Amantadine-induced corneal edema: A case and literature review

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ABSTRACT

Purpose: To present a case of irreversible corneal edema after 10 years of amantadine use. A literature review was carried out to describe the clinical characteristics and outcomes of amantadine-induced corneal edema.

Observations: A 36-year-old woman presented with a 6-week history of gradually progressive bilateral painless visual loss with visual acuity (VA) of 20/350 and 20/300 in the right and left eye, respectively. Examination showed bilateral diffuse central corneal edema with multiple Descemet membrane folds without endothelial guttata, keratic precipitates or intraocular inflammation. This did not respond to hypertonic saline drops and empirical treatment for presumed herpetic endotheliitis with oral acyclovir. Medication review revealed the use of amantadine 100mg daily for the past 10 years, prescribed by her neurologist for fatigue. Despite discontinuing amantadine, corneal edema was irreversible due to a markedly reduced endothelial cell count of 625 (right) and 680 cells/mm^2 (left).

Conclusions and Importance: This case highlights the need to consider amantadine as a cause of unexplained bilateral non-guttae corneal edema. A literature review of 33 case reports revealed broadly similar features of amantadine-induced corneal edema; whilst most cases had favorable outcomes with median VA 20/25 (inter-quartile range IQR 20/20–20/30) and complete resolution of corneal edema within 30 days (IQR 14–35) of amantadine discontinuation, most experienced low endothelial cell density 759 cells/mm^2 (IQR 621–1078). Taken together, screening specular microscopy ought to be considered for those in whom amantadine is likely required long-term.

1. Introduction

Amantadine is an N-Methyl-ᴅ-aspartate-type glutamate receptor antagonist, initially formulated for influenza A but has been increasingly repurposed for Parkinson disease, levodopa-induced dyskinesia, and fatigue related to multiple sclerosis.[1,2] Amantadine-induced corneal edema is a rare ocular adverse drug reaction. Previous reports described complete resolution upon stopping amantadine use.[3,4] Herein, we present a young patient with irreversible corneal edema with markedly reduced endothelial cell count after 10 years of amantadine use. Given a rising trend of amantadine prescriptions[5] and the grave implication of failing to recognise this association, our literature review summarises the clinical characteristics and outcomes of amantadine-induced corneal edema.

2. Case report

A 36-year-old Caucasian woman with known multiple sclerosis was referred to our corneal service. She described painless gradual reduction in her vision over six weeks. Best corrected visual acuities (BCVA) were reduced to 20/350 and 20/300 in the right (RE) and left eye (LE) respectively, from her previous baseline of 20/90 (RE) and 20/70 (LE) following previous episodes of optic neuritis.

Slit lamp examination showed bilateral diffuse central corneal edema with multiple Descemet membrane folds without endothelial guttata or keratic precipitates (KP). Intraocular pressure was normal in both eyes. Central corneal thickness (CCT) was 802μm (RE) and 796μm (LE). Both eyes were white with no signs of intraocular inflammation. She was phakic with a clear lens in both eyes. Fundus examination was limited, but did not show overt optic disc swelling. Retinal nerve fibre layer thickness remained stable on optical coherence tomography of the optic discs, compared to that taken a year prior. She denied any history of intraocular surgery, cold sores or herpetic keratitis. Corneal sensation was also intact. Specular microscopy could only image the paracentral corneal zone as the edematous central cornea precluded good image quality; this revealed markedly reduced endothelial cell count (ECC) of

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625 (RE) and 680 cells/mm^2 (LE) but assessment of polymegethism and pleomorphism was not possible.

Although herpetic keratitis was unlikely, she was empirically treated with acyclovir 400mg 5x/day for two weeks and 5% sodium chloride eyedrops but showed no improvement. Upon reviewing her medication, we noted that she has been taking amantadine 100mg daily for the past 10 years, prescribed by her neurologist for fatigue. Her other medications included solifenacin, levetiracetam, baclofen, propranolol, gabapentin, prednisolone 20mg/day, and omeprazole.

Upon discussion with her neurologist, amantadine was discontinued. Nevertheless, corneal edema persisted at 3 months. Clinically, there is worsening with development of painful bullous keratopathy in RE (Fig. 1). A bandage contact lens with prophylactic preservative-free topical antibiotic was required in the right eye to improve comfort. She was then put on the waiting list for the right Descemet membrane endothelial keratoplasty (DMEK). However, unfortunately, she passed away due to Covid-19 before going through the corneal transplantation.

