

Bilateral Irreversible Amantadine-Related Corneal Edema Successfully Treated With Descemet Membrane Endothelial Keratoplasty (DMEK)

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Abstract: Corneal edema is a recognized adverse reaction of chronic amantadine hydrochloride use. Fortunately, it is usually reversible with prompt discontinuation of the medication. We report a case of a patient with schizoaffective disorder–bipolar treated with high doses of amantadine for drug-induced akathisia, who developed irreversible bilateral severe corneal edema, and was successfully treated with Descemet membrane endothelial keratoplasty (DMEK). This case highlights the importance of recognizing amantadine-induced endothelial toxicity and confirms the utility of DMEK in the treatment of the condition.

Key Words: amantadine, corneal edema, endothelial keratoplasty, DMEK

(EBCT 2023;2:e0006)

Amantadine hydrochloride is a dopaminergic agonist originally developed for prevention and treatment of influenza A. It was later introduced in the treatment of Parkinson disease and other associated drug-induced dyskinesia.¹

Multiple reports^{2–5} have indicated that amantadine induces various adverse corneal reactions, including epithelial and stromal edema. The corneal edema is usually reversible after discontinuation of therapy; however, it can potentially be irreversible. This adverse effect on the corneal endothelium seems to be dose and duration dependent.^{6–8} Here, we report a patient with chronic use of amantadine to treat akathisia,⁹ who developed irreversible bilateral corneal edema despite discontinuation of amantadine for 6 months, and was successfully treated with combined phacoemulsification and Descemet membrane endothelial keratoplasty.

CASE PRESENTATION

A 64-year-old woman was referred to our clinic for evaluation of corneal edema. The patient had complaints of progressive bilateral decrease in visual acuity over the past 5 months.

The medical history revealed a long-standing history of psychiatric disorders, including schizoaffective disorder–bipolar, anxiety and depression as well as type II diabetes, asthma, gastroesophageal reflux disease, thyroid disease, arthritis, and drug-induced akathisia. Medications included amantadine, omeprazole, clonazepam, propranolol, Fetzima (Forest Pharmaceuticals Inc, New York, NY), montelukast sodium, bupropion, thyroxine, Fanapt (Vanda Pharmaceuticals, Washington, DC), and various dietary supplements and vitamins.

Eight months before presentation, the patient was diagnosed with drug-induced akathisia (related to psychotropic medications) and was started on 100 mg a day of amantadine hydrochloride therapy by her psychiatrist. Subsequently, the dose was increased to 100 mg 3 times a day and was continued for 5 additional months before presenting to our clinic.

The visual acuity on presentation was 20/400 in both eyes. Slitlamp examination revealed severe +4 corneal stromal edema with Descemet folds (Fig. 1) and no guttae. The anterior chambers were deep and quiet. There was evidence of 1+ nuclear sclerosis in both eyes. Dilated fundus examination was somewhat limited due to poor visualization, but there was no evidence of diabetic retinopathy or other pathology. Ultrasound pachymetry and specular microscopy were attempted but unobtainable (out of range) on her first visit. After review of her medications, the patient was instructed to discontinue amantadine. Three months later, the patient reported a mild improvement in visual acuity which was recorded as 20/300 in the right eye and 20/100 in the left eye. Pachymetry was 941 μ m in the right eye and 788 μ m in the left eye. Endothelial cell imaging was not captured in the right eye and extremely low (unable to determine an accurate endothelial cell density) in the left eye. On slitlamp examination, there was no clinical noticeable change in the degree of corneal edema compared with the initial presentation. Subsequent examinations over the following 3 months were unchanged, so the patient was offered combined phacoemulsification with intraocular lens implantation and Descemet membrane endothelial keratoplasty (DMEK).

She underwent uncomplicated triple DMEK procedure in the right eye and then in the left eye (6 and 9 months after

Received for publication February 7, 2023; revision received March 18, 2023; accepted March 28, 2023. Published online April 26, 2023.
From the Sacramento Eye Consultants, Sacramento, CA.
The authors have no funding or conflicts of interest to disclose.
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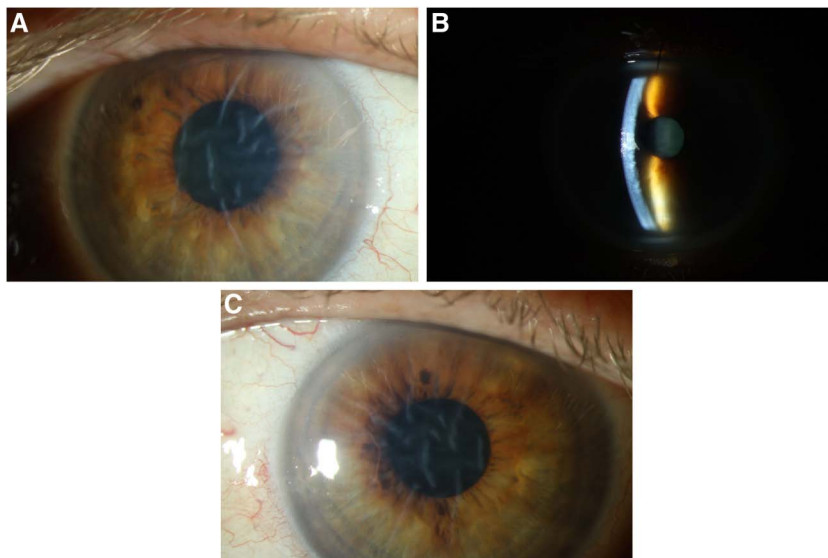


