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A Case of Cystoid Macular Edema Associated with Latanoprost Ophthalmic Solution

Takaharu Tokunaga*, Kenji Kashiwagi†, Junko Saito‡, Keiko Kobayashi†, Yuko Kobori†, Keitetsu Abe† and Shigeo Tsukahara†

*Iida Hospital, Iida, Nagano;
†Department of Ophthalmology, Yamanashi Medical University, Tamaho, Yamanashi; and ‡Koma-Kyoritsu Hospital, Shirane, Yamanashi, Japan

Background: Although there have been reports of adverse effects after use, it is unclear whether latanoprost ophthalmic solution contributes to the development of cystoid macular edema (CME).

Case: A 71-year-old man underwent lens extraction, the insertion of an intraocular lens, and vitrectomy for elevated intraocular pressure (IOP) associated with lens subluxation in the left eye. After the surgery, antiglaucoma ophthalmic solutions controlled IOP well for over a year, maintaining good visual acuity with no abnormalities in the fundus.

Observations: Two months after the previously prescribed antiglaucoma ophthalmic solutions were replaced by latanoprost, the patient's visual acuity decreased and CME developed. When latanoprost was replaced by other antiglaucoma ophthalmic solutions for controlling IOP, CME disappeared and visual acuity returned to the base level.

Conclusions: Latanoprost may be involved in the development of CME. Patients who have undergone vitreous surgery or those with aphakia should be carefully observed for the possible development of CME associated with the use of latanoprost, even a long time after surgery. **Jpn J Ophthalmol 2002;46:656–659** © 2002 Japanese Ophthalmological Society.

Key Words: Benzalkonium chloride, cystoid macular edema, glaucoma, latanoprost, optical coherence tomography.

Introduction

Latanoprost ophthalmic solution (Xalatan®; Pharmacia, Kalamazoo, MI, USA), which reduces intraocular pressure (IOP) effectively and with few complications, is now widely used as an antiglaucoma ophthalmic solution. However, of the reported complications, the development of cystoid macular edema (CME) is the most serious.[1,2] The mechanism underlying the development of CME is controversial and it is not clear how to prevent this reported adverse effect. We herein describe a case involving lens extraction, intraocular lens insertion, and three-port vitrectomy more than 1 year before CME developed after the initiation of latanoprost therapy.

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Correspondence and reprint requests to: Kenji KASHIWAGI, MD, Department of Ophthalmology, Yamanashi Medical University, 1110 Shimokato, Tamaho, Yamanashi 409-3898, Japan

Case Report

Case

A 71-year-old man, whose chief complaint was metamorphopsia in the left eye.

Present History

The patient consulted his local ophthalmologist about metamorphopsia in the left eye and was found to have lens subluxation and ocular hypertension in that eye (right eye, 20 mm Hg; left eye, 41 mm Hg) in April 1999. After the elevated IOP was reduced by infusion of hypertonic solution, he was referred to our hospital on the same day.

Findings at the First Visit

The corrected visual acuity was 20/20 with a lens of +2.0 D in the right eye, and 20/20 without a corrected lens in the left eye. The IOP was 16 mm Hg in the right eye and 21 mm Hg in the left eye. Lens sub-

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luxation and mild cataract were observed in the left eye. Physiological cupping was present in the left optic disc. The patient had no family history of ocular disease.

Course of Treatment and Outcome

The patient at first was treated with ophthalmic solutions containing isopropyl unoprostone (referred to as unoprostone) and 0.1% dipivalyl epinephrine (DPE). However, his IOP was not well-controlled under that regimen. Because a subluxated lens had been found, which possibly was associated with the fluctuation in IOP level, pars plana vitrectomy with phacoemulsification in the vitreous cavity was carried out (Figure 1). The subluxated lens was extracted and an intraocular lens was positioned with sulcus fixation in June 1999.

