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BRIEF COMMUNICATION

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## Deepening of Eyelid Superior Sulcus During Topical Travoprost Treatment

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### Abstract

**Background:** Topical travoprost, a prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) analog, has several well-known side effects, including a darkening of the eyelid and eyelash hypertrichosis, but there are no reports of a deepening of the eyelid superior sulcus associated with its use.

**Cases:** We examined one patient with unilateral normal-tension glaucoma and another with unilateral primary open-angle glaucoma, both of whom were treated with travoprost monotherapy unilaterally for 2 years.

**Comments:** Both patients gradually developed a deepening of the eyelid superior sulcus with hyperpigmentation in the eyelid skin of the treated eye. The disparity between the treated eye and the fellow eye was quite visible. However, the disparity returned to normal after discontinuation of travoprost for 15 months. A deepening of the eyelid superior sulcus is more significant in Asians, who seldom have an eyelid crease or deep sulcus. One proposed mechanism is a mechanical insult to the eyelid causing levator dehiscence. A second possible mechanism is fatty degeneration and reduced collagen fibers in the levator complex caused by the  $PGF_{2\alpha}$  analog. However, the exact mechanism remains to be determined.

**Conclusion:** A deepening of the eyelid superior sulcus should be considered a possible complication of topical travoprost that can be reversed by discontinuation of the medication. **Jpn J Ophthalmol** 2009;53: 176–179 © Japanese Ophthalmological Society 2009

**Key Words:** complications, eyelid sulcus deepening, travoprost

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### Introduction

Travoprost is a synthetic prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) analog and a high-affinity agonist for selective prostaglandin receptors. It is an ocular hypotensive, lipid-soluble agent that decreases the intraocular pressure (IOP) by increasing the uveoscleral outflow.<sup>1</sup> Travoprost 0.004% (Travatan, Alcon, Irvine, CA, USA) has several well-known side effects,

namely, conjunctival hyperemia, ocular irritation, iris pigmentation, eyelid skin darkening, and eyelash hypertrichosis.<sup>1</sup> However, there are no reports of a deepening of the eyelid sulcus associated with its use.

### Case Reports

#### Case 1

A 66-year-old Korean woman was diagnosed with unilateral normal-tension glaucoma and was started on travoprost 0.004% in the right eye at bedtime. She had a follow-up examination every 3 months. A mild eyelid erythema developed after 1 month of travoprost, but she tolerated this alteration well, so the topical travoprost was continued.

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Two years later, the patient stated that she had noticed a recent sunken appearance of the right eyelid, which resulted in a disparity in the appearance of the two eyes.

On examination, she had a mild hyperpigmentation of the upper eyelid and a deepening of the eyelid superior sulcus of the right eye. A clinically significant disparity of eyelid configuration was apparent between the eyes. The right eyelid showed mild ptosis with a higher skin crease than the fellow eye. The margin reflex distance (MRD1) was +0.5 in the right eye and +3 in the left eye. The levator functions were otherwise good and symmetrical in both eyes, but with evidence of unilateral levator dehiscence or weakening of the right eyelid.

Slit-lamp examination showed no significant conjunctival injection or other complications in the right eye. Because the IOP was well controlled and the patient was not unhappy about the appearance, travoprost monotherapy was continued in the right eye (Fig. 1, top left, top right, bottom left). Twelve months later, the deepening of the eyelid superior sulcus and aponeurotic ptosis of the right eye was not altered, and there was a significant disparity between the eyes (Fig. 1, bottom right).

### Case 2

A 67-year-old Korean man who was diagnosed with unilateral primary open-angle glaucoma was started on travoprost 0.004% in the left eye. He had a follow-up examination every 3 months. His IOP was well controlled, and there were no specific adverse effects except moderate eyelid skin darkening. At the 2-year follow-up visit, he complained of a marked eyelid disparity, with a sunken eye appearance and darkening of the left eyelid.