3. Discussion

Amantadine-induced corneal toxicity is a clinical diagnosis made after excluding other causes of corneal decompensation. This young 36-year-old patient did not have any previous intraocular surgery. Hence, pseudophakic bullous keratopathy was unlikely. An eye examination one year preceding presentation did not show any background of corneal dystrophies. In the absence of KP and anterior chamber inflammation, herpetic endotheliitis was unlikely; moreover, she did not respond to empirically treatment with oral acyclovir. Besides, this case shared many similar characteristics with other reported cases of amantadine-associated corneal edema: bilateral asymmetrical central corneal edema, reduced endothelial cell count, and the absence of endothelial guttata and signs of intraocular inflammation.[3,4,6–28]

Our literature review using search terms 'amantadine' and 'corneal edema' on PUBMED and Google Scholar generated 32 other cases (64 eyes) (Table 1).[3,4,6–28] Of all cases, 70% were females and the median age was 52 years (interquartile range IQR 39–64; range 8–80). Indications for amantadine use were Parkinson disease (n = 12), other movement-related disorders (n = 10), multiple sclerosis (n = 5), psychiatric illness (n = 4), influenza (n = 1), and neurostimulation (n = 1). The majority experienced gradually progressive blurry vision with bilateral asymmetric corneal edema and Descemet membrane folds with the median presenting BCVA and CCT being 20/200 (IQR 20/125–20/400) and 886 μm (IQR 810–937), respectively in the worse eye. In 22 of 32 (69%) cases, corneal edema primarily affected the central cornea.[3,4,7,8,10,11,13,17–19,21,23–29] Bullous/microcystic changes were reported in several cases.[11,18,21,22,24,25,27,29] Punctate keratopathy,[16] corneal infiltrates,[11] corneal deposits,[17] and guttate-like appearance[7] were each implicated in only one case – thus atypical of this condition. Intraocular inflammation, raised intraocular pressure and corneal neovascularisation were not a feature. Specular microscopy typically revealed polymegethism, pleomorphism and reduced endothelial cell density. The median ECC was 759 cells/mm^2 (IQR 621–1078) in the worse eye,[4,6,7,10–12,16,17,19,20,24–29] albeit baseline ECC prior to amantadine initiation was unknown.

The median daily amantadine dose was 200 mg (IQR 200–300), with the median treatment duration being 12 months (IQR 4.5–24). In most cases, corneal edema completely resolved within 30 days (IQR 14–35) of amantadine discontinuation; The median BCVA achieved was 20/25 (IQR 20/20–20/30). No significant correlation was found between duration of amantadine use and recovery time (spearman rank correlation coefficient r = 0.16, p = 0.43). Our case is unique, presenting the longest lag time reported (10 years) between amantadine initiation and onset of edema, indicating the potential cumulative toxic effect of amantadine on endothelial cells.

The corneal graft was required in 5 cases (10 eyes), who used amantadine for 12, 17, 27 and 120 months (our case); all are women, with median age 42 years (IQR 39–45). The duration of amantadine treatment varied considerably, but all had used amantadine for at least 12 months (range 12–120 months). Of note, the continual use of amantadine was thought to cause non-immunologic failure in four eyes (2 penetrating keratoplasties, PK,[27] and 2 Descemet stripping automated endothelial keratoplasty, DSAEK[20]); of these, three were reversible upon amantadine discontinuation, and one required a repeat transplant. This underlines the importance of recognising amantadine use in patients with corneal edema.

The link between amantadine and corneal edema has also been reported by two large database studies. Although individual patient notes were not examined, a two-year postmarketing surveillance study utilising the national Veterans Health Administration pharmacy and clinical database found increased risks of corneal edema amongst amantadine users (relative risk RR of 1.7 [95% confidence interval CI 1.1–2.8]).[30] Although only 36 of 13,137 (0.27%) patients developed corneal edema within the two-year study period, 12 events occurred within 1 month of starting amantadine. Another population-based Taiwanese study also echoed the increased risk of corneal edema in Parkinson disease (PD) patients with amantadine use (RR of 1.79 [95% CI 1.25–2.55], p = 0.0013).[31] In particular, those receiving higher daily dose (>100mg/day) had a higher risk than those with lower daily dose (≤100mg/day) (adjusted RR 2.71 and 1.69, respectively), demonstrating a dose-response relationship.

The mechanism of amantadine-related corneal edema is unclear but may represent an idiosyncratic reaction and/or dose-dependent endothelial cell toxicity. Since idiosyncratic reaction typically manifests within a month of drug initiation, the former is less likely since only 3 (9.7%) patients within our literature review experienced corneal edema within 1 month of amantadine use. The latter is supported by two cohort studies. A cross-sectional study of 169 PD patients on amantadine found lower endothelial cell density ((mean ± standard error; 2662.47 ± 29.06 vs. 2784.72 ± 25.89, P = 0.002), lower hexagonality and greater coefficient of variation compared to age- and gender-matched healthy controls.[32] In the age- and gender-adjusted multiple regression analysis, a longer treatment duration led to lower endothelial cell density (R^2 = 0.054, P = 0.011). Another prospective longitudinal study found that PD patients on amantadine had an accelerated decrease in endothelial cell density (1.51% vs. 0.94% vs. 0.55%) (P = 0.04), a decrease of percentage hexagonality of the cells ECH (4.98% vs. 3.56% vs. 2.31%) (P = 0.01), and increase of the coefficient of variation CoV (6.12% vs. 4.80% vs. 3.30%) (P = 0.03) compared with amantadine naive patients with PD and controls, respectively.[33]

