CORNEAL MELTS ASSOCIATED WITH TOPICALLY APPLIED NONSTEROIDAL ANTI-INFLAMMMATORY DRUGS*

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ABSTRACT

Purpose: Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to prevent miosis during cataract surgery, to treat ocular allergies, to prevent excessive postoperative inflammation following cataract surgery, and to treat cystoid macular edema following cataract surgery. They have also been used to control pain and photophobia following radial keratotomy and excimer laser photorefractive keratectomy. During August of 1999, severe complications following topical NSAID use, including corneal melting, were reported by members of the American Society of Cataract and Refractive Surgery (ASCRS) responding to a survey distributed in letters from ASCRS to its members. The purpose of this report is to review 11 cases of corneal melting in patients treated with topical NSAIDs, with special attention to the observed toxicity and its relationship to dose and duration of treatment, coexistent disease and therapies, and the indication for treatment. The goal of this study is to identify factors useful in minimizing the occurrence of corneal toxicity.

Methods: The medical records and/or histories of 11 patients with corneal melting associated with the use of topical NSAIDs are reviewed, with special attention to the indication for treatment, the dose and duration of treatment, and coexistent diseases and medical treatments. In addition, the relationship between NSAID treatment and surgery and between NSAID treatment and onset and extent of corneal toxicity are described.

Results: Each of the 11 patients appeared to suffer severe corneal toxicity following the topical use of 0.5% diclofenac ophthalmic solution. Generic diclofenac (Falcon) (Alcon Laboratories, Inc, Fort Worth, Texas) was associated with 7 and Voltaren (Ciba Vision, Atlanta, Georgia) with 4 of these cases. Duration of treatment prior to corneal melting varied from 6 days to 17 months. Associated ocular and systemic diseases and their respective treatments complicate the analysis of these cases. In addition, the indication for treatment with topical NSAIDs was frequently unclear.

Conclusions: The inconsistent and variable dose-toxicity relationships suggest that coexistent factors other than a simple drug toxicity are implicated, if not causative, in NSAID-associated corneal melting. These cases demonstrate the importance of making a clinical diagnosis before treatment and of following the clinical course of patients carefully during treatment.

Tr Am Ophth Soc 2001;99:205-212

INTRODUCTION

Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to prevent miosis during cataract surgery, to treat ocular allergies, to prevent excessive postoperative inflammation, and to treat cystoid macular edema following cataract surgery. These agents have also been used to control pain and photophobia following radial keratotomy and excimer laser photorefractive keratectomy.[1,2] During August of 1999, severe complications following topical NSAID use, including corneal melting, were reported by members of the American Society of Cataract and Refractive Surgery (ASCRS) responding to a survey distributed in letters from ASCRS to its members.[3,4] This led to a recall of Falcon, a generic form of diclofenac ophthalmic solution (Alcon Laboratories, Inc, Fort Worth, Texas).[5] Some have concluded that the availability of generic diclofenac was the sole reason that corneal toxicity was observed.[6] However, the potential importance of completing a careful review of all of these reported cases before concluding that an isolated drug toxicity explains the appearance of these severe corneal toxicities has been recently emphasized.[7] The purpose of this report is not to substitute itself for a complete analysis of the cases of corneal melting, but only to provide an interim review of 11 cases of corneal melting in patients treated with topical NSAIDs, with special attention to the observed corneal toxicity and its relationship to dose and duration of treatment, coexistent diseases and therapies,

*From the Department of Veteran Affairs, San Francisco, and the Department of Ophthalmology, University of California, San Francisco, School of Medicine. Supported by a Merit Review grant from the Department of Veterans Affairs, San Francisco; a grant from That Man May See, Inc; and a departmental core grant from the National Institutes of Health, Department of Ophthalmology, University of California, San Francisco, School of Medicine.

and indication for treatment. The goal of this report is to help identify factors potentially useful in minimizing the occurrence of corneal toxicity while we await a more thorough examination of the factors associated with these toxicities.

