Short communication

Corneal toxicity due to amantadine


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ABSTRACT

Case report: A 64-year-old female with Parkinson disease treated with amantadine for two years who suddenly suffered bilateral corneal oedema. It was initially treated as herpetic endotheliitis without improvement as we lacked information on her chronic treatment. The corneal oedema finally resolved after withdrawing the drug.

Discussion: Amantadine hydrochloride may produce endothelial dysfunction. Once the amantadine treatment is stopped, the corneal oedema may be reversible but endothelial density remains low. An ophthalmologist examination should be performed before the initiation of amantadine treatment in order to establish a risk: benefit ratio, especially in those patients with low endothelial density or any endothelial anomaly.

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Toxicidad corneal por amantadina

RESUMEN

Caso clínico: Mujer de 64 años en tratamiento con amantadina durante dos años por enfermedad de Parkinson, que presentó edema corneal bilateral de inicio brusco. Inicialmente se trató como una endotelitis herpética sin mejora, al desconocer la medicación empleada por la enferma. Finalmente el edema se resolvió tras la suspensión del fármaco.

Discusión: El hidrocloruro de amantadina puede producir disfunción endotelial. El edema corneal puede ser reversible tras su suspensión, pero la densidad endotelial permanece baja. Sería necesario realizar un control oftalmológico previo a iniciar el tratamiento para valorar el riesgo/beneficio del mismo, sobre todo en aquellos pacientes que presenten baja densidad endotelial o un endotelio alterado.

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Introduction

Amantadine hydrochloride is an antiviral for treating Parkinson’s disease. Some cases of corneal alterations secondary to its use have been published.

The case of a female, 64, in treatment with amantadine during 2 years due to Parkinson’s disease and who exhibited sudden bilateral corneal edema is presented.

Case report

Female, 64, who visited the emergency section due to pain and diminished visual acuity (VA) in her left eye (LE) starting 24 h ago. Referred ophthalmological history included cataract surgery in LE 6 months ago and Parkinson’s disease with pharmacological treatment of which she was unable to recall the details. The patient exhibited a corrected VA of finger counting at 2 m in the right eye (RE) and finger counting at 1 m in the LE. The slit lamp revealed bilateral corneal edema, epithelial with microbullae and stroma with Descemet folds. In the RE she exhibited McEwen nuclear cataracts. In the LE she exhibited several small, whitish and rounded subepithelial infiltrates with positive fluorescein stain (Fig. 1). Intraocular pressure and ocular fundus were normal.

Initially, the diagnostic assessment was bilateral bullous keratopathy with apparently infectious infiltrates in LE. Treatment was established with vancomycin (50 mg/ml) and ceftazidim (50 mg/ml) reinforced eyedrops every 2 h in the LE and hypertonic sodium chloride (Antiedema®) every 6 h in both eyes (BE).

After 48 h of treatment no significance clinical or visual changes were observed. A detailed anamnesis revealed the use of amantadine as antiparkinson treatment (Amantadine Level®, 100 mg every 8 h starting 2 years ago as well as repetitive lip herpes history. A diagnostic of suspected herpetic endothelitis or medication toxicity secondary to amantadine was established. A sample of aqueous humor was taken for analyzing with herpes virus polymerase chain reaction (PCR), adding oral aciclovir 400 mg every 3 h, prednisolone eyedrops every 8 h BE and tobramycin every 6 h in LE. The neurology service was consulted in order to withdraw amantadine, which was suspended 24 h later.

Four days later, the patient corrected VA was of 0.1 in RE and 0.16 in LE, with slight improvement of the bilateral corneal edema and disappearance of infiltrates in LE, although the central epithelial bullae persisted (Fig. 2). The PCR study was negative and therefore the oral aciclovir and also the reinforced eyedrops were suspended.

Ten days later, the VA was of 0.2 in RE and of 0.16 in LE. The edema had improved significantly, with persistence of the Descemet folds and a central macrobulla in LE. Pachymetry was of 677 μm in RE and 756 μm in LE. The treatment was reduced to prednisolone eyedrops every 24 h and Antiedema® every 8 h in BE.

Forty days later, corrected VA in RE was of 0.3 (stenoepic 0.6) and of 0.2 in LE, with complete resolution of the corneal edema and presence of a paracentral leukemia in LE (Fig. 3). Pachymetry was of 491 and 507 μm, respectively. Endothelial microscopy revealed an endothelial density of 798 cells/mm² in RE and 853 cells/mm² in LE, without the presence of guttae.

Discussion

Amantadine hydrochloride is an antiviral for the prophylaxis and treatment of high airway infections produced by
the influenza A virus, in attention deficit disorder with hyperactivity and the treatment of Parkinson’s disease as well as other dyskinetic alterations. It has also been used for treating fatigue associated to multiple sclerosis.1,2 Several cases of corneal toxicity due to amantadine have been described in the literature, both at an early stage and after several years,3 in adult as well as pediatric patients.4 The lesions this medication can cause include keratitis punctata, subepithelial opacification and epithelial or stromal edema. The mechanism by which these alterations occur is not known.3,4 It has been suggested that, as the drug is secreted in tears, it can cause superficial corneal deposits associated to epithelial edema and keratitis punctata.5 In addition, its
presence in the aqueous humor could be toxic for endothelial cells with the ensuing stromal edema. In the majority of cases, these alterations are reversible in days or weeks after suspending its use and reappear if intake is resumed. However, in some cases corneal edema is irreversible. A recent study suggests that endothelial toxicity due to amantadine could be caused not only by individual hypersensitivity but also by a dosage-dependent effect, so that a longer treatment time (higher aggregate dose) would cause more corneal damage. This damage would translate into diminished endothelial density, higher pleomorphism and higher polymegathism.

In the present case no previous endothelial count was available although the count made 40 days after withdrawing the drug was markedly low, which leads us to think that the previous endothelial count must have been quite higher.

In what concerns the differential diagnostic, initially pseudophakic bullous keratopathy was suspected although the patient had been intervened only in the LE. Due to the partially incomplete anamnesis which did not allow us to determine the systemic treatment, we also considered the possibility of herpetic endotheliitis (a rare entity but which can be bilateral). Finally, the edema was resolved after suspending amantadine. This example evidences the importance of obtaining thorough clinical records.

Despite the reversible nature of the edema and of the rest of corneal alterations, endothelial density remained low. For this reason, it is considered important that neurologists and ophthalmologists should take into account the importance of the possible adverse effects of this drug and of indicating a competent ophthalmological assessment before beginning this treatment in order to assess its risk/benefit ratio, above all in patients exhibiting low endothelial density or endothelial alterations.

Conflict of interests

No conflict of interests has been declared by the authors.

References