Balancing Visual Outcome and Systemic Function: A Rare Case of Amantadine Keratopathy in a Patient With Severe Parkinson's Disease

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Abstract

Amantadine is a medication increasingly prescribed for the treatment of Parkinson's disease that has significant side effects, including amantadine keratopathy. Amantadine keratopathy is a rare, dose-dependent, and cumulative disease process in which the drug amantadine causes severe corneal edema and subsequent decreased visual acuity. While the keratopathy is usually reversible upon discontinuation of the drug, this report details a unique case where drug termination was not an option, and co-management with the patient's neurologist was necessary to balance visual outcomes and systemic function. A review of Parkinson's disease along with the incidence, prevalence, and pathophysiology of amantadine keratopathy are discussed. Clinical considerations, such as risk factors and dosing patterns for developing keratopathy from this drug, are also presented.

KEYWORDS: Amantadine keratopathy, Parkinson's disease, amantadine, corneal edema

INTRODUCTION

Amantadine (Symmetrel, Endo Pharmaceuticals, Newark, DE) is a glutamate receptor antagonist originally indicated for the treatment of influenza in the 1950s. It is now increasingly utilized to treat tremors and dyskinesia associated with Parkinson's disease along with muscular rigidity and difficulty with balance and coordination that develop with this condition.[1] Amantadine-induced corneal edema is a rare adverse drug reaction that results in decreased vision. While the incidence and prevalence of the condition is unknown, keratopathy has been shown to be dose-dependent and cumulative but typically resolves once the drug is discontinued. This report presents a unique case in which discontinuation of amantadine was not an option and careful co-management with the patient's neurologist was required to improve the visual outcome while still controlling the patient's systemic symptoms of Parkinson's disease.

