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Corneal Changes due to the Treatment with Amiodarone and their Connection with the Plasma Concentration of the Medication when Analysed with HPLC

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ABSTRACT

The article reviews a study of 123 patients on continuous Amiodarone therapy, selected among 911 other people. The relation between the corneal damages due to the contamination with Amiodarone and plasma concentration of the medication in the blood of a dosage from 200 to 400 mg per day has been studied. It has been found that when the dosage regimen is systematically maintained, changes are observed in all the patients. In 5,7% of the cases the changes are of greater clinical importance and can be divided into 3 categories according to their significance. The ophthalmic examination is made by biomicroscopy which allows digital recording whereas the plasma levels of Amiodarone are determined by an adapted HPLC method. The observations have been conducted during a ten-year period from 2006 to 2016.

Keywords: Amiodarone, cornea vericillata, biomicroscopical examination, HPLC-UV

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INTRODUCTION

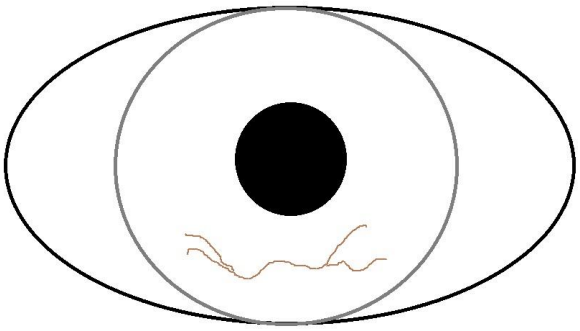
Amiodarone is a broad spectrum class III antiarrhythmic medication. It has multiple and complex effects on the electrical activity of the heart which is responsible for the heart's rhythm. It may be injected or taken orally in formulations of 100, 200 and 400mg tablets. Its named according to IUPAC is (2- {4-[(2- butyl-1-benzofuran-3- yl)carbonyl]-2,6- diiodophenoxy} ethyl)diethylamine and its CAS number is 1951-25- 3 [1]. The substance is known under 12 different names [2], the most popular trade names are Cordarone, Nextrone, Pacerone. Its bioavailability varies over wide ranges. Its absorption is between 22 and 95% and it increases in relation to the quantity and type of food taken [3]. Amiodarone is a lipophilic emulsion and is easily absorbed by the adipose tissue, liver, muscles and skin. In this way the volume of distribution reaches 71.4 l/kg. The therapeutic ranges are between 1,5 to 2.5 mcg/ml. High-performance liquid chromatography (HPLC) can detect the levels of Cordarone in the patients' blood. In 1981 Cervelli et. al [5] started a broad research on that topic.

Amiodarone has many side effects and several of them that are quite serious – pulmonary fibrosis, heart failure, liver failure, hypothyroidism or hyperthyroidism, blue skin discoloration [6, 7, 8]. Other common side effects include eye deposits and visual changes [9, 10, 11]. Widely known studies on the side effects deal with small number of highly-dosed patients and monitored plasma concentration, most often 20-30 people treated with 600-800 mg/day. New observations made of a groups of about 100 patients treated with low and continuous doses, but without a specific value of the plasma concentration of Amiodarone [12, 13]. Meanwhile a fast and simplified HPLC method has been adapted which allows keeping track of more people on Amiodarone therapy treated with the low-dose regimen of 100- 200 mg/per and also allows a comparison with the ophthalmic examination [14].

MATERIALS AND METHODS

For the purpose and in the course of this work a Top Cone-branded machine was used, Model SL-D7, 30W halogen slit lamp with Galilean optical system magnifications of 6X, 10X, 16X, 25X and 40X. Thanks to the additional plug DC-3, the video recorders 1/1.8 type CCD and its effective resolution about 8 megapixels, the slit lamp allows capturing flawless images of the cornea, endothelium and helps to accurately record the results. The converging eyepieces with 12.5 X magnification make it possible to obtain a stereoscopic image.