METHODS

The medical records and histories of 11 patients with corneal melting associated with the use of topical NSAIDs were reviewed, with special attention to the indication for treatment, the dose and duration of treatment, and coexistent diseases and medical therapies. These 11 cases consist of 5 published cases,[8] 3 cases reported as a poster presentation,[9] and 3 cases from the author's referral practice. Seven cases mentioned at the 104th Annual Meeting of the American Academy of Ophthalmology (AAO) are also included.[6]

RESULTS

Each of the 11 patients presented with severe corneal toxicity and a history of treatment with 0.5% diclofenac ophthalmic solution. Generic diclofenac (Falcon) was associated with 7 and Voltaren (Ciba Vision Corporation, Atlanta, Georgia) was associated with 4 of these cases. A summary of the 11 cases is provided in Table I. A brief description of each case follows:

CASE 1

A 76-year-old woman with a history of dry eye (Schirmer test results, 2 mm and 5 mm) developed a red, painful eye 3 months following cataract surgery. She was treated with Falcon for 10 days, and after a corneal infiltrate with 80% tissue loss was observed, she eventually perforated. Culture revealed group *B streptococcus*.

CASE 2

A 66-year-old woman with a history of dry eyes was treated with Voltaren and apraclonidine hydrochloride (Iopidine) (Alcon Laboratories, Inc) following cataract surgery. After 4 days of treatment, she complained of a foreign body sensation in the eye. The eye was red and photophobic, and she stated that the Voltaren burned more upon instillation. She was told to refrigerate the Voltaren to reduce the burning sensation and to continue treatment. She presented 29 days after surgery with 50% tissue loss. She had reduced values on the Schirmer test.

CASE 3

A 77-year-old man was treated with Voltaren and tobramycin-dexamethasone drops (TobraDex) (Alcon Laboratories, Inc) following cataract surgery. Although he had normal examination results 1 week after surgery, he presented with corneal perforation in the area of surgery 18 days after surgery. He had reduced values on Schirmer tests (12 mm and 8 mm) and diminished corneal sensation.

CASE 4

A 71-year-old diabetic man with systemic hypertension was treated with Falcon and 1% prednisolone given 6 times daily following cataract surgery. He experienced discomfort and hyperemia on postoperative day 7, and he noted decreased vision on postoperative day 9. Perforation occurred on postoperative day 11.

TABLE I. SUMMARY OF CASES

CASE(AGE/SEX)	TREATMENT DURATION	CORNEAL PERFORATION	NSAID (REGIMEN)	OTHER MEDICATIONS	INDICATION FOR TREATMENT (CULTURED ORGANISM)
1. 76 F	10 days	Yes	Falcon (QID)	Tears	Unknown (streptococci)
2. 66 F	29 days	No (keratitis)	Voltaren (QID)	Glaucoma medications, tears	Unknown (NP)
3. 77 M	18 days	Yes	Voltaren (QID)	Dexamethasone, tobramycin, tears	Postsurgery Inflammation (NP)
4. 71 M	11 days	Yes	(Falcon) (QID)	Prednisolone	Unknown (no growth)
5. 79 M	17 days	Yes	Falcon (QID)	Glaucoma medications, prednisolone	Unknown (NP)
6 27 M	5 days (6 hr)	Yes	Falcon (QID)	Rimexolone, Ciloxan	Unknown (NP)
7. 47 F	4 days	No (descemetocele)	Falcon (QID)	Corticosteroid	Unknown (NP)
8. 80 M	10 mo	No (descemetocele)	Voltaren (QID)	None	Unknown (NP)
	7 mo	No (descemetocele)	Falcon (QID)	None	Unknown (NP)
9. 65 F	5 mo	No (keratitis)	Voltaren (QID)	Flarex, Alcaine	Corneal abrasion? (NP)
10. 71 F	5 days	No (keratitis)	Voltaren (TID)	Econopred, Ciloxan	Dellen? (NP)
11. 77 F	14 days	Yes	Falcon (6/day)	Polymixin B sulfate, neomycin, dexamethasone	Unknown (NP)

NSAID, nonsteroidal anti-inflammatory drug; NP, not performed.