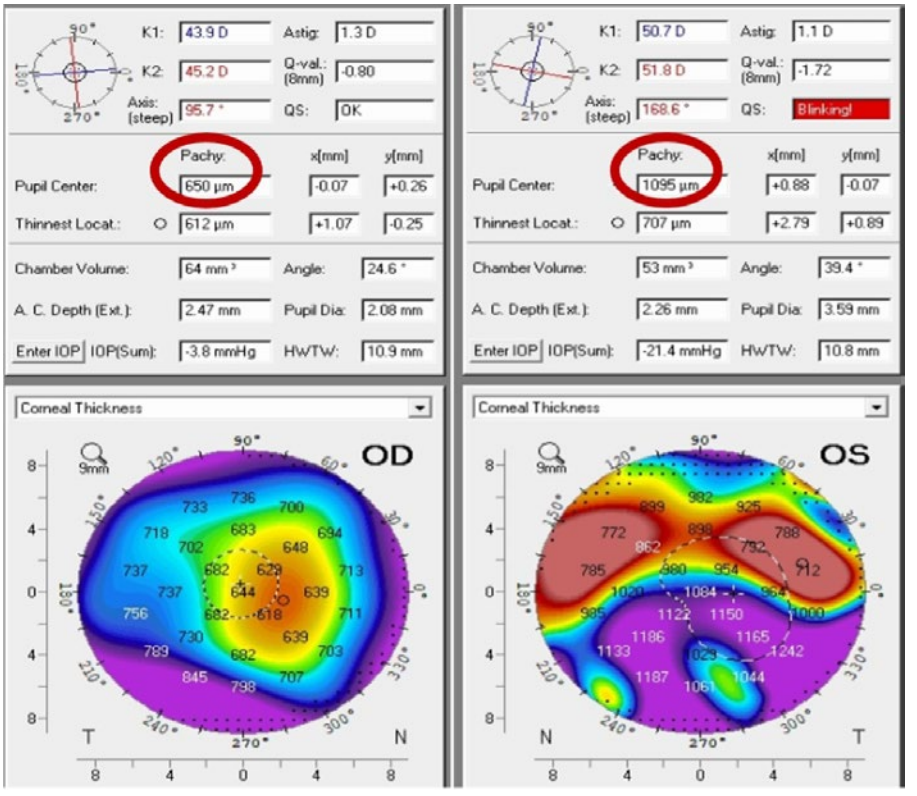
CASE REPORT

A 51-year-old Hispanic female presented to the eye clinic complaining of worsening vision which was greater in the left eye than in the right eye and which had persisted for a few months. Pertinent ocular history included anatomically narrow angles for which laser peripheral iridotomy (LPI) had been performed in each eye and bilateral corneal edema of unknown etiology for which an outside provider had recommended a corneal transplant. Pertinent medical history included Parkinson's disease, hypertension, and type 2 diabetes mellitus. Her Parkinson's disease was managed with a total dosage of 600 mg/day of amantadine, which she had been taking for 18 months. She had previously tried two other Parkinson's medications, 1 mg/day of clonazepam (Klonopin, Chela Pharmaceuticals, Greifswald, Germany) and 100 mg/25 mg of carbidopa/levodopa (Sinemet, Merck & Co, Rahway, NJ) daily, both of which were unsuccessful in controlling her symptoms. Her hypertension was controlled with

160 mg/day of valsartan (Diovan, Novartis Pharmaceuticals, Basel, Switzerland) and 10 mg/day of amlodipine (Norvasc, Pfizer, New York, NY), while her diabetes was controlled with 10 mg/day of empagliflozin (Jardiance, Boehringer Ingelheim, Rhein, Germany) and 2 mg weekly injections of exenatide (Bydureon, AstraZeneca, Cambridge, England) .

At the initial visit, her uncorrected visual acuity was 20/150 in the right eye and hand motion (HM) in the left eye. There was no improvement in the vision in either eye with pinhole. Her extraocular movements, pupillary function, confrontation visual fields, and intraocular pressure were all within normal limits. Anterior segment findings of the right eye included 1+ corneal edema with trace to 1+ Descemet's folds, patent LPI, narrow anterior chamber angles, and a clear lens. Anterior segment findings of the left eye included 1+ diffuse bulbar conjunctival injection, 2+ corneal edema, 2+ Descemet's folds, patent LPI, open anterior chamber angles, and a clear lens. The remainder of the anterior segment and posterior segment examination of both eyes was non-contributory and unremarkable. A baseline anterior segment optical coherence tomography (OCT) (Heidelberg, Franklin, MA) was acquired along with a baseline Pentacam® anterior segment tomography scan (OCULUS, Wetzlar, Germany). Figure 1 shows the baseline Pentacam® results demonstrating central corneal thickness values of 650uM of the right eye and 1,095uM of the left eye. The anterior segment OCT showed the presence of corneal edema that was worse in the left eye than the right eye, correlating with the Pentacam® scans results and overall clinical picture.

Figure 1: *Baseline Pentacam® demonstrating the right eye central corneal thickness was 650uM, while the left eye central corneal thickness was 1,095uM.*

