Corneal Melting Associated With Use of Topical Nonsteroidal Anti-inflammatory Drugs After Ocular Surgery

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely for systemic control of acute or chronic pain and inflammation. Topical NSAIDs have been used to effectively alleviate ocular inflammation after cataract removal and excimer laser photorefractive keratectomy. Additional indications include allergic conjunctivitis and the prevention of miosis during cataract surgery. Despite the increased topical use of this class of drug after ocular surgery, corneal complications due to NSAID use have been uncommon. Reported complications include superficial punctate keratitis, subepithelial infiltrates, stromal infiltrates, immune rings, and persistent epithelial defects. In August 1999, severe complications associated with topical NSAID use, including corneal melting, were reported by members of the American Society of Cataract and Refractive Surgery (ASCRS) responding to a survey and distributed in letters from ASCRS to members and nonmembers. We report 5 cases of corneal melting associated with the use of topical NSAIDs after ocular surgery referred to our service over a past 4-month period (Table). Four of the cases progressed to corneal perforation. Three eyes required tissue glue, 2 required a patch graft, and 1 required a penetrating keratoplasty. Of the 2 eyes for which cultures were obtained, 1 was positive for bacteria. We conclude that topical NSAID use after ocular surgery in healthy patients should be used with caution due to the potential of corneal melting.

Report of Cases. Case 1. A 76-year-old woman was referred for evaluation of a corneal ulcer in her left eye. She had undergone uncomplicated cataract surgery 3 months previously. By history, 2 weeks prior to her visit, she had developed a painful red eye and was prescribed diclofenac sodium (Falcon Ophthalmics, Inc, Fort Worth, Tex), 4 times daily, and artificial tears, as needed, by a local ophthalmologist. On examination, visual acuity was 20/25 OD and 20/50 OS. A 4 × 4-mm epithelial defect and corneal infiltrate associated with 80% tissue loss was noted in the inferior temporal cornea. She had fibrin, + cells, and a hypopyon in the anterior chamber. Corneal cultures were performed, and she was treated with topical fortified cefazolin (50 mg/mL) and tobramycin sulfate (15 mg/mL) every hour alternating around the clock. Diclofenac therapy was discontinued. Cultures were positive for group B streptococcus. Despite treatment, microbial keratitis was complicated by corneal perforation and required cyanoacrylate tissue adhesive 8 days later. Six weeks after diclofenac therapy was discontinued, the corneal sensitivity measured by Cochet-Bonnet esthesiometry was normal (60 mm OD and 55 mm OS). The basal Schirmer tear secretion test result was 2 mm OD and 5 mm OS. Her visual acuity was 20/400 OS. Basal Schirmer tear secretion test results were 12 mm OD and 8 mm OS, and the corneal sensitivity measured by Cochet-Bonnet esthesiometry was normal (55 mm OD and 50 mm OS).

Case 2. A 66-year-old woman was referred to the Cornea Service for evaluation of a peripheral corneal perforation in his left eye. He had undergone uncomplicated cataract surgery 21⁄2 weeks prior to his visit and had normal follow-up examination results 1 week previously. He had been taking topical tobramycin-dexamethasone drops and diclofenac drops (Voltaren) 4 times daily since surgery. On examination visual acuity was hand motions in the left eye. Slitlamp examination revealed a perforated corneal ulcer measuring 3.2 × 2.0 mm near the 11-o’clock position. The anterior chamber was flat. The Seidel test result was trace positive because a plug of iris was incarcerated in the perforation. Corneal sensitivity was severely diminished on the left eye. It measured 1 mm in the left eye by Cochet-Bonnet esthesiometer compared with 60 mm in the right eye. The patient was treated with tissue adhesive, a bandage soft contact lens,
topical ofloxacin, and intravenous cefazolin (1 g every 8 hours). One week later, his vision improved to finger counting. The tissue adhesive was in place, and the anterior chamber was deep. However, 2 weeks after the placement of tissue adhesive, he underwent a corneal patch graft for a recurrent leak and a flat anterior chamber. Two weeks after the corneal patch graft, basal Schirmer tear secretion test results were 5 mm OD and 9 mm OS. The corneal sensitivities measured by Cochet-Bonnet esthesiometry were 60 mm OD and 35 mm OS.