CASE 5

A 79-year-old man underwent argon laser trabeculoplasty and was treated with 1% prednisolone with good results. His eye became painful and developed an anterior chamber reaction 3 weeks following surgery. Falcon was added to a regimen of brimonidine tartrate ophthalmic solution (Alphagan) (Allergan, Inc, Irvine, California), dorzolamide (Trusopt) (Merck & Co, West Point, Pennsylvania), timolol maleate (Timoptic) (Merck & Co), and latanoprost (Xalatan) (Pharmacia Corp, Kalamazoo, Michigan). Increased pain, photophobia, and hyperemia developed over 2 weeks, and he presented with 99% tissue loss and a descemetocele 17 days after initiation of treatment with Falcon.

CASE 6

A 27-year-old man presented 5 days following excimer laser surgery complaining of pain. No corneal thinning was observed on examination. He was using rimexolone (Vexol) (Alcon Laboratories, Inc), ciprofloxacin (Ciloxan) (Alcon Laboratories, Inc), and Falcon ophthalmic medications. Falcon was discontinued, but he continued to use rimexolone and ciprofloxacin. He returned in 6 hours with a corneal perforation.

CASE 7

A 47-year-old woman with a history of radial keratotomy 20 years previously returned for excimer laser surgery. She received postoperative treatment with Falcon, fluorometholone acetate (Flarex) (Alcon Laboratories, Inc), and ciprofloxacin. She returned on postoperative day 4 complaining of pain. Her medical regimen was discontinued, and cephazolin and tobramycin eye drops were prescribed. The cornea continued to melt, and a topical corticosteroid was added to the regimen. She required a penetrating keratoplasty 5 months later.

CASE 8

An 80-year-old man developed cystoid macular edema 5 months after cataract surgery. He was treated with Voltaren for 10 months without toxic effects. Falcon was substituted, and after 7 months he presented with pain. Corneal thinning was observed, and a descemetocele was noted after 48 hours.

CASE 9

A 65-year-old woman with trichiasis and a history of cataract surgery 3 years previously underwent a YAG capsulotomy during which she suffered a corneal abrasion. After treatment with Voltaren without patching, she developed a recurrent corneal erosion. She was treated with intermittent patching, Voltaren, proparacaine hydrochloride (Alcaine) (Alcon Laboratories, Inc), fluorometholone, and a bandage contact lens for 2 weeks. Voltaren was discontinued, after which she developed bullous keratopathy. Despite intermittent debridement, epilation, and treatment with Voltaren and Flarex, her cornea continued to exhibit a superficial punctate keratitis. She eventually underwent a penetrating keratoplasty with good results.

CASE 10

A 71-year-old woman was treated with Voltaren, prednisolone acetate (Econopred) (Alcon Laboratories, Inc), and ciprofloxacin following cataract surgery. She presented on postoperative day 5 with ocular pain, and a dellen was observed during examination. Voltaren was discontinued, and goniosol hydroxypropyl methylcellulose (Ciba Vision) was added to the Econopred treatment. Following a poor response to patching, she underwent conjunctival grafting with good results.

CASE 11

A 77-year-old woman with an eye that had been irritated for many months following a complicated cataract surgery presented with increased pain and redness in that eye and an associated "injection of the upper tarsus" of unknown origin. She was treated with Voltaren every 4 hours. She returned in 2 weeks using Falcon and a steroid-antibiotic eye drop. She eventually suffered corneal melt with central perforation.

OTHER CASES

In addition to these 11 cases, corneal melting in 7 "healthy, asymptomatic eyes" following refractive or cataract surgery in patients treated with Falcon were reported at the 104th Annual Meeting of the AAO.[6] Although detailed clinical descriptions were not provided for these cases, at least 2 of the patients were said to have a history of punctal plug insertion, which suggested clinically significant dry eyes. In addition, it was noted that all 7 cases had occurred in one practice, while the nation's "top 15 presribers of Voltaren" have yet to report a severe case of corneal toxicity with use of topical NSAIDs. The speaker concluded that use of Falcon was the cause of all of the cases of corneal melting observed.