However, the patient's IOP was still above the normal range after surgery. Treatment with timolol ophthalmic solution (0.5%) was therefore initiated in September 1999, and unoprostone ophthalmic solution was added to his regimen in September 2000 because of insufficient IOP control. Although the IOP in the left eye was controlled at less than 20 mm Hg, unoprostone ophthalmic solution was replaced by latanoprost ophthalmic solution for better IOP control in November 2000.

At the time that latanoprost ophthalmic solution was initiated, his corrected visual acuity was 20/20 and no abnormal appearance of the fundus was observed in the left eye. However, the corrected visual acuity decreased to 20/25 in January 2001, then to 20/30 in February 2001. Fundus examination revealed CME in the left eye, and fluorescein angiography confirmed the development of CME (Figure 2a). Latanoprost ophthalmic solution was replaced by 0.5% timolol ophthalmic solution and 0.1% fluorometholone ophthalmic solution was added to his regimen for approximately 1 month. Upon consent of the patient, he was given oral indomethacin (cyclooxygenase inhibitor COX) at three capsules per day. His visual acuity improved gradually, and disappearance of CME was confirmed by ophthalmoscopic observation and optical coherence tomography (data not shown). The corrected visual acuity in the left eye had recovered to 20/20 by May 21, 2001.

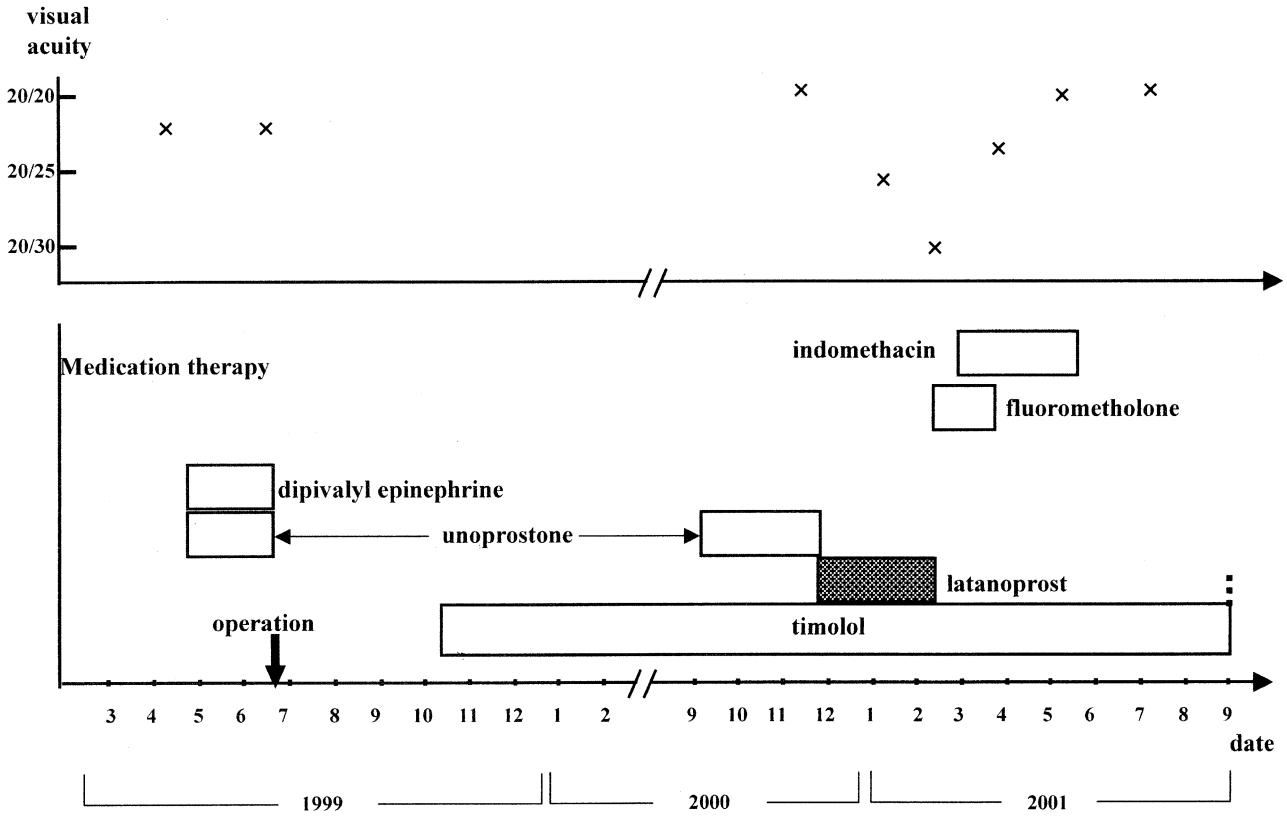

Figure 1. Course of treatment and visual acuity in cystoid macular edema patient. (Top) ×: visual acuity. (Bottom) Box bar shows the medication period of each drug.

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Oral indomethacin was discontinued on June 4, and fluorescein angiography performed on June 15 showed the disappearance of CME (Figure 2b). Subsequently, IOP and visual acuity improved. As of July 2001, at the most recent examination, the corrected visual acuity in the left eye was 20/20. The patient was being treated with 0.5% timolol alone and showed a well-controlled IOP of less than 21 mm Hg. No visual field defect or enlarged optic disc cupping was observed at that time.

Discussion

