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Corneal Edema in Glaucoma Patients After the Addition of Brinzolamide 1% Ophthalmic Suspension

Topical brinzolamide and dorzolamide lower intraocular pressure (IOP) by inhibiting carbonic anhydrase type II isozyme (CA-II) in the ciliary processes and suppressing aqueous humor production.[1] CA-II is also expressed in the corneal endothelium, and its inhibitors attenuate bicarbonate efflux, which could lead to corneal edema. We describe two cases where reversible corneal edema occurred after topical dorzolamide had been switched to brinzolamide.

Case Reports

Case 1

A 36-year-old woman visited us for contact lens fitting in November 1999. Visual acuity was 0.8 OU. The IOP was 23 mmHg OD and 20 mmHg OS. Fundus examination revealed enlarged optic disc cups bilaterally. The angles were wide.

Nipradilol 0.25% (Hypadil, Kowa Shinyaku Co., Ltd., Japan) was prescribed twice daily for her, but bilateral superficial punctuate keratitis (SPK) resulted. One month later, nipradilol was replaced by timolol gel 0.5% (Rysmon-TG, Wakamoto Pharmaceutical Co., Ltd., Japan) once daily. Latanoprost (Xalatan, Pfizer Japan Inc., Japan) once daily and dorzolamide 1% (Trusopt, Banyu Pharmaceutical Co., Ltd., Japan) three times daily were added thereafter. Because IOP exceeded 20 mmHg OU on April 19 2003, dorzolamide was changed to brinzolamide 1% (Azopt, Alcon Pharmaceutical Ltd., Japan) three times daily.

On 19 May, her IOP was 21 mmHg OD and 20 mmHg OS. Corneal stromal edema and SPK were found in both eyes (Fig. 1a, b). Antiglaucoma medications were discontinued; artificial tears (Soft Santear, Santen Pharmaceutical Co., Ltd., Japan) and levofloxacin 0.5% (Cravit, Santen Pharmaceutical Co., Ltd., Japan) were started. The corneal stromal edema disappeared within 3 days, and SPK disappeared in 18 days. Latanoprost once daily was reintroduced on May 24, when her IOP was 24 mmHg OD and 22 mmHg OS. The keratopathy did not recur with latanoprost (Fig. 1c, d), and her IOP was 18 mmHg OD and 19 mmHg OS at her last visit on February 14, 2004.

Case 2

A 74-year-old man visited us in October 1997 with blurred vision. Visual acuity was 0.8 OU. His IOP was 25 mmHg OU. Calcific band keratopathy in the corneal periphery was noted in both eyes. Fundus examination revealed enlarged optic disc cup bilaterally. The angles were narrow. The patient had no history of uveitis.

Treatment with pilocarpine 0.5% (Sanpilo, Santen Pharmaceutical Co., Ltd., Japan) four times daily and timolol 0.5% (Timoptol, Santen Pharmaceutical Co., Ltd., Japan) twice daily was prescribed for him. Because of poorly controlled IOP, timolol was then changed to latanoprost once daily in August 1999. Two months later, latanoprost was replaced by timolol gel once daily because of the bilateral development of SPK. Dorzolamide 1% three times daily was then added because of poorly controlled IOP. On April 22, 2003, dorzolamide was changed to brinzolamide 1% three times daily, because IOP exceeded 20 mmHg OU.

The patient presented with pain in both eyes on May 17, 2003. His IOP was 20 mmHg OU. Bilateral corneal stromal edema and SPK were noted (Fig. 2a, b). Antiglaucoma medications were discontinued; hyaluronate sodium 0.1% (Hyalein, Santen Pharmaceutical Co., Ltd., Japan) and levofloxacin were started. Bilateral iridocyclitis was noted on May 22, 2003. The iridocyclitis subsided in 4 days with oral prednisolone; SPK disappeared 14 days thereafter. Latanoprost once daily was reintroduced on June 16, 2003, when his IOP was 26 mmHg OD and 23 mmHg OS.

There was no recurrence of the keratopathy with latanoprost (Fig. 2c), and the patient's IOP was 17 mmHg OD and 16 mmHg OS at his last visit on February 24, 2004.

Comments

The affinity of brinzolamide for CA-II is approximately four times that of dorzolamide;[1] therefore, we should consider the potential corneal toxicity of brinzolamide as well as of dorzolamide.[2] In the present cases, it seems most likely that brinzolamide triggered the development of corneal edema.