DISCUSSION

Corneal complications related to topical NSAID use are uncommon. Superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported following the use of these anti-inflammatory agents.[10-13] These findings are not surprising, because most topically applied medications, particularly those with preservatives, are associated with potential corneal toxicity.[14,15] However, the

reports of corneal melting associated with topical NSAID treatment are surprising and of great interest. Because both infectious and noninfectious corneal melting disorders have many different causes, careful examination of patients is important before a drug toxicity is identified as the cause in all of these cases.[16]

Generic diclofenac (Falcon) may be the sole reason that corneal melting occurred in 2000. Unfortunately, this conclusion is supported only by anecdotal presentations that include a minimum of data with limited analysis and little or no discussion or consideration of complicating factors and alternative explanations.[6] The 7 cases of corneal melts in Falcon-treated patients that were presented at the AAO annual meeting[6] are difficult to discuss because the associated environmental factors and clinical descriptions were not provided. Furthermore, it appears that potentially important coexistent ocular disease was largely ignored during the review of these cases. For example, 2 patients requiring punctal plugs were included as "healthy, asymptomatic patients," ignoring the fact that patients with Sjögren's syndrome can develop sterile corneal ulcerations and perforations without any medical treatment or surgical procedure.[17] In addition, patients with mild and clinically insignificant keratitis sicca have developed severe penetrating and perforating ulcers following cataract surgery without any associated medical treatments.[18] Finally, it is impressive that there appears to be an unbalanced geographic distribution of these cases of corneal melting. An asymmetric distribution of an observed drug toxicity can reflect production or manufacturing problems in a specific lot of drug.[19] Therefore, it is of paramount importance to complete a careful review of all of the reported cases of corneal toxicity before concluding that an isolated drug toxicity explains the appearance of these severe corneal toxicities.[7]

This review of 11 cases of corneal toxicity observed in patients using topically applied diclofenac does not provide compelling evidence of an isolated drug toxicity. The potential causes of acute corneal melting suggest that many cases are unrelated to medical treatment, as summarized in Table II.[20] There is little evidence that these potential causes were carefully excluded from these 11 cases. A clinical diagnosis and therefore an indication for anti-inflammatory treatment were lacking in 8 of 11 cases. It is particularly impressive how seldom an infectious cause was ruled out despite the presence of an uncomfortable red eye of uncertain origin (9 of 11 patients). Three patients (cases 1, 2, and 3) had dry eyes. A deficient tear film has been associated with corneal melting[11,17,18] In addition, abnormal tear production may contribute to enhanced corneal toxicity from topical therapy, particularly if preservatives are present. Therefore, coexistent diseases may have contributed to any or all of the observed corneal melting in this small series of 11 cases.

Coexistent local and systemic medical treatments complicate the analysis of these cases of corneal toxicity. For more than 2 decades, corticosteroids have been recognized as a cause of corneal toxicity. In fact, 25 cases of corneal perforation reminiscent of these cases of corneal melting have been reported by a single observer.[21] Therefore, the use of corticosteroids by 8 of 11 of these patients may be important. In further support of this possibility, it is of note that in case 7, a descemetocele formed despite discontinuation of Falcon and during use of only a corticosteroid. In addition, patient 5, who eventually perforated, was using not only a corticosteroid but also multiple medications, some of which predispose to dry eye (hydrochlorothiazide and timolol) and others that have significant potential for inducing corneal toxicity (dorzolamide, timolol, brimonidine, and latanoprost).

A touchstone for the determination of pharmacologic toxic disease has been proposed.[22] I advocate use of the following Koch-type postulates for a toxic etiology:

- The clinical signs of toxicity must be reproducible in experimental animals.
- The toxic dose-response may show normal scatter of random distribution, but no patient must get toxic effects from doses differing by several orders of magnitude.
- Cessation of dosage should be followed by a decrease in toxicity.

The corneal toxicity reported in these 11 cases does not fulfill these criteria.

