Journal of Movement Disorders 2013;6:34-36 **CASE REPORT**
pISSN 2005-940X / eISSN 2093-4939

Amantadine Induced Corneal Edema in a Patient with Primary Progressive Freezing of Gait

Young Eun Kim[a,b]
Ji Young Yun[b,c]
Hui-Jun Yang[b,d]
Han-Joon Kim[b,e]
Mee Kum Kim[f]
Won Ryang Wee[f]
Beom S. Jeon[b,e]

[a]Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[b]Parkinson's Disease Study Group, Seoul National University Hospital, Seoul, Korea
[c]Department of Neurology, Ewha Womans University Mokdong Hospital, Seoul, Korea
[d]Department of Neurology, Ulsan University Hospital, Ulsan, Korea
[e]Department of Neurology and Movement Disorder Center, Seoul National University College of Medicine, Seoul, Korea
[f]Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea

Amantadine is commonly used for Parkinsonism. However amantadine can induce adverse corneal reaction. Here we report a patient with primary progressive freezing of gait who had severe corneal edema associated with amantadine, which was reversible after discontinuation of the amantadine. This report alerts neurologists for this reversible but potentially critical corneal edema in patients with Parkinsonism who are receiving amantadine.

Journal of Movement Disorders 2013;6:34-36

Key Words: Amantadine, Corneal edema, Parkinsonism.

Amantadine has been used in the treatment of early Parkinson disease, and has come into the spotlight again for the treatment of levodopa-induced dyskinesia recently.[1] Furthermore, there is increasing interest on freezing of gait (FOG) in Parkinsonism.[2-4] However, amantadine can induce adverse corneal reactions, such as superficial punctuate keratitis, punctuate subepithelial opacification, epithelial edema and stromal edema although ocular toxicity is extremely rare.[5] These reactions are critical but usually reversible after cessation of amantadine except for chronic corneal damage.[6,7] Therefore, it's important to notice these critical but reversible causes of visual problems because visual problems associated with amantadine can be misdiagnosed as aging-related ocular changes. Here, we report a patient with primary progressive FOG who had severe corneal edema associated with amantadine, which was reversible after discontinuation of the amantadine.

Case

A 63-year-old woman presented with progressive FOG for 3 years. She had no bradykinesia, rigidity, and tremor, even though she had hypophonia and postural instability. She did not have abnormal ocular movement and autonomic dysfunction. Her cognition andbrain MRI was normal. Her FOG did not respond to levodopa. However, amantadine 400 mg per day was somewhat effective for treating her FOG. After taking amantadine for about 7 months, her bilateral visual acuity had decreased for over 1 week. Accordingly, she visited an eye clinic at another hospital. Severe corneal edema was found in both eyes. Her treating physician recommended corneal transplantation. This information was given to us during her regular follow-up. She was immediately referred to our ophthalmology department. Upon slit lamp examination, profound corneal edema was found (Figure 1A). Corneal evaluation revealed Descemet's folds, and punctate epithelial erosion as well as profound corneal edema. Her uncorrected visual acuity was 0.15 in the right eye and 0.2 in the left eye. Because amantadine was considered to be the cause of this problem, amantadine was discontinued and the scheduled corneal transplantation was postponed. One month after ceasing the amantadine, her uncorrected visual acuity recovered back to 0.3 in the right eye and 0.7 in the left eye. Best corrected visual acuity was 0.9 and 1.0 in each eye. Her corneal pachymetry (normal value, 0.53-0.55 mm) had improved from 0.661 mm to 0.532 mm in the right eye, and from 0.651 mm to 0.523 mm in the left eye. Although both corneas showed no edema, endothelial cell density

Received June 6, 2013
Revised July 10, 2013
Accepted August 2, 2013

Corresponding author
Beom S. Jeon, MD, PhD
Department of Neurology,
Seoul National University Hospital,
101 Daehak-ro, Jongno-gu,
Seoul 110-744, Korea
Tel +82-2-2072-2876
Fax +82-2-3672-7553
E-mail brain@snu.ac.kr

· The authors have no financial conflicts of interest.

