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Corneal Densitometry as a Novel Technique for Monitoring Amiodarone Therapy

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Purpose: The clinical efficacy and toxicity of amiodarone may be determined more effectively by tissue deposition than by levels of the agent in serum. Therefore, corneal densitometry might be useful for therapeutic monitoring. The aim of the study is to evaluate Scheimpflug corneal densitometry in patients with amiodarone keratopathy (AK).

Design: Comparative case series.

Participants: Sixty-six patients receiving amiodarone therapy and 66 healthy controls were consecutively enrolled in this study.

Methods: Patients were examined using the Oculus Pentacam (Wetzlar, Germany).

Main Outcome Measures: Densitometry data from different corneal layers and different annuli were extracted, analyzed, and compared with densitometry values of healthy controls. Duration of treatment, cumulative dose, Orlando stage (slit-lamp biomicroscopy), and serum concentrations of amiodarone and N-desethylamiodarone also were determined, and the correlation to different densitometry data was evaluated.

Results: The total corneal light backscatter at total corneal thickness and at total diameter was significantly higher in the amiodarone group compared with the control group (AK group: 28.3±5.2; control group: 24.4±4.2; $P < 0.001$). Upon dividing the corneal surface into different layers at total thickness, the differences were significant in all layers ($P < 0.001$). The serum concentrations of the metabolite N-desethylamiodarone correlate with densitometry values, especially in the 0- to 2-mm annulus in the anterior layer ($r = 0.419$; $P = 0.001$), whereas the cumulative dose and duration of treatment correlate significantly with the densitometry values in the 0- to 2-mm annulus at total thickness ($P = 0.014$ and $P = 0.022$, respectively).

Conclusions: Corneal densitometry is a useful, objective method for quantifying AK and can help in monitoring amiodarone therapy. The serum concentration of the active metabolite N-desethylamiodarone correlates with the extent of keratopathy in the anterior layer, whereas chronic changes in the stroma correlate with the cumulative dose and duration of treatment. *Ophthalmology 2016;■:1–6 © 2016 by the American Academy of Ophthalmology*

Amiodarone is the most effective antiarrhythmic drug, especially for maintaining sinus rhythm in patients with atrial fibrillation.[1,2] Therefore, it is still frequently prescribed as a class III antiarrhythmic agent,[3] although several known side effects affect numerous organs, especially the thyroid, lung, skin, nervous system, and eyes.[4] Because of its long half-life and its large volume of distribution in adipose tissue, serum concentrations of amiodarone are of limited clinical use. However, tissue concentrations might be better monitored by measuring the extent of bilateral corneal micro-deposits, which are the most common ocular finding in patients treated with amiodarone. However, lens opacities, retinopathy, and optic neuropathy also have been reported in association with amiodarone treatment. Amiodarone keratopathy (AK) was described soon after introduction of the drug in the 1960s.[5–7]

The prevalence of AK varies between 70% and 100%. Also, AK does not cause impairment of visual acuity and usually disappears after discontinuation of amiodarone medication.[5,7,8] Amiodarone keratopathy is classified in 3 stages, and this grading system usually is used to describe the degree of deposition.[6,9] Ocular symptoms are not common, and patients usually have mild symptoms, such as seeing blue-green rings or haloes around light, or of dryness of the eyes or glare.[5]

The evaluation of corneal densitometry in patients with different corneal pathologies has recently attracted increasing interest. It has been described in keratoconus and in patients with infectious keratitis and corneal dystrophies. It has also been described after corneal surgery and after endothelial keratoplasty and has been used to evaluate the long-term effect of cross-linking in patients with keratoconus.[10–17]

The aims of the study were to evaluate the effect of AK on the corneal backscattered light using the Pentacam (Oculus, Wetzlar, Germany) densitometry module and to explore the correlation of cumulative dose and duration of treatment with plasma concentrations of amiodarone and with corneal densitometry.

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Methods

Study Population

Sixty-six patients receiving amiodarone therapy at the University of Müenster Medical Center were consecutively enrolled for this study. The study was approved by the Ethics Committee of the University of Müenster, Müenster, North Rhine Westphalia, Germany. Before any examinations were performed, the study protocol was explained in detail to the patients, and all patients signed informed consent forms before any examination or Pentacam imaging. The study followed the tenets of the Declaration of Helsinki and was registered at the German Clinical Trials Register (DRKS) (no. DRKS00008890).