Corneal melting has not been reproduced in experimental animals with use of topically applied, commercially available, brand-name NSAIDs. To the contrary, well-designed laboratory studies suggest that these topically administered NSAIDs may be beneficial in protecting animals from corneal melting.[20] In addition, carefully

TABLE II: POTENTIAL CAUSES OF ACUTE CORNEAL MELTING

Herpes simplex keratitis
Mooren's ulcer
Rheumatoid arthritis
Bacterial keratitis
Keratoconjunctivitis sicca
Erythema multiforme
Alkali burn
Anterior-segment dysgenesis
Herpes zoster
Neuroparalytic keratitis
Wound melt/keratoplasty
Pemphigoid
Rosacea keratitis
Thermal burn
Vernal keratoconjunctivitis

Information from Kenyon.[20]

controlled, prospective, double-masked, randomized clinical studies in hundreds of patients indicate that topically applied brand-name NSAIDs appear safe for use in patients.[1,2] Therefore, it is unlikely that there is something distinctive about the diclofenac molecule that predisposes to severe corneal toxicity. It remains to be seen how carefully the generic NSAID Falcon has been tested for the potential of inducing a corneal melt in experimental animals.

An incredibly inconsistent dose-toxicity relationship exists within the group of 11 cases described here. In case 8, for example, the patient was treated with Voltaren for 10 months and Falcon for 7 months for cystoid macular edema following cataract surgery without apparent toxicity. Then, for unexplained reasons, the patient developed corneal thinning with descemetocele formation over 48 hours while using Falcon. This history of prolonged exposure without corneal toxicity followed by an acute corneal melt is not typical of an isolated drug toxicity.

Patient 9 was referred to the author as a possible case of NSAID-induced corneal melt. This case clearly demonstrates how resistant a cornea can be to the potential corneal toxicity of Voltaren. The patient was treated for various indications, including corneal abrasion, recurrent corneal erosion, and bullous keratopathy with Voltaren therapy. Despite concurrent treatment with Flarex and Alcaine, with and without patching, bandage contact lens application, and intermittent debridement, no significant thinning of the cornea was noted during 5 months of treatment. This is remarkable. The coexistent corneal treatments could have in and of themselves caused considerable corneal damage, but little was observed.

Finally, in case 6, the patient had a normal corneal examination 5 days after excimer surgery only to have perforation 6 hours later while using Falcon. It is difficult to find any drug or chemical toxicity reported within the literature with such a rapid course. Therefore, a comparison of cases 6, 8, and 9 makes clear an unusual inconsistency of observed corneal toxicity with topically administered diclofenac. This is unlike an isolated drug toxicity.

Case 10 demonstrates the importance of careful postoperative examinations. This patient was referred to the author because she was unhappy despite a good visual outcome. She believed that she had suffered an "eye melting" due to Voltaren use. Five days following cataract surgery, she had a painful eye and was treated with Voltaren and Econopred. She was carefully examined, and a dellen was recognized and appropriately treated. Fortunately, the patient was not simply treated aggressively for a resistant postoperative inflammatory response without benefit of an examination. It is likely that the careful follow-up care that she received helped her to avoid severe corneal damage related to an improperly treated dellen. It is ironic that the patient ignored the extensive diagnostic and therapeutic efforts of her surgeon and the resultant excellent visual outcome, but instead gravitated toward a potential toxicologic explanation that was at the time popularized in the tabloids and debated on the Internet.

Overall, this review of 11 cases of corneal toxicity observed in patients using topically applied diclofenac reveals an inconsistent and variable dose-toxicity relationship. Furthermore, all of the cases are complicated by coexistent diseases and medical therapies. This makes it difficult to establish a definitive diagnosis for the observed corneal melting. These cases underscore the importance of making a clinical diagnosis before initiating nonspecific anti-inflammatory treatment and the need for careful follow-up of patients after surgical procedures.

While we await a definitive analysis of all the reported cases of corneal melting associated with topical NSAID use, it seems prudent to keep in mind an admonishment from Sir William Osler concerning the potential toxicity of medications, quoted by Dr Fred Wilson II in his American Ophthalmological Society thesis:[23]

> In the fight which we have to wage incessantly against ignorance and quackery among the masses and follies of all sorts among the classes, diagnosis, not drugging, is our chief weapon of offence. Lack of systematic personal training in the methods of the recognition of disease leads to the misapplication of remedies, to long courses of treatment when treatment is useless, and so directly to that lack of confidence in our methods which is apt to place us in the eyes of the public on a level with empirics and quacks.