Case 4. A 71-year-old white man was referred for evaluation of sclerokeratitis in his left eye. He had undergone cataract surgery 10 days previously and was receiving diclofenac (Falcon Ophthalmics, Inc) 4 times daily, and 1% prednisolone acetate 6 times per day since surgery. He had a 3-day history of mild hyperemia and discomfort and a 1-day history of decreased vision in his left eye. Examination showed a 4.5 × 12.0-mm epithelial defect and diffuse infiltrate in the area of his cataract wound superiorly at the limbus with 90% tissue loss. His visual acuity was 20/400. The anterior chamber was deep with fibrin and 4+ cells (Figure 1, A). Cultures were performed, and he was admitted to the hospital and given fortified tobramycin (15 mg/mL) and cefazolin (50 mg/mL) every hour alternating around the clock, and aqueous suppressants. The next day he progressed to corneal perforation with iris prolapse. A corneoscleral patch graft was performed. Cultures were negative and no organisms were identified in the corneal button (Figure 1, B). Three months after patch penetrating keratoplasty, his visual acuity was 20/200 OS (Figure 1, C). At that time basal Schirmer tear secretion test results were 12 mm OD and 30 mm OS, and the corneal sensitivity measured by Cochet-Bonnet esthesiometry was normal (60 mm OD and 55 mm OS).

Case 5. A 79-year-old white man was referred to the Cornea Service for evaluation of a descemetocele in the left eye. He had undergone argon laser trabeculoplasty in his left eye 5 weeks previously for chronic open-angle glaucoma. His visual acuities were 20/30 OD and 20/40 OS. Postoperatively he was instructed to use 1% prednisolone acetate 4 times daily for 3 days. Results of a follow-up examination 1 week after argon laser trabeculoplasty were unremarkable. Three weeks after laser surgery he returned with a red eye and was noted to have anterior chamber inflammation. Diclofenac (Falcon Ophthalmics, Inc) 4 times daily, was added to his regimen of glaucoma medications (brimonidine tartrate, dorzolamide hydrochloride, timolol maleate).

<table>
<thead>
<tr>
<th>Summary of Cases*</th>
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<tr>
<td><strong>Patient No.</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<td>66</td>
<td>77</td>
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<td>Left</td>
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<td><strong>Date started</strong></td>
<td>5/31/1999</td>
<td>6/16/1999</td>
<td>7/22/1999</td>
<td>4/30/1999</td>
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<td><strong>Days of diclofenac therapy</strong></td>
<td>10</td>
<td>29</td>
<td>18</td>
<td>11</td>
<td>17</td>
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<tr>
<td><strong>NSAIDs used†</strong></td>
<td>Diclofenac QID (generic)</td>
<td>Diclofenac QID (brand name)</td>
<td>Tobramycin-dexamethasone</td>
<td>Diclofenac QID (generic)</td>
<td>Diclofenac QID (generic)</td>
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<td><strong>Other topical medications used</strong></td>
<td>Tears</td>
<td>Apaclonidine hydrochloride</td>
<td>Tobramycin-dexamethasone</td>
<td>Diclofenac QID (generic)</td>
<td>Diclofenac QID (generic)</td>
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<td><strong>Medical history</strong></td>
<td>Angina, hiatal hernia, hypertension, hyperlipidemia</td>
<td>Hypothyroid</td>
<td>Arrhythmia</td>
<td>Hypertension, gastritis, coronary artery disease, type 2 diabetes</td>
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<tr>
<td><strong>Schirmer test results, OD/OS</strong></td>
<td>2 mm/5 mm</td>
<td>12 mm/8 mm</td>
<td>5 mm/9 mm</td>
<td>12 mm/30 mm</td>
<td>9 mm/8 mm</td>
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<td><strong>Pain</strong></td>
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<td><strong>Esthesiometry, OD/OS Before surgery</strong></td>
<td>60 mm/55 mm</td>
<td>55 mm/55 mm</td>
<td>60 mm/1 mm</td>
<td>60 mm/35 mm</td>
<td>60 mm/35 mm</td>
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<td><strong>Iris color</strong></td>
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<td>Blue</td>
<td>Hazel</td>
<td>Brownish green</td>
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<td>Inferior-central</td>
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<td><strong>Initial % tissue loss</strong></td>
<td>80</td>
<td>50</td>
<td>100</td>
<td>90</td>
<td>99</td>
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<td><strong>Progression to perforation Culture</strong></td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
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<tr>
<td><strong>Treatment</strong></td>
<td>Tissue adhesive</td>
<td>Antibiotics, lubrication</td>
<td>Tissue adhesive, patch graft</td>
<td>Patch graft</td>
<td>Tissue adhesive, penetrating keratoplasty</td>
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</table>