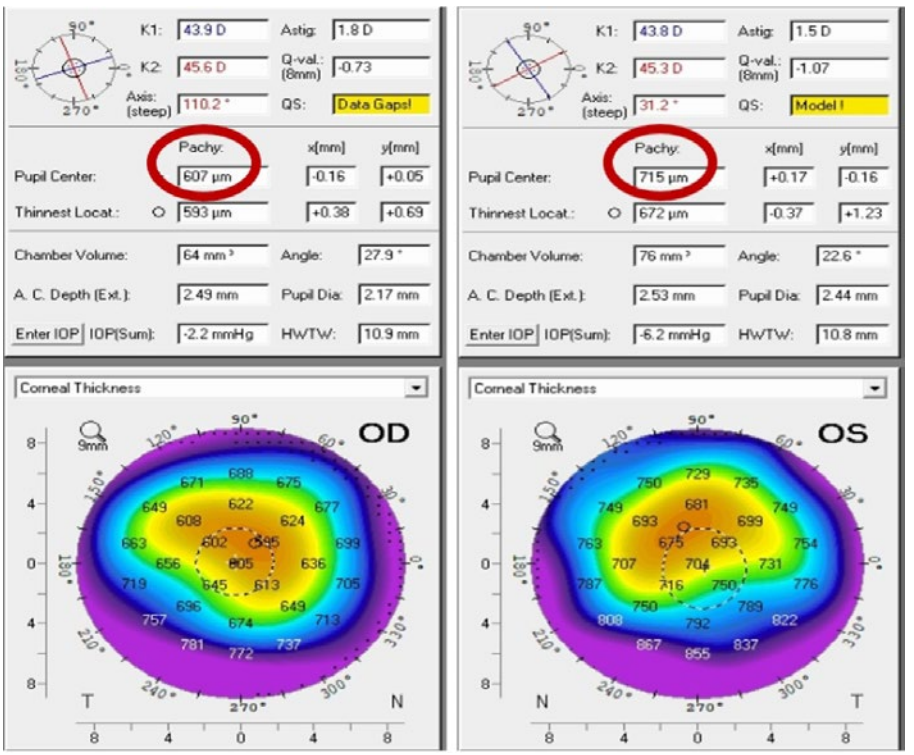


Differential diagnoses at this time included amantadine keratopathy, Fuchs' endothelial dystrophy, posterior polymorphous corneal dystrophy (PPMD), iridocorneal endothelial (ICE) syndrome, and pseudophakic bullous keratopathy. The diagnosis of amantadine keratopathy was made based on patient history and medication use, age, clinical presentation, and the lack of clinical signs correlating to the other differential diagnoses.

At the time of presentation, the patient was taking a total amantadine dosage of 600 mg/day. She had tried clonazepam and carbidopa/levodopa in the past, but these medications were unsuccessful in adequately controlling her Parkinson's disease symptoms. Amantadine was the only drug that worked to control her severe symptoms. Her worsening vision was coincidental with the initiation of this medication regimen, and the severity of her clinical signs were consistent with amantadine keratopathy.

Through co-management with the patient's neurologist, options were carefully considered to both maintain control of her systemic symptoms and improve the corneal edema and her vision. Options included discontinuing the drug and trying another, which the neurologist stated was not possible due to the severity of the patient's Parkinson's disease and previous failure of alternate medications. Another consideration was to try lowering the daily dose of amantadine to see if her systemic symptoms could continue to be controlled while simultaneously leading to an improvement in corneal edema. While a rigid gas-permeable (RGP) contact lens may have been successful in improving the visual acuity by shaping to the altered cornea, this mechanism would not address the underlying edematous cornea and other ocular symptoms the patient was experiencing. After several different dosage trials, we determined that 300 mg/day (half of the initial dose) was the most successful in controlling the patient's systemic symptoms while also leading to an improvement in corneal edema and visual outcome. At this dosage, we noted the greatest regression of corneal edema at the 3-month follow-up in the right eye and at the 1-month follow-up in the left eye. As seen in Figure 2, central corneal thickness values decreased in the right eye, improving from a baseline of 650uM to 607uM (43uM reduction), and considerably decreased in the left eye, from 1095uM to 715uM (380uM reduction). This resulted in improvement of visual acuity from 20/150 to 20/50 in the right eye and from HM to 20/125 in the left eye. With the adjustment of the patient's amantadine dosage, corneal edema and visual acuity improved, and an unnecessary corneal transplant was avoided.

Figure 2: *Three-month follow-up Pentacam® scan of the right eye and 1-month follow-up Pentacam® scan of the left eye, the respective visits where each eye demonstrated the most significant improvement in corneal edema. Right eye central corneal thickness improved to 607uM and left eye central corneal thickness improved to 715uM.*



After the reduction of corneal edema and the improvement in visual acuity, the patient reported that she was now able to complete her activities of daily living (ADL) while also maintaining control of her systemic Parkinson's disease symptoms. We will continue to reassess the patient every 3 months with serial anterior segment OCT and Pentacam® scans to monitor corneal edema with continued neurology co-management to ensure the amantadine dosage is still controlling the patient's symptoms.