CONCLUSIONS

The inconsistent and variable dose-toxicity relationships reflected in these 11 cases of corneal melting in patients using topical diclofenac suggest that coexistent factors other than a simple drug toxicity are implicated, if not causative, in these toxicities. Concurrent ocular and systemic disease in many of these patients, as well as their use of medications including corticosteroids, complicates this analysis. The occurrence of corneal melting can be minimized by attempting to make a definitive diagnosis before initiating anti-inflammatory treatment and by careful follow-up examinations of patients after surgery.

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DISCUSSION

DR MICHAEL A. LEMP. Dr Flach has called our attention, by way of a retrospective series of 11 patients, to the contemporary vexing problem of keratolysis associated with the use of non-steroidal anti-inflammatory topical medications. He points out the compounding variables in these cases and suggests that co-existing factors rather than a simple drug toxicity are implicated.

Indeed, the conditions associated with these, and other previously recorded cases include cataract surgery, dry eye in a significant number of these patients, autoimmune disease and co-existent bacterial ulcers in some of these patients. Both the brand (Voltaren) diclofenac and the generic brand have been implicated, about 60% of the cases having been treated with the generic brand.[1]

Corneal melting or keratolysis in the absence of treatment with NSAIDs, occurs in the association with autoimmune disease, keratoconjunctivitis sicca, diabetes and steroid use (which occurred in a number of these patients). Recently analysis of tissue removed from a patient suffering a corneal melt associated with NSAID use suggests that this keratolysis was mediated by matrix metalloproteinases (MMPs). MMP is a family of degradative enzymes. They degrade collagen I, II, III, V, VII, in addition to basement membrane, laminin, and proteoglycans. In a case report by O'Brien et al, MMP8 was identified.[2] The source of this is thought to be neutrophils and epithelium; this enzyme degrades collagens I, II and III. In addition, MMP2 and MMP9 have been identified after refractive surgery and in patients with keratoconjunctivitis sicca.[3]

It seems likely that possible triggers of MMPs include: keratoconjunctivitis sicca, ocular surface disease, bacterial infections, NSAIDs, preservatives in topical medications, and surgery. In a predisposed ocular surface, the use of NSAIDs may substantially increase the risk of a clinically significant episode of keratolysis.

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[Editor's note] DR OLIVER SHINE discussed the paper he co-authored that analyzed 140 patients with corneal toxicity associated with the use of NSAID's, and the problem of multiple events and underlying diseases which could affect the cornea in these patients. DR TAYLOR ASBURY mentioned that Dr Philips Thygeson was one of the first physicians to describe corneal melting associated with the use of topical medicines (corticosteroids).

DR ALLAN J. FLACH. First I want to thank Dr Michael Lemp for agreeing to discuss my paper and also Drs Tuck Asbury and Oliver Shine for their interest and comments. Dr Asbury reminds us that it was Dr Philips Thygeson who first emphasized the dangers of corneal melts associated with corticosteroids and that he was elected to the

AOS in 1936. I would like to add that Dr Thygeson, while not physically as active as he would like to be, is still intellectually active at 97 years of age. Although he must lift himself from his bed with block and tackle, he continues to have many interests including the history of American Indians of the southwestern United States. In fact, I recently sent him an article concerning Geronomo as reflected in the writings of Edgar Rice Burroughs.

One of my greatest fears is to prepare to present a paper and submit a copy of the manuscript, only to have a similar paper appear in print just prior to my presentation. Today my greatest fear has been fully realized. Not only 1 but 3 papers have been recently published on corneal melts associated with topical NSAIDs.[1,2,3] Dr Lemp has mentioned one of them and Dr Shine is a co-author on another.[1,2] Fortunately, my paper is reasonably consistent with all 3 of them in terms of its observations and conclusions. Dr Lemp has summarized the results of O'Brien et al's case study of 1 case in which the matrix metalloproteinases (MMPs) may have been implicated in the observed corneal melting reported in a patient using topical NSAIDs.[1] This report compliments a poster presentation provided by Apte et al at the 104th Annual Meeting of the American Academy of Ophthalmology on this same subject as is mentioned within the text of my presentation.[4] While both paper and poster share the common suggestion that the observed corneal melts are consistent with enhanced MMP activity, both presentations agree that clear evidence for a definitive etiologic relationship between NSAIDs and corneal melts is lacking and more study is indicated to clarify the role of MMPs and possibility of NSAID associated corneal melts.