On examination, he had eyelid hyperpigmentation, hypertrichosis of the eyelashes, and deepening of the eyelid superior sulcus of the left eye. The MRD1 was +2 in both eyes, and levator function was good and symmetrical. The crease in the upper eyelid was slightly higher in the left eye, but the skin above the tarsal plate did not appear to be thin or semitransparent. The lower eyelid of the right eye had a baggy appearance suggesting a palpebral fat herniation, but the left eye was definitely not baggy. A significant asymmetry of eyelid configuration was apparent between the eyes (Fig. 2, top left, middle left, bottom left).

The patient preferred to discontinue the drug, so 2.0% dorzolamide-0.5% timolol mixed ophthalmic solution (Cosopt, MSD, Whitehouse Station, NJ, USA) was substituted for travoprost. After 6 months, hyperpigmentation and hypertrichosis of the upper eyelid had slightly decreased in the left eye, but the eyelid superior sulcus deepening did not change. The lower eyelid palpebral fat of the left eye had slightly increased, but was still less baggy than the fellow eye (Fig. 2, top middle, center, bottom middle). Fifteen months after discontinuation of travoprost, the upper eyelid hyperpigmentation and sulcus deepening had much improved in the left eye. The lower eyelid palpebral fat in the left eye had increased after discontinuation of

travoprost, but was still less baggy than the fellow eye. (Fig. 2, top right, middle right, bottom right).

### Comments

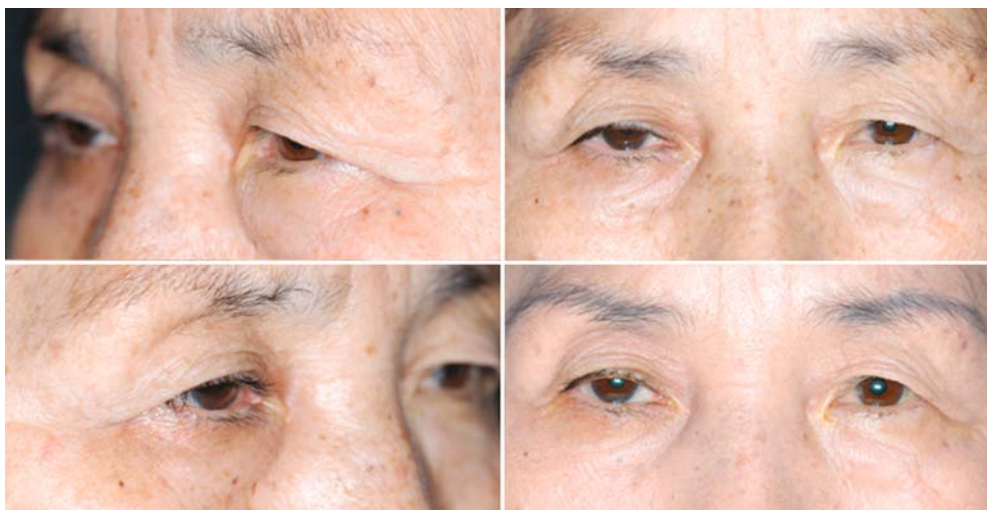
A deepening of the eyelid superior sulcus after topical drug use has been reported only after topical bimatoprost.<sup>2</sup> The deepening is also prominent after travoprost use, and no other drug has been reported with this side effect. The deepening of the eyelid superior sulcus causes a disparity in the appearance of the eyes and can be the main reason for discontinuing topical travoprost. Monocular use can lead to asymmetrical eyelid appearance, causing significant cosmetic problems. These findings seem to be more significant in Asians, because a deep superior eyelid sulcus is not common in Asians in whom the levator complex is inserted low onto the tarsus. In addition, Asians seldom have an eyelid crease or a deep sulcus.

The photographs of our patients can be compared with those of Caucasian patients with the same complications after topical bimatoprost. The sulcus deepening is more striking in Caucasians because of a preexisting deep eyelid sulcus (presumed by the fellow eye).<sup>2</sup> However, the incidence and exact mechanism for this side effect are unknown.

