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Case Report

Netarsudil-induced reticular epithelial oedema: An uncommon side effect

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ABSTRACT

Netarsudil ophthalmic solution 0.02% (Netalo) is a new drug in the armamentarium for lowering intraocular pressure in open-angle glaucoma or ocular hypertension. It is a rho-associated protein kinase (ROCK) and norepinephrine transporter inhibitor with multiple mechanisms of action at various cellular levels. Apart from its effect on glaucoma, it has been reported to be beneficial in acute corneal endothelial damage. Its reported common side effects are conjunctival hyperaemia, corneal verticillata and subconjunctival haemorrhage. Corneal oedema arising from its use has been infrequently reported from abroad. We have presented two cases of such oedema acutely induced by Netarsudil, in the absence of any pre-existing corneal problems and which resolved on discontinuation. Such incidences warrant further studies to understand their clinical significance, the mechanism of corneal oedema arising from ROCK inhibitors and the use of these drugs in patients with compromised corneas.

Keywords: Rho-associated protein kinase inhibitors, Netarsudil, Reticular corneal oedema

INTRODUCTION

The treatment modalities of glaucoma include medications, laser therapy and surgery. Rho kinase is a serine/threonine protein kinase involved in the regulation and modulation of cell shape and size through action on the cytoskeleton, thereby claimed to be involved in glaucoma, Fuch's corneal endothelial dystrophy and diabetic retinopathy.[1] It is hypothesised that Rho kinase inhibitors could play a part in increasing cell adhesion and proliferation in the corneal endothelium, helping to preserve corneal endothelial cells and retard apoptosis, thereby proving beneficial in acute corneal endothelial damage. Positive effects of Rho-associated protein kinase (ROCK) inhibitors in corneal endothelial wound healing in rabbit and primate models have been noted.[2] Few authors have demonstrated the success of ROCK inhibitors in patients of Fuchs' endothelial corneal dystrophy, through preservation of corneal clarity and visual acuity (VA).[2]

Two Rho kinase inhibitors have been launched recently as anti-glaucoma agents–Ripasudil and Netarsudil. Netarsudil 0.02% is a ROCK and norepinephrine transporter inhibitor, resulting in increased trabecular outflow and decreased episcleral venous pressure.[3] Inhibition of nor epinephrine causes vasoconstriction leading to decreased blood flow to the ciliary processes thereby also inhibiting aqueous humour production.[3] Other benefits include neuroprotection, improved ophthalmic perfusion, decreased inflammation, prevention of scarring following filtration procedures and improved corneal healing. Regarding their safety profile, the typical adverse event (AE) noted is diffuse conjunctival hyperaemia. Other commonly reported ones include corneal verticillata, eye pain and subconjunctival haemorrhage and less frequent ones include decreased VA, watering, lid erythema and corneal staining.[1] Systemic AEs are almost unknown. Very few international reports have mentioned episodes of reticular bullous epithelial corneal oedema which improve with drug discontinuation.[4,5] With the drug recently launched in the Indian market and just beginning to find its way into prescriptions, AEs apart from conjunctival hyperaemia are yet quite unnoticed and unreported. We present here two unusual cases of netarsudil-induced corneal toxicity. With its reported beneficial effect on the corneal health, corneal oedema resulting from its use is surprising, inviting the question of its effect on cornea.

CASE REPORT

Our first patient was a 64-year male, diabetic and hypertensive, diagnosed with left eye (LE) neovascular

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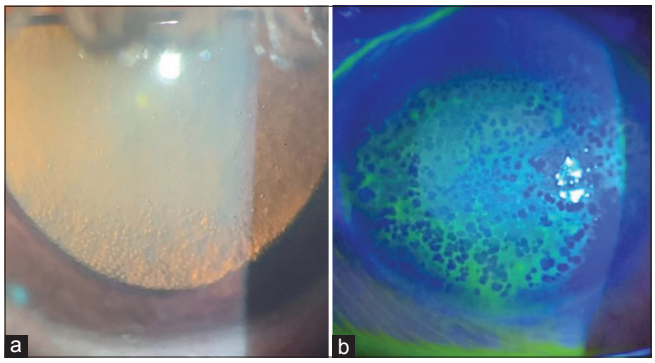