Inclusion criteria were as follows:

1. Systemic amiodarone treatment for recurrent ventricular tachycardia or atrial fibrillation at the time of examination
2. Therapeutic saturation achieved (amiodarone therapy for a minimum of 3 months)
3. Absence of lysosomal storage diseases
4. Absence of any history of corneal disease, corneal trauma, or eye surgery (except cataract surgery >6 months before examination)

An age-matched control group of 66 eyes of 66 patients was included. Inclusion criteria for the control group were as follows:

1. Absence of amiodarone therapy in the medical history
2. Absence of cornea verticillata on slit-lamp examination
3. Absence of lysosomal storage diseases
4. Absence of any history of corneal disease, corneal trauma, or eye surgery (except cataract surgery >6 months before the examination)

Exclusion criteria for both groups were eye medication (except for artificial tears), wearing of contact lenses, or corneal scarring on slit-lamp examination.

Outcome Measures

During the same admission, complete medical and ocular histories were taken, amiodarone and N-desethylamiodarone concentrations were measured in plasma, and patients underwent ophthalmic examination, including best-corrected visual acuity testing, slit-lamp biomicroscopy, stereoscopic fundus biomicroscopy, and Pentacam imaging.

The stage of AK was classified according to the staging system proposed by Orlando et al[9]: stage 1: horizontal linear pattern in the inferior cornea; stage 2: arborization of the lines in a pattern resembling a cat's whiskers; and stage 3: whorl-like pattern in which the lines can reach the visual axis.

Corneal Densitometry

In this prospective study, all patients underwent Pentacam imaging with a new Pentacam software module for analysis of corneal densitometry. The clinical validity of corneal densitometry for the quantification of corneal opacification has been described in different studies.[10–17] It measures corneal backscattered light over a 12-mm-diameter area and full corneal thickness. Corneal densitometry can be measured in 4 annular zones of the cornea (Fig 1). The zones are centered on the apex of the cornea; the first zone is 2 mm in diameter, the second zone is 2 to 6 mm, the third zone is 6 to 10 mm, and the fourth zone is 10 to 12 mm.[10,11] The densitometry measurement can be provided for the anterior part (first 120 μm), central part (from the first 120 μm to the posterior 60 μm), and posterior part (60 μm) of the cornea (Fig 1). Densitometry is expressed in grayscale units, ranging from a minimum light scatter of 0 (maximum transparency) to a maximum light scatter of 100 (minimum transparency).[10,11] In patients with AK and those in the control group, densitometry values were measured and analyzed in different corneal layers and in different annuli. All patients were examined under the same conditions, the automatic release mode of the Pentacam was used to minimize examiner-induced errors, and only Pentacam images of good quality were included (labeled "OK" by the Pentacam in the "Examination Quality Specification"). Only 1 eye per subject was selected randomly for statistical analysis.

Statistical Analysis

Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) was used for data management. Statistical analyses were performed with IBM SPSS Statistics 22 for Windows (IBM Corporation, Somers, NY). The normality of the data distribution was tested using the Kolmogorov–Smirnov test, and the data did not fit a normal distribution. Therefore, the 2 groups were compared using the Mann–Whitney U test, and correlation was analyzed using Spearman's correlation coefficient. All data are reported as mean ± standard deviation. The level of statistical significance was set at $P \leq 0.05$. Inferential statistics are intended to be exploratory, not confirmatory, and were interpreted accordingly.

Results

In this prospective study, 66 patients (8 female and 58 male) were enrolled between June 2015 and February 2016 in our department. Mean patient age was 65.7±11.6 years (range, 26–86 years). An age-matched control group of 66 subjects (8 female and 58 male; mean age, 64.7±9.6; range, 37–83 years) also were included.

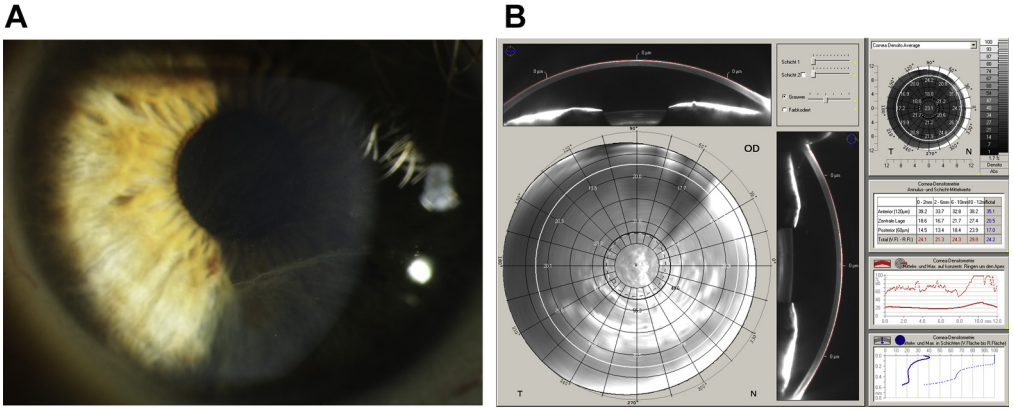

Figure 1. Amiodarone keratopathy. **A**, Slit lamp view. **B**, Corneal densitometry display in the Pentacam (Oculus, Wetzlar, Germany).