Netarsudil-associated epithelial keratopathy

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1. Introduction

Netarsudil ophthalmic solution 0.02% (Rhopressa) is a rho-kinase (ROCK) inhibitor recently approved for lowering intraocular pressure in open-angle glaucoma or ocular hypertension. The most frequent adverse effects are conjunctival hyperemia and hemorrhage. Corneal verticillata have also been reported in up to 24% of patients in the ROCKET-1, -2, and -4 trials. Adverse effects are conjunctival hyperemia and hemorrhage. Corneal verticillata have also been reported in up to 24% of patients in the ROCKET-1, -2, and -4 trials. Netarsudil ophthalmic solution 0.02% (Rhopressa) is a rho-kinase inhibitor recently approved for lowering intraocular pressure in open-angle glaucoma or ocular hypertension. As netarsudil continues to be increasingly used, physicians and patients need to be aware of this new possible adverse effect.

1.1. Case 1

A 72-year-old African-American male with bilateral moderate primary open-angle glaucoma and cataracts, and quiescent central serous chorioretinopathy (CSR) in the left eye presented to glaucoma clinic with new maximal intraocular pressures (IOP) of 28 mmHg in the right eye and 32 mmHg in the left eye despite compliance with timolol twice daily and brinzolamide-brimonidine three times daily. He reported running out of latanoprost one week prior. Visual acuity (VA) was 20/25 in the right eye and 20/70 in the left eye, with 2+ nuclear sclerosis bilaterally, and a cup-to-disc ratio of 0.8 in the right eye and 0.9 in the left eye. Given a goal IOP of <13 mmHg, netarsudil once daily in both eyes was added to his regimen.

On one month follow up, he reported bilateral eye redness, foreign body sensation, photophobia, and decreased vision that started 3 days after starting netarsudil, which he continued to use despite severe discomfort. Examination of the right and left eyes, respectively, revealed VA of 20/40 and 20/400, and IOP of 24 mmHg and 19 mmHg. In both eyes, there was significant conjunctival hyperemia (Fig. 1A) and predominantly inferior corneal epithelial edema and bullae (Fig. 1B). Keratic precipitates and mild anterior uveitis were present without hypopyon. These findings were more severe in the left eye. Netarsudil was discontinued. He was started on oral methazolamide 50mg three times daily and prednisolone acetate four times daily in both eyes, after which symptoms resolved on one week follow up. VA improved to 20/30 daily.

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Purpose: To report 2 cases with a novel finding of bullous epithelial keratopathy associated with netarsudil use. Observations: A 72-year-old man with history of primary open angle glaucoma was started on netarsudil daily in both eyes for uncontrolled intraocular pressures despite treatment with latanoprost, brimonidine, and dorzolamide-timolol. One month later he presented with bilateral conjunctival hyperemia, predominantly inferior corneal epithelial bullae, and keratic precipitates without hypopyon. Netarsudil was discontinued, and the patient was started on topical steroids. One week later, the hyperemia and corneal edema had resolved while many small keratic precipitates persisted.

A 29-year-old man with history of rubella-associated glaucoma and chronic postoperative inflammation on prednisolone was started on netarsudil in his left eye only for elevated intraocular pressures despite latanoprost, brimonidine, and dorzolamide-timolol. Two months later, he complained of eye pain and decreased vision since starting netarsudil. Examination revealed mild hyperemia and inferior corneal epithelial bullae without keratic precipitates. Netarsudil was discontinued, and two weeks later, conjunctival injection resolved and cornea cleared.

Conclusions and importance: Netarsudil ophthalmic solution 0.02% (Rhopressa) is a rho-kinase inhibitor recently approved for lowering intraocular pressure in open-angle glaucoma or ocular hypertension. As netarsudil continues to be increasingly used, physicians and patients need to be aware of this new possible adverse effect.
2. Discussion

We present two cases with epithelial keratopathy associated with netarsudil use, with symptoms which started days after exposure to netarsudil and resolved after discontinuation. This adverse effect to netarsudil has not been previously reported to our knowledge. These corneal changes resembled microcystic edema and bullous keratopathy and were predominantly in the inferior cornea. One patient also presented with concurrent anterior uveitis, while the second patient didn’t. Perhaps, the second patient’s chronic prednisolone use masked the inflammatory response seen in the first patient. The first patient had primary open angle glaucoma, as well as CSR in the left eye that had more severe involvement; the second patient had rubella-associated glaucoma, and in the involved eye has a history of cataract surgery with resulting aphakia, as well as chronic postoperative inflammation from vitrectomy. Neither patients had central corneal thickness or endothelial cell counts records prior to the incident. Both patients were male and have a history of timolol, carbonic anhydrase inhibitor, and brimonidine use prior to starting netarsudil, but otherwise do not have unifying ocular or systemic co-morbidities. Both prescriptions had different lot numbers. Therefore, it is difficult to speculate which patients may be at risk for developing this reaction.

Both patients in our series failed to report these changes when they first experienced symptoms. Fortunately, these changes were reversed with topical steroids and discontinuation of netarsudil. Patients with eye pain and vision changes after starting netarsudil should be advised to notify their ophthalmologist so they can be evaluated sooner in follow-up.

The underlying mechanism for this reaction is unclear. In the ROCKET trials that evaluated the safety and efficacy of netarsudil, conjunctival hyperemia was observed in nearly 50% of patients and blurred vision in 3% of patients, but no mention of corneal epitheliopathy besides verticillata were reported, and no changes to corneal endothelial cell density or hexagonality were seen on specular microscopy. Another ROCK inhibitor, ripasudil, used to treat ocular hypertension in Japan, has in fact shown efficacy against corneal endothelial dysfunction like Fuchs corneal dystrophy, and there are again no reports of corneal epitheliopathy. As ROCK inhibitors continue to be increasingly used, physicians and patients need to be aware of this new possible adverse effect, especially if patients complain in the right eye and 20/80 in the left eye, and IOP was 13 mmHg bilaterally. Conjunctival hyperemia and epithelial keratopathy had resolved (Fig. 1C). Many small pigmented keratic precipitates persisted bilaterally.

1.2. Case 2

A 29-year-old Filipino male with a history of bilateral glaucoma and aphakia secondary to congenital rubella presented to glaucoma clinic for routine follow up. The patient had a remote history of bilateral lensectomy as a child. The right eye underwent tube shunt surgery with Ahmed valve 7 years prior with subsequent stable IOP. The left eye had a history of vitrectomy with silicone oil for macula-off retinal detachment 5 years prior, for which he remains on prednisolone acetate twice daily for chronic postoperative inflammation. VA was at baseline 20/200 and count fingers at 1 foot, and IOP was 15 and 21 mmHg in the right and left eye, respectively, on dorzolamide-timolol and brimonidine twice daily and latanoprost. Optic discs were tilted with cup-to-disc ratio of 0.2 bilaterally, and were overall difficult to assess. Netarsudil once daily in the left eye was started for goal IOP <15 mmHg. On follow up two months later, he complained of left eye redness, irritation, and decreased vision in the left eye that started 3 days after netarsudil, which he continued to use until follow up. Left eye VA was hand motion only, IOP was 22 mmHg, with mild conjunctival injection, inferior epithelial edema and bullae, without keratic precipitates or uveitis (Fig. 2A). The right eye was unchanged. Netarsudil was discontinued. Two weeks later, the conjunctival injection had resolved and cornea cleared (Fig. 2B).
of vision changes and eye pain.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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