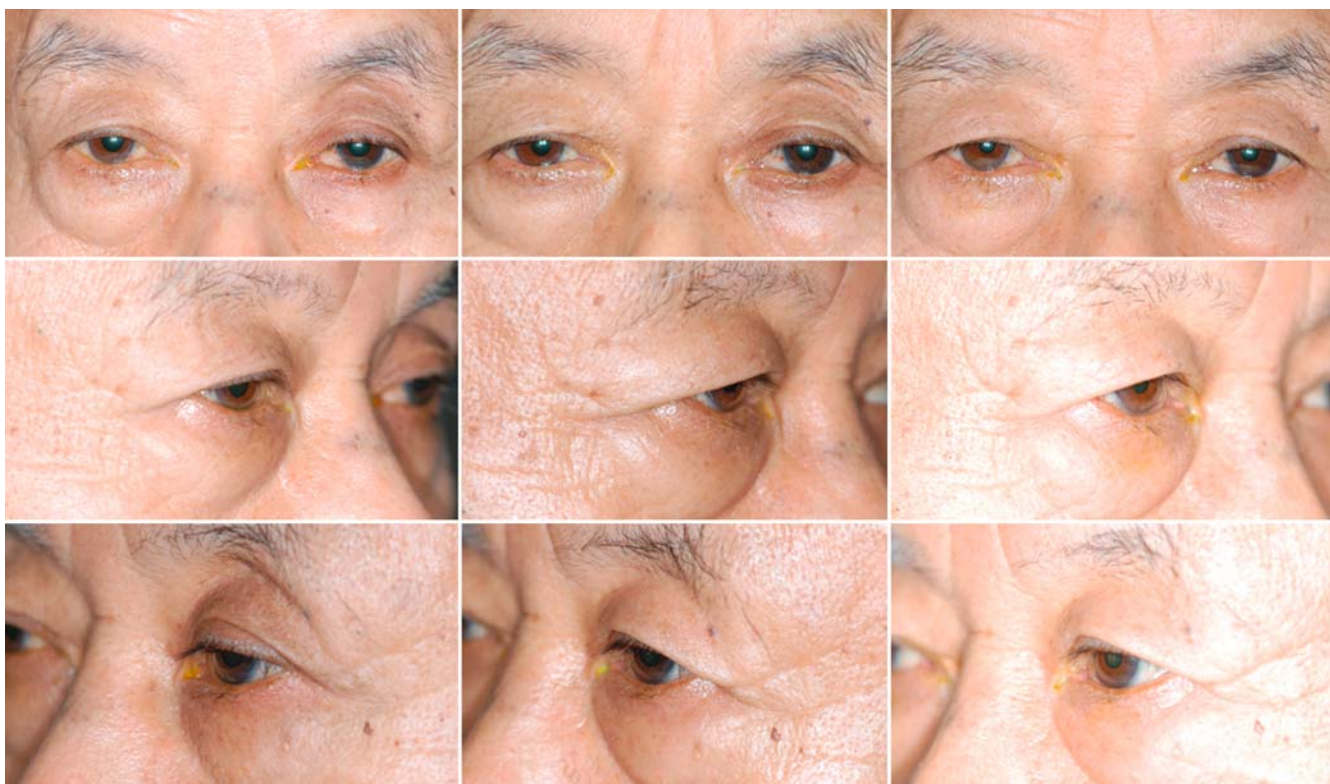
To exclude conditions that may have contributed to the unilateral superior sulcus deepening, a careful history and physical examination were performed. Neither patient had a history of eyelid trauma, contact lens use, or upper or lower blepharoplasty. The exophthalmometry values were not significantly different between the eyes, excluding the possibility of a contralateral exophthalmos. The pupillary reflexes and ocular motility were normal in both cases.

In the first case, the eye using topical travoprost showed a unilateral aponeurotic ptosis, but in the second case, levator dehiscence was not definite. Aponeurotic ptosis is mainly caused by either an involutional levator dehiscence or atrophic changes, which are bilateral and symmetrical in most cases. An aponeurotic ptosis has also been reported after long-term hard contact lens wear, and the mechanism for the levator dehiscence is mechanical, namely, the pulling of the lids laterally at the lateral canthus followed by a harsh blink.<sup>3</sup> After many years of repeated mechanical rubbing of the upper eyelid and levator complex, a levator aponeurosis dehiscence, with histological features of mild fibrosis of Mueller muscle or fatty degeneration of the aponeurosis and Mueller muscle, can develop.<sup>3</sup> This may also explain the present cases, that is, the repeated stretching of the upper eyelid during topical drug instillation can result in levator dehiscence and eyelid superior sulcus deepening. However, because other topical drugs used more frequently (e.g., >2 times/day) are not known to develop such side effects, it is more likely that the specific effects of travoprost contributed to the eyelid sulcus deepening.