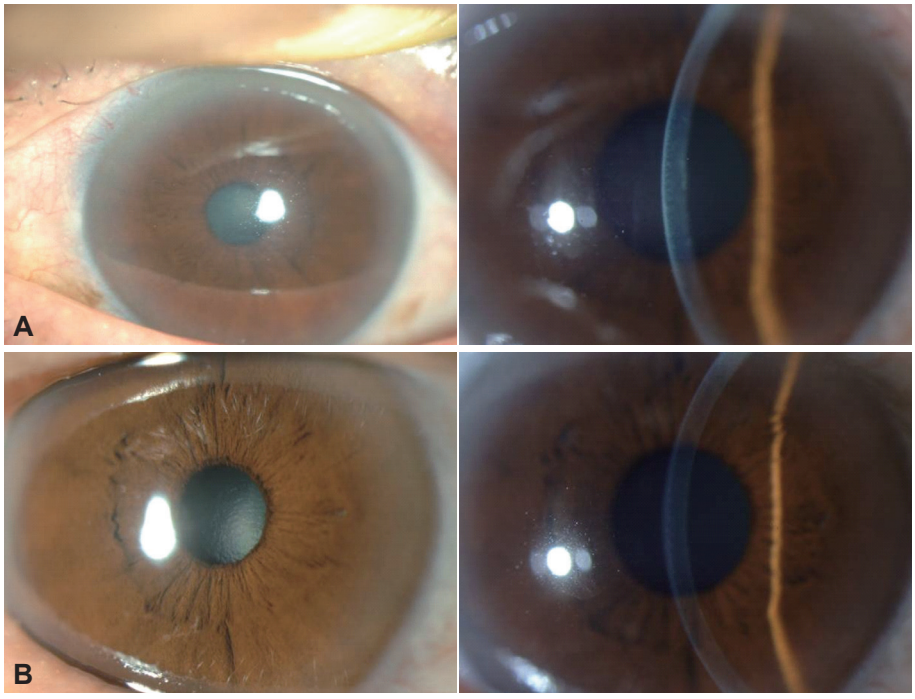

Figure 1. A: Slit-lamp examination of the anterior segment showing amantadine induced corneal edema. B: Resolution at 1 month after the cessation of amantadine. Corneal opacity and punctate epithelial erosion improved.

(normal density in age range of 60s is mean 2613/mm^2)[8] was irreversibly decreased (608/mm^2 in the right eye and 621/mm^2 in the left eye) (Figure 1B).

Discussion

There have been few reports on corneal edema associated with amantadine use. All patients experienced bilateral diffuse corneal edema while receiving systemic amantadine therapy at a dose of 100-400 mg a day for a duration ranging from several days to 8 years.[6,7,9-18] Corneal edema in most of the cases resolved within 8 days to 2 months after the discontinuation of amantadine.[6,7,9-18] However, in our case, endothelial cell density decreased irreversibly after having taken amantadine for 7 months, although the corneal edema improved. Previous case reports identified permanent endothelial cell loss in amantadine users with a long duration from 1 year to 6 years.[7,13,14] In addition, a cross-sectional study demonstrated that amantadine users are more likely to have a lower endothelial cell density when used over the long-term.[5]

Although the mechanism of the adverse effect of amantadine is not clear, the drug in the tear film, which is secreted form the lacrimal glands, can create superficial corneal deposit, associated epithelial edema and keratitis. In addition, drug hypersensitivity to amantadine and toxic effect to corneal endothelial cells are suggested mechanisms as well.[5]

Ophthalmologic adverse events of amantadine are rare and hence, are sometimes underrecognized.[10] It is important to detect amantadine associated corneal edema because this side effect is potentially reversible. In addition, regular monitoring of ophthalmology should be recommended to patients receiving amantadine to detect acute and chronic complications. This report alerts neurologists for this reversible but potentially critical corneal edema in patients with Parkinsonism who are receiving amantadine.

Acknowledgments

This study was supported by a grant from the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A101273).

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