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

BY *Allan J. Flach, MD*

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.

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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,

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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
A kali 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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