The development of CME associated with latanoprost has been occasionally reported; however, the mechanism underlying CME development remains unclear. Many of the patients who develop CME had received latanoprost after intraocular surgery for cataracts and other optical problems.[1,2] The current patient had undergone lens extraction, sulcus fixation of the intraocular lens, and vitrectomy. Thus, intraocular surgery is likely to be a risk factor for the development of CME associated with latanoprost. In fact, in a recent study we found that latanoprost caused no retinal disorders such as CME in glaucoma patients who had never undergone intraocular surgery.[3]

Miyake et al[4] reported that the benzalkonium chloride contained in ophthalmic solutions might be associated with the development of CME. Although it is unclear whether latanoprost itself or benzalkonium chloride resulted in CME, the current case may indicate some important points to clarify the mechanism by which latanoprost ophthalmic solution could induce the development of CME. The current case had consistently used several ophthalmic solutions containing benzalkonium chloride before the initiation of latanoprost ophthalmic solution, and he did not develop CME until the regimen with latanoprost began. Further, despite the continued use of 0.5% timolol containing benzalkonium chloride after onset, CME disappeared after discontinuation of the latanoprost ophthalmic solution. The concentrations of benzalkonium chloride in currently used ophthalmic solutions, timolol, unoprostone, DPE, and latanoprost, are 0.005%, 0.01%, 0.005%, and 0.02%, respectively. Therefore, a significant increase in the amount of benzalkonium chloride in contact with the eye is unlikely to occur after switching to latanoprost from other antiglaucoma ophthalmic solutions. Considering the above points, at least in this case, latanoprost is more likely than benzalkonium chloride to have been associated with the development of CME. Therefore, the simultaneous occurrence of CME with latanoprost initiation cannot be disregarded. Because we could not rechallenge the latanoprost ophthalmic solution, from the ethical point of view, it is impossible to conclude that latanoprost itself induces CME in the current case. Further investigations would be necessary to establish a guideline for the safe usage of latanoprost ophthalmic solution in clinics.