Figure 1: Corneal oedema after use of Netarsudil – (a) without fluorescence stain (b) with fluorescence stain.

glaucoma with central retinal venous occlusion and macular oedema. His VA was hand movement perception and intraocular pressure (IOP) by Goldmann applanation tonometer was 20 mm Hg. Gonioscopy using Goldmann 4 mirror goniolens revealed completely closed angles. His right eye (RE) showed VA of 6/60, IOP 14 mm Hg, normal open angles and normal fundus. His LE was treated with intravitreal inj. Ranibizumab 0.5 mg (Lucentis) followed by 360° pan retinal photocoagulation and maximal glaucoma medications. Since the IOP was not in the target range and patient was reluctant for surgery, he was prescribed Netarsudil eye drops 0.02% once a day additionally. At the 7-day follow-up, he presented with LE diffuse reticular/honeycomb corneal oedema with an IOP of 18 mm Hg by Goldmann applanation tonometer. Netarsudil eye drops 0.02% (Netalo) were omitted and 3 days after omission, oedema decreased significantly and at 5 days, resolved completely [Figures 1a and b].

Our second patient was a 34-year male, juvenile diabetic, with bilateral advanced neovascular glaucoma following long-standing proliferative diabetic retinopathy and multiple photocoagulation procedures. His VA was counting fingers 1 meter in both eyes, IOP 30 mm Hg and 28 mm Hg, respectively, in RE and LE and gonioscopy revealed bilateral 360° synechial closure. Patient was advised both eyes brimonidine 0.15%w/v plus timolol 0.5% w/v eye drops (Brimolol)bd, dorzolamide 2%w/v eye drops (Dorzox) bd, prednisolone 1% eye drops(Predmet) qid, atropine 1% w/w eye ointment (Atro) tid and tablet acetazolamide 250 mg (Diamox) qds with a potassium supplement. At the 3-day follow-up, the IOP was 18 mm Hg and 16 mm Hg, respectively, in RE and LE by Goldmann applanation tonometer. Netarsudil eye drops of 0.02% once a day were added to both eyes. At the 7-day follow-up, the patient presented with similar bilateral reticular/honeycomb-type corneal oedema in inferior quadrants. Netarsudil was omitted and on 5-day follow-up, the oedema was completely resolved.

DISCUSSION

Conjunctival hyperaemia is the most common side effect reported with Netarsudil. In the ROCKET-2 trial, the common side effects noted were conjunctival hyperaemia, corneal verticillata and subconjunctival haemorrhage. It is important to appreciate that cornea oedema can be the result of many aetiologies, such as Fuchs dystrophy, elevated IOP, trauma and scleral lenses, among others. Nevertheless, it is reasonable to consider the role that Netarsudil played in the development of the observed reticular honeycomb changes of the cornea given the timeline of these developments following the initiation of this agent. In several cases, reticular corneal epithelial oedema preferentially impacted the inferior cornea rather than being evenly distributed. A possible explanation is that this is secondary to the pooling of the medication after the administration of drops. Mark M Fernandez reported that use of Netarsudil in patients with oedematous corneas developed reticular epithelial oedema which resolved on omission.[4] Wisely *et al*. reported similar oedema in five patients, where four patients did have pre-existing endothelial oedema.[5] Both our patients also presented with a characteristic reticular corneal oedema after initiation of Netarsudil which resolved completely after omission but neither of them had pre or coexisting corneal oedema. Since the oedema developed soon after initiation of Netarsudil and resolved on omission, the causality could be established. Sahu *et al*. also reported a case of honeycombing corneal oedema in a 60-year-old male patient.[6]

Although the previous research has supported the use of ROCK inhibitors for corneal healing and reduction of corneal oedema, development of honeycomb oedema causes concern.[2]

CONCLUSION

Netarsudil 0.02% is a new drug in the armamentarium for lowering IOP. As it is gradually getting incorporated into glaucoma drug prescriptions, one needs to be aware of its possible adverse effect of reticular corneal oedema. We have presented two cases of such oedema acutely induced by Netarsudil, in the absence of any pre-existing corneal problems and which resolved on discontinuation. Such incidences warrant further studies to understand their clinical significance, the mechanism of corneal oedema arising from ROCK inhibitors and the use of these drugs in patients with compromised corneas.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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