*QID indicates 4 times daily; NSAIDs, nonsteroidal anti-inflammatory drugs; and NA, not applicable.
†Generic diclofenac, Falcon Ophthalmics, Inc, Fort Worth, Tex; and brand-name diclofenac (Voltaren), Ciba Vision Ophthalmic, Atlanta, Ga.
lol maleate, and latanoprost). Five weeks after argon laser trabeculoplasty, the patient presented with hyperemia, pain, photophobia, and decreased vision in the left eye. His visual acuity in the left eye was finger counting. A 2.5 × 2.0-mm epithelial defect with 99% tissue loss and a descemetocele were noted inferocentrally. There was fibrin and 4+ flare in the anterior chamber. The ulcer appeared sterile (Figure 2, A). Corneal sensitivities measured by Cochet-Bonnet esthesiometry were 50 mm OD and 35 mm OS. Basal Schirmer tear secretion test results were 5 mm OD and 15 mm OS. Tissue adhesive and a bandage soft contact lens were applied over the melt. One week later the contact lens had torn and moved and the tissue adhesive had dislodged. Both the epithelial defect and the descemetocele had enlarged. The ulceration was weakly Seidel positive (Figure 2, B). He underwent therapeutic penetrating keratoplasty the next day. Two weeks later basal Schirmer tear secretion test results were 9 mm OD and 8 mm OS, and corneal sensitivities measured by Cochet-Bonnet esthesiometry were 60 mm OD and 45 mm OS.

Comment. Diclofenac is an anti-inflammatory drug that inhibits cyclo-oxygenase activity and decreases the synthesis of prostaglandins. Prostaglandins contribute to postoperative inflammation and pain. Topical diclofenac has also been used to minimize postsurgical pain. Four drops of the NSAIDs ketorolac and diclofenac instilled over 20 minutes have been shown to significantly decrease normal corneal sensation.5,6 Although decreased corneal sensation was confirmed in only 2 of our patients at time of presentation and was not tested in the other 3, hypesthesia may be why our patients reported little pain and delayed seeking medical attention. All our patients used diclofenac. Seitz et al7 reported that repeated instillation of diclofenac had more pronounced and longer lasting effects on corneal sensitivity than ketorolac. This finding may have predisposed our patients to the severe complication of corneal melting. In all our patients corneal sensitivity was in the normal range after the NSAIDs were discontinued.
Topical NSAIDs are used frequently. NSAIDs, especially diclofenac, are used for the treatment of cystoid macular edema for up to 3 months. Topical indomethacin has been used for inflamed pterygia and pinguecula. Ketorolac (Acular; Allergan, Irvine, Calif) is effective in relieving ocular itching caused by seasonal allergic conjunctivitis. Surprisingly, despite the frequent use of topical NSAIDs, there have been few reports of corneal complications.

In addition to reducing pain, NSAIDs have been shown to affect corneal epithelial healing. Topical diclofenac retards epithelial healing to a significantly greater extent than dexamethasone. Topical diclofenac has been associated with persistent epithelial defects in patients after undergoing penetrating keratoplasty. In addition to the patients described in this report, we have treated 2 other patients who developed acute corneal surface breakdown when given topical NSAIDs for cystoid macular edema. One had severe ocular surface disease due to dry eyes associated with graft-vs-host disease and the other had neurotrophic keratitis following a cerebral vascular accident. The first patient was treated with topical ketorolac and the second with diclofenac.

