of members of the American Society of Cataract and Refractory Surgery³. The finding was so dramatic that shortly thereafter a large pharmaceutical company, Alcon, suspended the distribution of its ocular diclofenac⁴. Multiple case reports and small series followed this seminal observation. By now, all but one of the NSAIDs used in the eye have been associated with corneal melt and its existence is no longer in doubt⁴⁻¹⁶.

Several questions regarding NICM remained, however, not fully addressed. Most prominent among them is the one concerning the true incidence of NICM. The highest reported incidence was 7.5%¹⁷, but this is probably an overestimate. Considering all reports, the true incidence of NICM remains unknown and given the size of studies that are required for such a determination it will likely be so in the foreseeable future. For clinical purposes, one should consider the incidence of NICM 'fairly low' but certainly a real possibility, especially in the right clinical setting. Equally uncertain is the effect of NSAID dose and duration of treatment on NICM. Reports in the literature indicate that it can occur as early as within 3 days and as late as 17 months after the initial administration of ocular NSAIDs. Finally, notwithstanding the fact that one of the ocular NSAIDs has not been associated with NICM, it is clinically prudent to consider all ocular NSAIDs as potential inducers of NICM.

What is clinically relevant is that administration of ocular NSAIDs often requires an additional 'trigger' to induce corneal melt. Conditions predisposing to NICM include: diabetes mellitus, systemic immune diseases and ocular surface diseases that compromise the

cornea, as well as recent ocular surgery¹⁸. Notable among the immune systemic diseases are rheumatoid arthritis, Sjögren's syndrome and rosacea. Keratoconus and dry eye disease are ocular surface diseases that predispose to NICM. In fact, dry eye disease is considered a contraindication to the administration to NSAIDs to the eye¹⁹. Finally, surgery of the anterior chamber of the eye can make the ocular surface susceptible to NICM.

A point that lingers in the literature is whether vitamin E, when part of the formulation of ocular NSAIDs, is responsible for the corneal melt. Based on some in vitro studies and likely over-interpretation of results, it was proposed that it was this vitamin that caused corneal melt and not the NSAID in those preparations. Numerous reports have confirmed that vitamin E does not cause corneal melt. A compelling argument was provided, for example, by reports of corneal melt associated with diclofenac and other NSAIDs that did *not* contain vitamin E, that establishing the NSAID as the offending agent²⁰.

The pathogenesis of corneal melt has been surmised from the available literature, by necessity often not thorough or exhaustive. It appears that corneal melt begins with a corneal epithelial defect, which, if not corrected, is followed by a breakdown of the stroma (hydrolysis of collagen fibers), resulting in corneal thinning, descemetocele and, in some cases, corneal perforation. Infiltrating inflammatory cells may contribute to the early corneal destruction. The suppression of the corneal epithelium propagates the damage.

Of the various signaling molecules in this setting, eicosanoids and matrix metalloproteinases (MMPs) are the major players. Eicosanoids, such as prostaglandin E₂ (PGE₂), are cytoprotective to the cornea²¹. Since NSAIDs inhibit their biosynthesis, their absence accelerates corneal melting, contributing to the destruction of the epithelial layer. It was reported that NSAIDs delay corneal wound healing by reducing production of 12-HHT (12-hydroxyheptadecatrienoic acid), a COX product²². Studies with transgenic mice identified this pathway as the main target in diclofenac-induced delayed corneal wound healing. MMPs, which can degrade components of the extracellular matrix, participate in corneal matrix remodeling²³. Enhanced expression of MMPs -1, -2, -8 and -9 in the cornea has been implicated in NICM^{17, 24}. Their activity erodes the stroma, which, when prolonged, culminates in true perforation.

We proposed a two-stage mechanism of NICM. It begins with the *epithelial stage*, followed by the *stromal stage*. The initiating event is the corneal epithelial defect induced by exposure to the NSAIDs of an already compromised cornea. The rapid reduction of PGE₂ levels prevents the repair of the mucosa. Infiltrating leukocytes compound the damage and activation of MMPs disrupts tight junctions of epithelial

cells enhancing the damage. The net result is to advance the cornea to the stromal stage, which is dominated by activated MMPs; MMPs hydrolyze the collagen fibrils of the stroma below the denuded epithelium. Advancing lysis of collagen reaches Descemet's membrane producing a demescetocele. Further action by the MMPs completes the process by generating a perforation.

A recent report by us indicated that, unlike conventional NSAIDs, the so-called modified NSAIDs (phosphosulindac being a prime example), are extremely unlikely to have corneal melt as a side effect²⁵. There are two reasons for this conclusion. First, phosphosulindac, not a cyclooxygenase (COX) inhibitor, does not affect PGE₂ levels in the cornea. Second, phosphosulindac suppresses the expression and activity of MMPs. This dual effect protects the cornea instead of damaging it. In stark contrast, conventional NSAIDs such as diclofenac and ketorolac, two NSAIDs frequently implicated in NICM, suppress PGE₂ almost completely and have no effect on MMPs.

Many clinicians view NICM as Damocles' sword when prescribing ocular NSAIDs, especially in vulnerable patients or for prolonged periods of time. Our assessment of the existing data helped us formulate the following suggestions to help mitigate the risk of NICM.

1. Awareness of this side effect and of its severity is the first step towards risk control.
2. Risk factors should inform the decision to prescribe ocular NSAIDs. Diabetes, systemic immune diseases, and ocular surface diseases that compromise the cornea are clear risk factors. Ophthalmic surgery ought to be considered a risk factor. Some ocular surface diseases, such as dry eye disease are considered relative, and for most experts absolute, contraindications to the use of ocular NSAIDs.
3. The frequency and duration of administration of ocular NSAIDs should be restricted to the minimum required; their open-ended administration should be avoided.
4. Patients receiving topical ophthalmic NSAIDs should be monitored closely, especially those with risk factors for corneal melt or after ocular surgery.
5. When corneal melt is diagnosed, NSAID eye drops should be discontinued and aggressive and timely treatment be instituted.

The clinical importance of NICM creates a veritable challenge for ocular pharmacology. This problem can be addressed by developing approaches to both rapidly and effectively treat NICM or agents that control pain and inflammation but devoid of this side effect. It is hoped that the therapeutic conundrum in the use of ocular NSAIDs will be resolved soon. Until then, sensible awareness of this entity should serve our patients well.

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