4. Conclusion

In summary, we highlight the importance of recognising amantadine as a cause of corneal edema. Whilst most amantadine-associated corneal edema resolved upon amantadine discontinuation, some experienced permanent reduction in endothelial cell count as sequelae and will therefore be vulnerable to future corneal decompensation. Although the
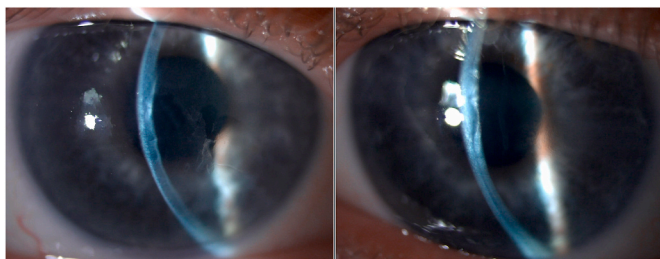

Fig. 1. Amantadine-induced *corneal edema primarily affects central cornea and spares the periphery. Microcystic epithelial changes, stromal edema, subepithelial bullae and Descemet membrane folds were noted.*

Table 1

Summary characteristics of 33 cases of amantadine-induced corneal edema. CCT: Central corneal thickness; ND: Not documented; BCVA: Best corrected visual acuity; M: Male; F: Female; RE: Right eye; LE: Left eye; BE: Both eyes. *recovery time indicates the duration between amantadine discontinuation and complete resolution of corneal edema.

First author, year	Age, sex	Indication	Dose (mg/day)	Duration (month)	Presenting CCT	Presenting BCVA	BCVA at recovery	Recovery time*	Endothelial cell count (cells/mm²)
Chao,2022[3]	8 M	Tardive dyskinesia	100	10	ND	RE 20/200 LE 20/500	RE 20/30 LE 20/25	2 weeks	ND
Pond, 2009[4]	12F	Attention deficit hyperactive disorder	200	4	RE 851 LE 886	BE 20/200	RE 20/20 LE 20/25	10 days	RE 1242 LE 1412
Beran, 2018[16]	14 M	Neuro-stimulant post- tumour resection	200	7	RE 917 LE 937	RE 20/200 LE 20/400	RE 20/50 LE 20/60	7 weeks	RE 1395 LE 1054
Hughes,2004[22]	14 M	Tremor	300	ND	RE 973 LE 950	RE 20/400 LE 20/160	BE 20/25	10 days	ND
Santiago-Cabán, 2012[23]	16F	Extra-pyramidal drug side effects	300	6	ND	BE 20/400	RE 20/40 LE 20/30	1 month	ND
Esquenazi, 2009[24]	39F	Multiple sclerosis (MS) & tremor	200	8	RE 940 LE 802	BE 20/400	RE 20/40 LE 20/30	2 months	RE 1504 LE 1596
Chang, 2008[25]	52F	Parkinson disease (PD)	250	78	ND	BE HM	RE 20/30 LE 20/60	2 weeks	RE 569 LE 453
Lin, 2014[26]	53F	PD	ND	1.5	RE 739 LE 697	BE 20/200	BE 20/30	6 weeks	ND
Lin, 2014[26]	72F	PD	ND	18	ND	RE 20/500 LE 20/320	RE 20/40 LE 20/30	4 weeks	RE 1149 LE 1256
Lin, 2014[26]	66 M	PD	200	12	RE 834 LE 851	RE 20/100 LE 20/50	RE 20/40 LE 20/25	1 month	RE 1730 LE 1704
Jeng, 2008[27]	57 M	MS	200	2	RE 838 LE 1000	RE 20/70 LE 20/100	RE 20/25 LE 20/30	14 days	ND
Jeng, 2008[27]	44F	Bipolar affective disorder	200	3	ND	BE 20/400	RE 20/50 LE 20/40	1 month	ND
Yang, 2015[28]	46 M	Treatment-resistant depression	200	36	RE 803 LE 911	BE 20/60	BE 20/20	54 days	RE 702 LE 707
Hoteham, 2011[6]	77F	Tremor	150	0.5	BE > 1000	RE 20/1000 LE CF	RE 20/25 LE 20/32	14 days	RE 901 LE 1134
Hessen, 2018[7]	44F	Ataxic cerebral palsy	400	36	RE 927 LE 641	RE 20/125 LE 20/60	BE 20/30	5 weeks	RE 609 LE 1387
Pond, 2009[4]	55F	PD	200	84	RE 930 LE 934	RE 20/100 LE 5/200	RE 20/25 LE 20/200 (amblyopia)	'within days'	ND
Kubo, 2008[8]	61 M	PD	300	8	ND	RE 20/100 LE 20/200	RE 20/20 LE 20/16	8 days	ND
Blanchard, 1990[9]	64F	Influenza	ND	19 days	ND	BE 20/20 'misty vision'	NA	10 days	ND
Kim, 2013[10]	63F	Freezing of gait	400	7	RE 661 LE 651	RE 20/125 LE 20/100	RE 20/25 LE 20/20	1 month	RE 608 LE621
Avendano-Cantos, 2012[11]	64F	PD	300	24	ND	BE CF	RE 20/60 LE 20/100	40 days	RE 798 LE 853
Park, 2011[12]	43 M	Resting tremor	200	4	RE 954 LE 828	BE CF	BE 20/20	2 weeks	RE 729 LE 730
Deogaonkar, 2011[13]	61F	PD	ND	72	RE 810 LE 780	BE 20/200	BE 20/20	1 month	ND
Ghaffariyeh, 2010[14]	68F	PD	200	24	RE 871 LE 746	RE 20/200 LE 20/100	RE 20/40 LE 20/30	3 weeks	ND
Dubow, 200,8[15]	74F	PD	200	24	ND	RE 20/200 LE 20/40	ND	1 month	ND
Cennamo, 2022[17]	78 M	PD	200	24	ND	RE 20/60 LE 20/100	BE 20/25	1 month	RE 691 LE 700
Soin, 2017[18]	50F	Essential tremor	200 mg/day for 12 months, then 300 mg/day for 7months		RE 798 LE 827	RE 20/70 LE 20/50	BE 20/20	3 months	ND
Lin, 2014[26]	80F	Unspecified psychiatric illness	200	0.75	RE 650 LE 731	RE 20/80 LE 20/400	BE 20/32	4 weeks	RE 1828 LE 1927
Hwang, 2009[19]	35 M	Parkinsonism	400	37	ND	RE 20/100 LE 20/50	RE 20/40 LE 20/30	1 month	RE 876 LE788
Cases requiring corneal graft									
Jeng, 2008[27]	55F	MS	200	72	RE 688 LE 677	BE 20/200	RE 20/40-2 LE 20/40 + 2	Graft done prior to amantadine discontinuation	Atrophy of endothelial cell layer with large areas of absent endothelium on histopathologic evaluation of host corneal button