Three of our patients had corneal melts that were located inferiorly consistent with neurotrophic ulcers. These patients had a normal lid position and lid closure and no evidence of exposure. The melt in the other 2 patients was located superiorly at the limbus near the phacoemulsification entrance wound. The corneal and scleral melting in our patients resembled that seen in patients without any such history may also develop severe complications.

The authors have no proprietary interest in the development or marketing of the drugs mentioned. The authors have no financial interest in any of the products mentioned herein.

Corresponding author: Elisabeth Cohen, MD, Cornea Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107 (e-mail: ejcohen@hslc.org).


A Case of Suspected Alphagan-Induced Psychosis

Brimonidine tartrate is an α2-agonist that currently is used to treat glaucoma by decreasing aqueous production and by possibly increasing uveal scleral outflow. It is a lipid-soluble agent that can cross the blood-brain barrier and can have, in theory, some psychoactive properties. It has been reported that dizziness and depression could occur owing to the aforementioned properties. I report a case involving acute psychosis and delirium in a patient receiving brimonidine (Alphagan; Allergan Inc, Irvine, Calif), which resolved immediately after cessation of the agent.

Report of a Case. A 68-year-old man with mild open-angle glaucoma received brimonidine after β-blockers failed to lower his intraocular pressure. The patient received brimonidine for about 3 months before the family began to notice dramatic behavioral changes. In retrospect, the patient's wife reported that he began having subtle lapses in memory almost on initiation of treatment. Following this, the patient started complaining of being constantly tired and began exhibiting signs of depression. Shortly thereafter, he began a downward course during which time he became more and more delusional. Anxiety overcame him, and he worried about myriad irrational concerns, ranging from imminent blindness, death, financial ruin, and even concerns about people spying on him. His wife became concerned that the medication may have been contributing to his behavioral change and read the package insert. When there was no mention of this type of behavioral change, they sought a second opinion and came to my office. On examination, the patient was unkempt and quite confused, only recognizing his name. His visual acuity was 20/20 OU, and intraocular pressure was 16 mm Hg OD and 14 mm Hg OS. The cup-disc ratio was 0.65 OU. When the son described the behavioral changes in his father, I instructed the patient to discontinue brimonidine and to start

0.005% latanaprost. After leaving the clinic, the son saw that the father had a loaded gun, stating that the police were out to get him. With this discovery, the son took his father to a psychiatric hospital. At the hospital, the admitting psychiatrist telephoned me and stated that the patient told him that I had instructed him to discontinue latanaprost and initiate brimonidine therapy. When I told the psychiatrist that it was the other way around, the patient told him that I was lying, trying to withhold care, and that he would go blind without the brimonidine. The psychiatrist indeed stopped brimonidine administration and gave the patient an anxiolytic. Within 48 hours of discontinuing brimonidine treatment, the patient returned to baseline, and his paranoid ideation also dissipated.

Comment. I report a case of brimonidine causing acute psychosis, paranoid delusions, and auditory hallucinations in a patient without a notable medical or psychiatric history. The psychiatric symptoms reversed within 48 hours on cessation of brimonidine. On contact with Allergan Inc, no known cases of psychosis were ever reported. Thus, when prescribing brimonidine, careful monitoring of patient behavior is necessary, and the patient’s family should be made aware of potential behavioral changes that can be associated with the drug. In addition, one may wonder whether brimonidine should be considered a relative contraindication in any patient with a history of depression.

David D. Kim, MD
Green Bay, Wis


Granulomatous Local Cell Reaction to Intravitreal Silicone

Intense local cell reactions to silicone implants, gels, and oils have been described in various human tissues. Several articles have described histopathologically reactions to long-standing silicone oil in the human eye and the migration of silicone vacuoles into various ocular tissues. However, to our knowledge, only 1 previous article described an intraocular giant cell reaction, and none have described a granulomatous reaction to intraocular silicone. We report a case in which an extensive granulomatous reaction to intraocular silicone oil was associated with enhanced serum IgG binding to silicones.