The second proposed mechanism, which would make the levator complex more vulnerable to mechanical insult, may be fatty degeneration and reduced collagen fibers of the



**Figure 1.** Case 1: external photographs of both eyes. A 66-year-old Korean woman with unilateral normal-tension glaucoma was treated with 0.004% travoprost in the right eye. *Top left, top right, bottom left.* Two years after 0.004% travoprost treatment of the right eye. Eyelid superior sulcus deepening of the right eye and unilateral aponeurotic ptosis was evident. Note the disparity of eyelid appearance between the two eyes. *Bottom right.* Twelve months after continuous travoprost treatment, the deepening of the eyelid superior sulcus and aponeurotic ptosis in the right eye has not changed.



**Figure 2.** Case 2: external photographs of the eyes of a 67-year-old Korean man with unilateral primary open-angle glaucoma treated with 0.004% travoprost in the left eye. *Top left, middle left, bottom left.* Two years after 0.004% travoprost treatment in the left eye. Eyelid superior sulcus deepening and hyperpigmentation of the left eye can be seen. Note the superior sulcus deepening of the left eye in comparison to the right eye. The lower eyelid of the left eye was not baggy compared to the right eye. *Top middle, center, bottom middle.* Six months after discontinuation of travoprost, eyelid skin pigmentation has decreased but superior sulcus deepening is not changed in the left eye. *Top right, middle right, bottom right.* After 15 months, the upper eyelid skin pigmentation and sulcus deepening of the left eye have much improved. The lower eyelid of the left eye was slightly more baggy than before but still less than the fellow eye.

levator complex caused by  $\text{PGF}_{2\alpha}$ . Similar changes have been reported for luteal cells and ciliary muscles.<sup>4,5</sup> Whether such actions develop after topical  $\text{PGF}_{2\alpha}$  on the levator complex requires further experimental studies. The asymmetrical, less baggy appearance of the lower eyelid fat her-

niation in case 2, also assumes fatty degeneration or fat absorption caused by  $\text{PGF}_{2\alpha}$ .

One limitation of this study was that photographs of the eyes before travoprost was used were not available. However, the patients were convinced of the change in the

symmetry of eyelid configuration after unilateral travoprost use, and a disparity found with the fellow eyes is apparent in the photographs.

Patients reported with the same complications caused by topical bimatoprost did not have ptosis, and the palpebral fissure changes were not noted during or after halting the drug.<sup>2</sup> However, a close inspection of the photographs of these patients show the brow of the treated eye actively raised higher than the fellow eye, with lifting of the preseptal upper eyelid skin unveiling a deeper configuration of the superior sulcus, masking a mild ptosis of the drug-using eye in two of the three cases.<sup>2</sup> The proposed mechanism of eyelid superior sulcus deepening in this report was that Mueller muscle was somehow affected by the prostamide, and this may have caused aponeurotic ptosis of the affected eye.<sup>2</sup>

The time course of eyelid sulcus deepening after beginning travoprost seems to be more gradual than that of other side effects, and the deepening was therefore detected only after 1 or 2 years after initiation of travoprost. In addition, the changes were not reversible up to 6 months after discontinuation, but gradually improved after 15 months. This result is quite different from other side effects, such as hyperpigmentation or hypertrichosis, which develop as early as 1 month after topical travoprost is begun, and are reversed within several months after drug cessation.<sup>1</sup> The same complication of eyelid sulcus deepening caused by bimatoprost appeared and disappeared as soon as 1 month

after initiation or discontinuation of the treatment. These differences may not be fully explained by individual differences or different drug actions, and they remain to be elucidated.

In conclusion, patients and clinicians should be aware that eyelid superior sulcus deepening can be a possible complication of travoprost therapy, especially when used unilaterally. This may cause significant asymmetry of eyelid configuration and cosmetic problems. However, the findings are reversed by discontinuation of therapy.

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