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Table 1 (*continued*)

First author, year	Age, sex	Indication	Dose (mg/day)	Duration (month)	Presenting CCT	Presenting BCVA	BCVA at recovery	Recovery time*	Endothelial cell count (cells/mm^2)
Koenig, 2009[20]	39F	Schizophrenia & tardive dyskesia	200	12	ND	BE 20/400	RE CF LE 20/70	Graft done prior to amantadine discontinuation	Severe endothelial cell loss on histopathologic evaluation
Welder[29]	42F	Huntington disease	300	ND	RE 890 LE 900	RE 20/125 LE 20/80	RE 20/70 LE 20/60	Irreversible	No endothelial cells on specular microscopy and histology
Hood, 2010[21]	45F	MS	ND	17	RE 867 LE 700	RE 10/400 LE 20/400	RE 20/25 LE 20/40	irreversible	Paucity of endothelial cells on histopathologic exam of Descemet membrane
Current case	36F	MS	100	120	RE 802 LE 796	RE 20/350 LE 20/300	NA	Irreversible	RE 625 LE 680

idiosyncratic reaction is still a possible mechanism of this condition, the majority of patients (90.3%) within our literature review experienced corneal edema at least one month after using amantadine. Given the likely cumulative toxic effect of amantadine on endothelial cell count, baseline and regular eye examinations in asymptomatic amantadine users with specular microscopy ought to be considered, especially for young patients or those requiring amantadine long-term or at higher doses. Baseline examination may identify patients with Fuch's endothelial dystrophy (FED) in whom amantadine should be used with caution. As the median treatment duration preceding the onset of amantadine-induced corneal edema was 12 months within our literature review, we recommend a review at one year after starting amantadine. Subsequent monitoring frequency should be tailored case-by-case, considering changes in specular microscopy parameters at one year and other factors that may theoretically increase the risk of corneal decompensation (such as low baseline ECC, presence of FED, high daily amantadine dose, and poor kidney function since amantadine is renally cleared). Further studies are required to assess the viability and cost-effectiveness of such a screening programme and to determine the optimal screening intervals.

Patient consent

Written consent to publish the case report was 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

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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