DISCUSSION

Parkinson's disease is a chronic and progressive neurodegenerative disease that causes unintended or uncontrollable movements, resting tremor, bradykinesia, muscular rigidity, and difficulty with balance and coordination. As the disease advances, patients may have difficulty walking and talking. They may also have mental and behavioral changes, sleep problems, depression, memory difficulties, and fatigue.[1] The most common medications used to treat Parkinson's disease are levodopa, dopamine receptor agonists, catechol-o-methyl transferase inhibitors, monoamine oxidase inhibitors, anticholinergics, and amantadine.[2]

Amantadine was originally developed in the 1950s as an anti-viral therapy to treat influenza. In the 1960s, the drug began to be widely used to treat tremors and dyskinesia associated with Parkinson's disease. This drug improves muscular rigidity, muscle control, balance, and coordination and reduces stiffness, allowing for more normal body movements and a reduction of Parkinson's symptoms.[1] The primary action of amantadine as a neurologic drug is through an indirect increase in extracellular dopamine by non-competitive inhibition of NMDA receptors. Since 1995, the rate of amantadine being prescribed to treat Parkinson's disease has increased linearly, with an overall increase of 350%.[2]

Amantadine keratopathy is a rare, dose-dependent, and cumulative disease process in which the drug amantadine damages corneal endothelial cells through unknown mechanisms. For the treatment of Parkinson's disease specifically, amantadine is given orally with a typical dosage between 200 and 400 mg/day.[3] Doses greater than 200 mg/day are associated with higher risks of corneal edema.[4] 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). Additionally, a 4000 mg cumulative dose prescribed within 30 days is shown to lead to a 3-fold increased risk of corneal edema. Patients prescribed amantadine for Parkinson's disease specifically have an increased risk of developing amantadine keratopathy when compared to individuals taking amantadine for other reasons.[5] Due to this patient's severe Parkinson's disease, she had been prescribed 600 mg/day for the past 18 months. This amounted to a cumulative dosage of 18,000 mg per month, putting her at great risk of developing keratopathy.

While the exact mechanism of amantadine keratopathy remains unclear, several studies demonstrate that amantadine has deleterious effects upon the corneal endothelium, even in the absence of clinically evident changes. Damage to the endothelium can ultimately lead to severe corneal edema resulting in decreased visual acuity.[5] Light sensitivity can also be a common symptom in these patients as the cornea becomes more and more irregular. Based on specular microscopy and histopathologic findings, endothelial cell death appears to be induced or accelerated.[6] Corneal edema from amantadine may be due to its off-target effects as well. Amantadine was shown to inhibit potassium channels similar to the effect of the potassium channel blocker clotrimazole in a study with bovine corneal cultures. Cells in these cultures showed an increase in area and cell volume consistent with edema caused by disruptions in gap junctions. Other dopaminergic agonists such as ropinirole induce corneal edema with a similar clinical presentation to amantadine keratopathy. These dopamine D1 receptors have been found on corneal endothelial cells, and their sensitivity has been linked to decreased endothelial transparency. Based on this, corneal edema in amantadine keratopathy may occur secondary to interactions with endothelial cell receptors that lead to disruption of fluid osmolarity and corneal endothelial cell organization.[5]

Incidence and prevalence of amantadine keratopathy in the general population are not known as the majority of studies exclude patients with ocular comorbidities (e.g. glaucoma, prior history of corneal edema) where amantadine keratopathy may have been present. There is an equal preponderance in males and females. In a 2-year study among veterans, corneal edema was shown to be uncommon, with a rate of 0.27%. In the same study, out of 13,137 patients receiving amantadine over 2 years, only 36 of those patients were diagnosed with amantadine keratopathy.[7] There is also an increased incidence of amantadine keratopathy within months of treatment initiation, but cases have been reported as late as 6 years after starting therapy. Additionally, it has been reported that patients experienced bilateral diffuse corneal edema while receiving systemic amantadine therapy at a dose of 100–400

mg/day for a duration ranging from several days to 8 years.[6] Other risk factors for worsening visual prognosis include patient age, as endothelial cell density decreases with age, previous ocular trauma/injury, corneal toxicity from certain long-term topical medications (ex. glaucoma medications), and previous ocular surgery which may predispose a patient to endothelial cell damage.[5]