A hypothesis for the causal relationship between latanoprost and CME is proposed as follows. It is accepted that latanoprost is a derivative of $PGF_2\alpha$ and that it binds to the prostaglandin F and E receptors

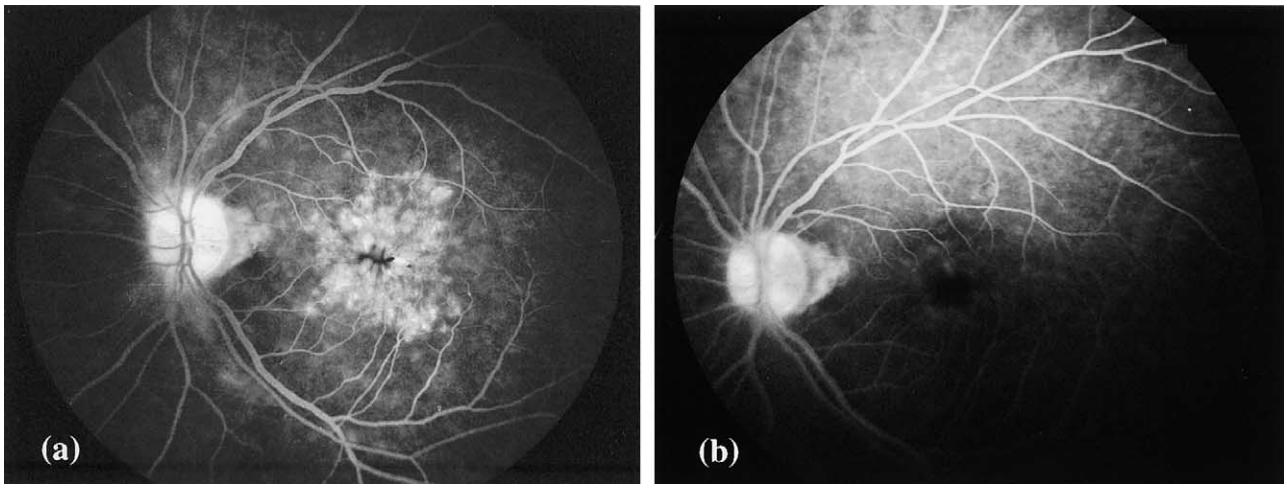

Figure 2. Fluorescein angiography (FAG) images during the course of follow-up. (**a**) The late phase FAG shows a 1.5 disc diameter of cystoid macular edema (CME) observed 2 months after the initiation of treatment with latanoprost ophthalmic solution. The visual acuity was 20/30. (**b**) The late phase FAG shows disappearance of CME after the discontinuation of latanoprost. The visual acuity was 20/20.

to reduce IOP. In addition, latanoprost has been reported to elicit endogenous PGE_2 production in the anterior segment.[5] PGE_2 plays an important role in intraocular inflammation; it induces the breakdown of the blood—ocular barrier. In eyes with a normally functioning blood—ocular barrier, the induced PGE_2 will not easily reach the posterior segment. However, if the lens and vitreous are extracted, as was the case in this patient, causative agents could easily spread into the vitreous cavity. Therefore, endogenous PGE_2 might easily reach the posterior segment and impair the blood—retinal barrier.

In the present case, indomethacin was administered as an aggressive blocker against latanoprost mediation in the endogenous PGE_2 production pathway. This treatment was based on the finding that the COX inhibitor, both in vivo and in vitro, inhibits endogenous PGE_2 production following the administration of latanoprost.[5] The duration of the increase in endogenous PGE_2 levels, and the extent to which the administration of COX inhibitor was effective in this case, are unknown. In the current case, we employed a nonsteroidal anti-inflammatory drug (NSAID) systemically to resolve CME, because NSAID ophthalmic solutions contain benzalkonium chloride, which might be associated with the development of CME. It is necessary to investigate how to treat the CME possibly associated with the use of latanoprost ophthalmic solution.

As mentioned earlier, in our previous study concerning the use of topical latanoprost in glaucomatous eyes with normally functioning blood—ocular barrier, we found that latanoprost caused no retinal disorders in the patients who had never undergone intraocular surgery. In this study, we report a case of CME in whom the use of latanoprost ophthalmic solution seemed to be associated with the development of CME more than 1 year after intraocular surgery. It is concluded that patients who have undergone intraocular surgery, such as sulcus fixation of the intraocular lens or vitrectomy, should be carefully observed for the development of CME associated with latanoprost treatment.

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