Report of a Case. A 50-year-old man with a history of cirrhosis secondary to alcoholic liver disease but an otherwise unremarkable medical and ophthalmic history was referred for the treatment of floaters and decreased vision in his right eye. The patient’s visual acuity on initial examination was 20/200 OD, and findings from funduscopic examination revealed a small, yellow, parafoveal retinal lesion with a satellite lesion adjacent to the optic nerve. In addition, leukocytic sheathing of the vessels was noted along the superotemporal arcade with prominent vitreous cell and flare. Serum Toxoplasma gondii IgG titers were positive at a level of 1:32, and the patient started receiving triple drug therapy (sulfadiazine, clindamycin, and leucovorin calcium) along with oral prednisone.

During the course of his treatment, a stainless steel transjugular intrahepatic portosystemic shunt was implanted for ascites and worsening liver failure. Although his visual acuity initially improved to 20/40 OD, the patient was seen 1 month later for increased floaters. Findings from funduscopic examination revealed 2 peripheral retinal tears at the 10- and 12-o’clock positions, which were treated by laser photocoagulation. Three months later, a vitrectomy was performed for progression of vitritis and worsening of visual acuity to light perception only. Results of intraoperative fundus examination revealed spreading of the toxoplasma lesion into the macula. Six weeks later, the patient experienced sudden loss of vision secondary to an extensive retinal detachment. He underwent a repeated vitrectomy with intravitreal injection of liquid silicone (1000 centistoke, medical grade) but was subsequently lost to follow-up. He was seen 3 months later with a dense cataract, pupillary block glaucoma, and corneal perforation. The patient refused any further therapeutic intervention and underwent an evisceration.

On gross examination, the globe contents were firm and rust colored. Findings from microscopic examination revealed fragments of disorganized atrophic retina. There was massive fibrovascular proliferation in the vitreous cavity and subretinal space, which contained a moderate chronic inflammatory infiltrate and occasional eosinophils. Within this mass were numerous large and small vacuoles consistent with silicone (Figure 1), many of which were...
surrounded by epithelioid histiocytes and foreign body giant cells (Figure 2). Giant cells were not found elsewhere in the eye. In areas remote from the silicone vacuoles, there was necrosis and a solitary granuloma with a necrotic center. Rare T gondii cysts were present but were not associated with either the foreign body giant cells or the granuloma. The serum level of IgG binding to silicone, as determined by a microplate modification of a previously described enzyme-linked immunosorbent assay technique, was 15.8 ± 0.58 arbitrary units, 4 SDs above the mean for adult sera in the reference range (3.2 ± 2.1 arbitrary units).

Comment. Enhanced binding of serum IgG to silicones has been observed in patients who develop intense local inflammatory reactions to implanted silicone materials such as ventriculoperitoneal shunts. Intravitreal injection of liquid silicone is an effective therapy for complex retinal detachments. A recent prospective study revealed that the complication rate and frequency of enhanced serum IgG binding to intraocular and extraocular silicone devices, even after extended periods of exposure, was a rare event and should not alter their clinical use. The authors of that study noted that the only patient who developed significantly elevated levels of silicone-specific IgG and also had complications to silicone devices used in retinal surgery may have had predisposing rheumatologic risk factors. Additionally, aberrant immunological function, including elevated IgG and IgA production, has been correlated with decreased suppressor T-cell activity in patients with cirrhosis of the liver. Whether such abnormalities of immunoregulation dynamics in our patient with cirrhosis secondary to alcoholic liver disease were predisposing factors for the granulomatous reaction to silicone and elevated levels of silicone-specific IgG is speculative. Therefore, although intraocular silicone oil is usually well tolerated, its use in individuals with immunological risk factors may require some caution.

Saad Shaikh, MD
Peter R. Egbert, MD
Randall S. Goldblum, MD
Mark R. Wieland, MD
Stanford, Calif

Corresponding author: Saad Shaikh, MD, Department of Ophthalmology, Stanford, Stanford University School of Medicine, CA 94305 (e-mail: saads@earthlink.net).

Reprints: Peter R. Egbert, MD, Department of Ophthalmology, Stanford University School of Medicine, Stanford, CA 94305.