SPK was coincidentally noted in both patients when corneal edema developed. It has been reported that growth inhibition of human corneal epithelial cells by antiglaucoma eyedrops is caused also by the vehicle.[3] Topical brinzolamide suspension contains 0.01% benzalkonium chloride, which is twice as high as that in topical dorzolamide solution. Latanoprost and timolol gel contain benzalkonium

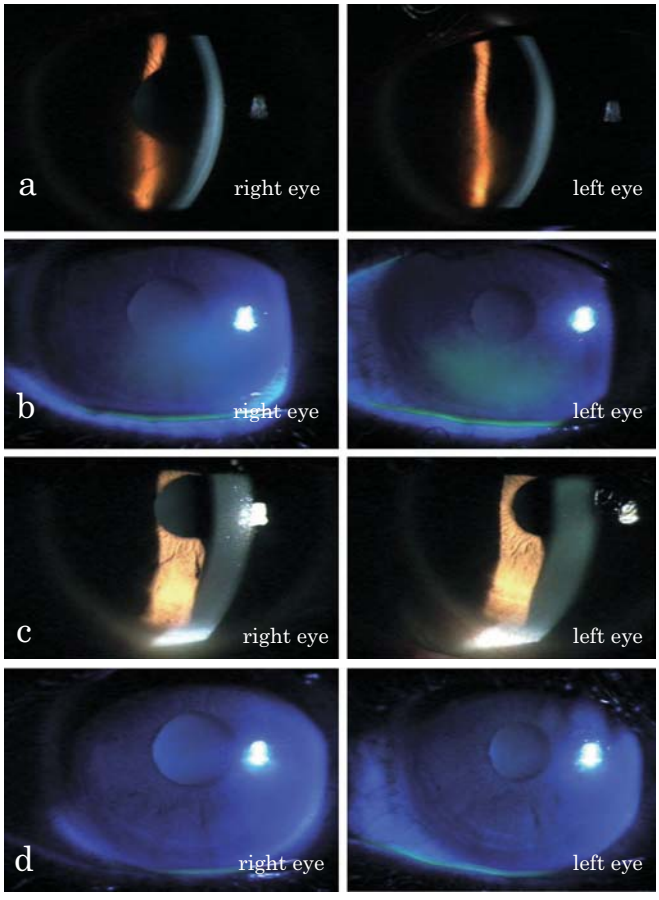

Figure 1a–d. Slit-lamp images of the cornea of a 36-year-old female patient (case 1). **a** Corneal stromal edema with folding of Descemet's membrane was observed in both eyes. The central corneal thickness (CCT) was 600 µm OD and 553 µm OS, and the endothelial cell count (ECC) was unmeasurable in the right eye and 2745 cells/mm^2 in the left (May 19, 2003). **b** Superficial punctuate keratitis (SPK) with late staining centered on the inferior cornea was noted in both eyes (May 19, 2003). **c, d** Corneal edema and SPK disappeared after antiglaucoma medications were discontinued. The CCT decreased to 524 µm OD and 521 µm OS. The ECC was 2641 cells/mm^2 OD and 2687 cells/mm^2 OS (January 17, 2004).

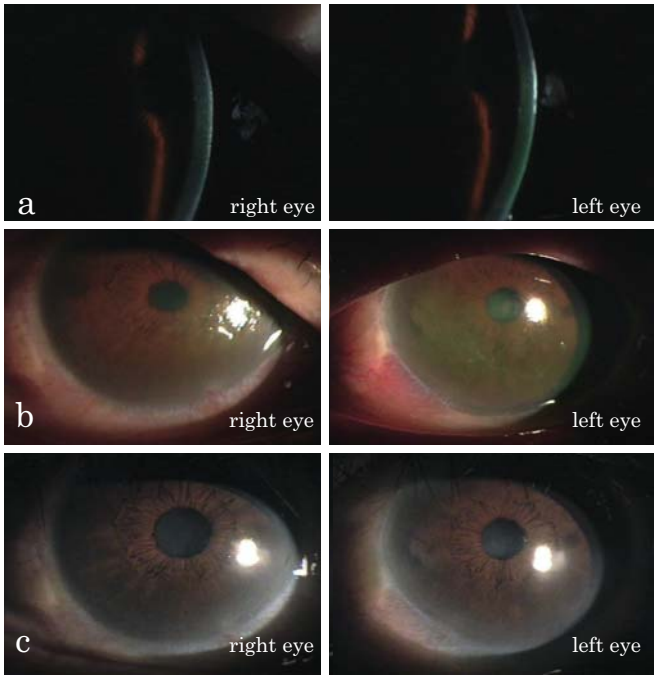

Figure 2a–c. Slit-lamp images of the cornea of a 74-year-old male patient (case 2). **a** Corneal stromal edema was observed in both eyes. The CCT was 564 µm OD and 580 µm OS (May 20, 2003). **b** SPK with late staining centered on the inferior cornea was noted in both eyes (May 20, 2003). **c** Corneal edema and SPK disappeared after antiglaucoma medications were discontinued. The CCT decreased to 489 µm OD and 516 µm OS. The ECC was 2657 cells/mm^2 OD and 2673 cells/mm^2 OS (January 15, 2004).

chloride with concentrations of 0.02% and 0.005% respectively. Timolol gel 0.5%, which was used in both patients, has also been reported to cause severe corneal damage along with a reduction of tear break-up time.[4] An incompetent epithelial barrier in these patients may have increased the risk of endothelial dysfunction. Brinzolamide 1% was used at a dose of three times daily in the present cases, although its standard dose is twice daily, which thus may have aggravated toxicity.

This report should draw attention to the potential for corneal dysfunction with topical brinzolamide when used adjunctively in antiglaucoma medication, especially together with topical timolol gel.

Key Words: brinzolamide, corneal edema, dorzolamide, glaucoma

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