It has been found that a change in the underlying epithelial layers of the cornea occurs in all patients on long-term Amiodarone therapy. In some of the cases the changes are more significant; they can be divided into three groups - mild stage 1, moderate stage 2 and severe stage 3 (Fig. 1). The first stage is characterized by the coalescence of fine grayish or golden-brown punctuate opacities into a horizontal linear pattern in the inferior cornea. The second stage shows additional arborizing and horizontal lines in a pattern resembling a cat's whiskers. The third stage is characterized by a verticillate whorl-like pattern, and the arborizing lines can extend into the visual axis. Graphically they look like these:



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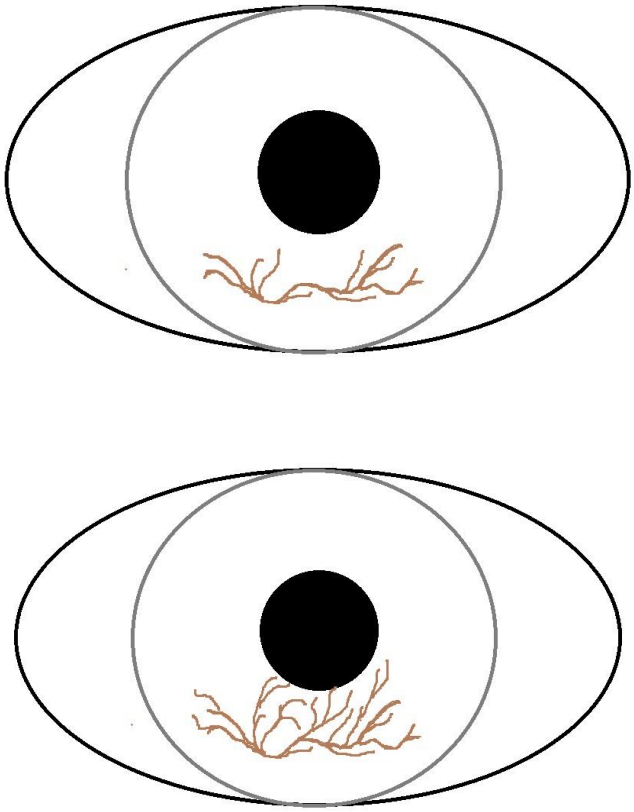

Fig.1 Stages of amiodarone keratopathy

All solvents and reagents were of analytical grade of quality. The blood samples are treated with centrifuge by 4000 rpm for 5 min, from the upper layer 0.7 ml are mixed with 0.7 ml ethylacetate, used as deproteinizer and extragent. After mixing with Vortrex for 20 s. both phases charged in Eppendorf 1.5 ml vessel which was fitted in a micro centrifuge by 9000 rpm for 5 min. Then the extract from the upper layer was transferred into a next 1.5 ml vessel and evaporized with dry air stream to dryness. The pH working range was determined from the pH = 7.36 − 7.34 level of the blood. There was no need to adjust the pH level of the sample and the mobile phase by a buffer. The dry sample from the 1.5 ml vessel was transferred to the autosampler vials in inserts from 50 µl with 20 µl methanol from HPLC degree.

The rapid and simple HPLC method with UV detection is used for the quantitative determination of Amiodarone in blood samples. A Thermo Finnigan Surveyor liquid chromatography with multidiode detector and Thermo Fisher Hypersil Gold C18 (150 mm × 4.6 mm; 5 µm) chromatographic column are used. The UV detection wavelength was 215 nm and the retention time for Cordarone was 5.408 min. The column temperature was 55 ◦C and the mobile phase consisting of methanol – water (80:20 v/v), was pumped at flow rate of 0.4 ml/min. The standard substance with purity grade 98.5% (according to the USP 2014) was used for preparing of calibration standards.

Experimental:

911 people have been studied for 10 years (from June2006- to June.2016). 123 who are on long-term Amiodarone therapy with doses of 200-400 mg/day. Based on that data the correlation between the plasma level of medication and the ophthalmic discovery was studied. Figure 1 shows the progression of the defined plasma concentration that occurs with time observed on 123 patients. Those with pronounced corneal deposits from 1st to 3rd degree are also indicated.

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Figure 2 shows a typical chromatogram of Amiodarone in blood serum.