FIGURE 1. Slitlamp photographs of the right (A, B) and left (C) eyes revealing marked stromal and epithelial edema with Descemet folds.

her initial visit, respectively). After both surgeries, visual acuity improved, and steroids were tapered monthly. On her last visit, 15 and 18 months after the corneal surgeries, the grafts were clear (Fig. 2) and pachymetry was 541 and 536 μm in the right and left eyes, respectively. Endothelial cell density (ECD) was measured as 2564/ mm^2 in the right eye and 3030/ mm^2 in the left eye. The uncorrected visual acuity was 20/20 in the right eye and 20/30 in the left eye improving to 20/20 in the left eye with correction.

DISCUSSION

Previous reports in the literature indicate that the adverse corneal effects of amantadine are rare and usually reversible with discontinuation of therapy. However, in 2008, Jeng proposed that the corneal edema secondary to amantadine use could potentially be irreversible.⁶

The pathogenesis of amantadine-induced corneal edema is unclear. It is likely that the corneal edema occurs secondary to interactions with dopamine corneal endothelial cell receptors that ultimately disrupt intracellular fluid osmolarity and corneal endothelial cell organization.^{10,11} Amantadine damages the corneal endothelial cells in a dose-dependent manner.⁷ The greatest relative risk of corneal edema is seen in patients who are given a high dose for a short period (2000 mg within 30 days relative risk = 2.38).⁸ A 4000 mg cumulative dose prescribed within 30 days leads to a 3-fold increased risk in corneal edema.⁸

Our patient was kept on a high amantadine dose (100 mg 3 times a day) for 5 months. Our case provides additional evidence that the toxic endothelial effects of amantadine can be irreversible despite discontinuation of amantadine, requiring surgical intervention.

Descemet stripping automated endothelial keratoplasty (DSAEK) has been successful in restoring corneal clarity related to amantadine toxicity if the medication is discontinued before surgery.¹¹ In 2009, Koenig described a similar case on a young patient with schizophrenia and tardive dyskinesia, who developed bilateral corneal edema, after chronic treatment with amantadine. Both eyes underwent successful phakic DSAEK, but despite initial clearing of the donor lenticules, both eyes later developed nonimmunologic graft failure related to continued amantadine corneal toxicity.¹² He concluded that chronic amantadine may be responsible for irreversible corneal edema and may lead to graft failure in unrecognized cases.

To the best of our knowledge, there have been no reports in the literature of DMEK described as a treatment of irreversible corneal edema related to amantadine use. Compared with DSAEK, DMEK provides a significantly higher rate of 20/20 and 20/25 vision, comparable endothelial cell loss, more exact anatomic replacement of dysfunctional host endothelium without the addition of any donor stromal tissue, and lower risk of immunologic graft reactions.¹³ Our case report confirms that endothelial dysfunction related to

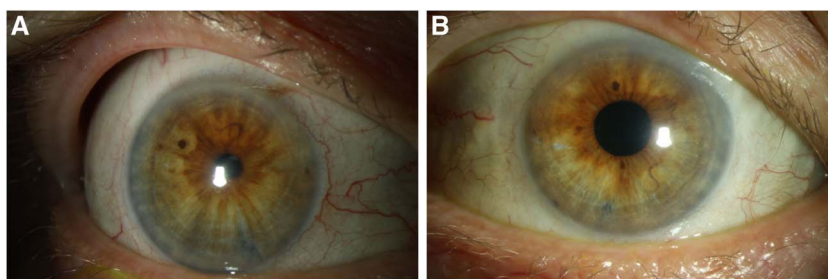


FIGURE 2. Slitlamp photograph of the (A) right eye and (B) left eyes after combined phacoemulsification and DMEK surgery demonstrating clear corneas and complete resolution of corneal edema.

amantadine use can be irreversible and successfully treated with DMEK or triple DMEK in cases where there is presence of a cataract.

It is important to keep in mind that in cases of corneal edema without an obvious causative disease, the systemic medication list of the patient must be reviewed and amantadine must be considered as a possible cause. This is particularly critical in older patients with Parkinson disease, psychiatric disorders, depression, or other physical illness in whom visual deterioration is easily overlooked due to poor verbal expression. Ophthalmic consultation is suggested before and during amantadine therapy. Careful medication review is crucial in patients with an unknown etiology of corneal edema.

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