Dr Shine has mentioned an analysis of 140 patients demonstrating corneal toxicity associated with the use of topically applied nonsteroidal anti-inflammatory agents (NSAIDs) that he has recently co-authored.[2] He has appropriately underscored the difficult issues complicating the review of these cases including the presence of multiple compounding events, multiple chronic diseases and questions about the actual identity of the NSAID in question. However, even within these limitations some distinct patterns found within the analysis speak to causality in association with the generic diclofenac, which is no longer on the market, and severe keratitis. Corneal toxicity may have been occasionally associated with brand name diclofenac (Voltaren, Novartis) or ketorolac (Acular, Allergan), when used for long periods of time in patients with underlying pre-existing eye disease but it is not possible to know for certain these were actually the drugs dispensed by the pharmacist.

Since its publication I have had the opportunity to review this study and, unfortunately, its design has several significant shortcomings.[2] The analysis does not include the geographical distribution and specific origin of the 34 cases of severe corneal toxicity. As mentioned in my presentation this afternoon, we know at least 7 of these cases of severe corneal melting are reported from a single surgeon's practice.[5] In addition, less than 2% of the entire membership (over 5000 ophthalmologists) of the American Society of Cataract and Refractive Surgery reported corneal problems with NSAIDs.[2] This unequal distribution of cases of corneal melts may reflect a difference between individual batches or lots of a given drug or other important localized differences in technique or practice. This deserves further study to help understand the origin and pathogenesis of the observed corneal melts.

It does not seem appropriate to analyze cases of uncomplicated keratitis and corneal melts with equal attention and emphasis as was done in this study because keratitis is such a common finding during any eyedrop treatment as mentioned within my paper. Of greatest importance and interest are the 34 cases of severe corneal toxicity. Therefore, the report of this study would benefit greatly from a more careful description and discussion of each of the 34 severe cases of corneal toxicity with special attention to the working diagnosis and indication for treatment with a topical NSAID in each case, to the presence of coexistent ocular and systemic disease and coexistent medical treatments, in particular the use of corticosteroids. This data is largely omitted from the publication of this study.[2]

The study has unexpected outcomes that must be explained or at least discussed. More specifically, the study fails to find an association of corneal melts, or even keratitis, with dry eye. This is not consistent with past experience and our existing literature both of which clearly identify dry eyes, even asymptomatic dry eyes, as predisposed to corneal melts with or without coexistent surgery or medical therapy.[6,7] It is also of concern that this study states within its discussion that postoperative sterile corneal ulcers are most often associated with Mooren's ulcer or collagen vascular disease with no mention of the potential association with dry eyes with this complication. The report concludes that there was no association of increased toxicity with off-label use of NSAIDs. This conclusion seems inconsistent with the study's finding that the more severe cases of corneal toxicity were more likely to have other than cataract surgery and that nonsurgical cases tended to have much greater doses of NSAIDs than surgical cases. Both these statements suggest off-label use. These inconsistencies deserve discussion.

Although it is clear that the authors of this report of 140 patients devoted a great deal of time and effort to the study the final publication provides less information and discussion of this important issue than it deserves.

The third paper recently published reports 16 cases

of keratitis, ulceration and perforation associated with topical NSAIDs.[3] Some of these cases may be the same cases included in previously discussed studies. However, all of the 16 cases had extenuating circumstances including dry eye, coexistent steroid treatment, rosacea and often an unclear indication for the treatment with an anti-inflammatory agent. Therefore, the observations and results from this study are consistent with the presentation and conclusions that I have provided this afternoon.

Unfortunately, at present, no controlled study exists that permits us to make any conclusions about the risks associated with topical NSAID use and severe corneal toxicity. Although it seems clear that there is a small but definite incidence of corneal melting following cataract surgery associated with dry eye and other predisposing diseases, the question remains whether any specific drug treatment or changes in our current surgical techniques or regimens increase the likelihood of these corneal melts following contemporary anterior segment surgery.

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