Other corneal disease entities may present similarly to amantadine keratopathy, so it is important that these are ruled out to determine accurate treatment. Progressive loss of corneal endothelial cells, thickening of Descemet's membrane, and guttata characterize Fuchs' endothelial dystrophy, which is similar to amantadine keratopathy based on pathophysiology and presentation.[5] Differentiating features include the presence of guttata on slit-lamp examination. Guttata was not present in this study's patient. Isolated or coalesced posterior corneal vesicles and a bandlike configuration of Descemet's membrane with scalloped edges characterize PPMD, a condition that is more prevalent in younger patients.[8] Our patient was older and did not present with posterior corneal vesicles or snail-tracking defects in Descemet's membrane. ICE syndrome is found unilaterally in young to middle-aged patients. An abnormal epithelial-like endothelial layer, which proliferates and leads to corneal edema, iris abnormalities, and glaucoma, characterizes this disease. Our patient had bilateral cornea edema and no iris abnormalities. We easily ruled out pseudophakic/aphakic bullous keratopathy due to the patient being phakic. It is important to recognize key differentiating factors associated with other disease entities as well as patient history, age, and medication history to aid in making the correct diagnosis.

The majority of reported cases of amantadine keratopathy have shown complete resolution of corneal edema with discontinuation of the medication.[5] Furthermore, corneal edema resolves and visual acuity improves within 8 days to 2 months after discontinuation.[6] However, there have been a few reported cases of persistent corneal edema despite discontinuation for which a corneal transplant was needed. In these cases, visual acuity returned to normal after the corneal transplants. Other adverse effects of persistent corneal edema include painful ruptured corneal bullae which can be treated with bandage contact lenses and an antibiotic eye drop.[6] A more recent case report showed that a patient with a history of resolved amantadine keratopathy was able to re-start amantadine concurrently with topical steroids with no recurrence of edema or decrease in endothelial cell density.[10] Although topical steroids have not been shown to decrease corneal edema in patients with amantadine keratopathy, they could be useful as a prophylactic measure in susceptible individuals.

The nature of our patient's systemic condition posed great difficulty in treating her ocular conditions. As drug discontinuation was not an option, alternative approaches were considered to improve visual outcome. In cases like these, co-management with neurology is essential to find a method to manage both visual and systemic function. Many different amantadine dosages were prescribed to try to provide symptomatic stabilization, and when indicated, close ophthalmic monitoring was initiated to follow the corneal edema. In this case, we evaluated the progression and regression of corneal edema primarily with Pentacam® anterior segment tomography scans, but the symptoms could also be assessed with anterior segment OCT, pachymetry, or specular microscopy. In our case, the patient's left eye's corneal edema improved much more quickly than the right eye, but in the end, the right eye also saw a reduction in corneal edema. The severity of the corneal edema and the asymmetric nature of the condition can result in differences in resolution time between eyes. All patients respond to treatment differently, so careful monitoring is key, and constant co-management with the patient's neurologist is essential to ensure systemic control continues to be maintained. While the patient's visual acuity was not 20/20 after the reduction in corneal edema, her visual acuity improved enough so that she could adequately perform her ADLs. It is important to recognize that in patients with complex visual and systemic pathology, improvement in quality of life does not necessarily correlate with only achieving 20/20 vision; rather it is relative to overall improvements in the patient's situation and severity of their disease.

CONCLUSION

Amantadine is a drug that is being increasingly used for the treatment of Parkinson's disease. However, amantadine keratopathy is a possible side effect of this regimen and often has significant visual sequelae. While amantadine keratopathy is usually reversible with discontinuation of the drug, some severe presentations of Parkinson's disease, such as in this case, may not allow for drug termination. Careful co-management with neurology is paramount in improving visual outcome while maintaining systemic control of symptoms. It is important to recognize that in patients with complex visual and systemic pathology, even a small improvement can have a significant impact on their ability to perform daily activities and overall quality of life. As amantadine continues to be prescribed for Parkinson's disease, it is important that optometrists and ophthalmologists be familiar with the

visual sequelae that can result from the medication and accurately diagnose the condition to avoid any unnecessary surgical intervention and treat the condition in a prompt and correct manner. ●

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