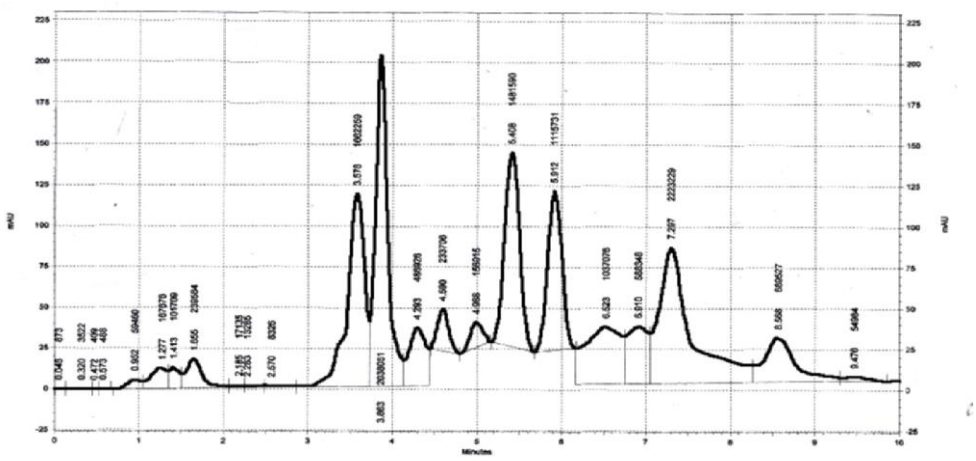

Fig.2 Chromatogram of amiodarone

Figure 3 shows the distribution of time starting from the beginning of the study, concentration of blood sample and indicated degree of ocular manifestation.

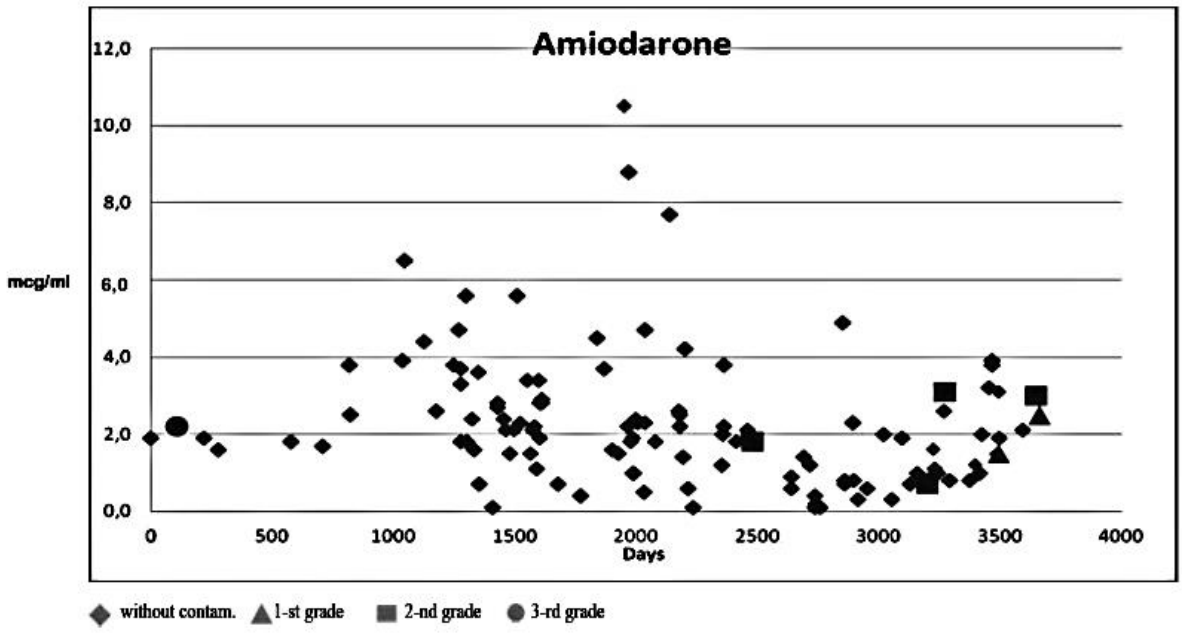

Fig.3 Distribution of keratopathy among patients according to time

RESULTS AND DISCUSSION:

Taking into account not the prescribed oral dosage but the real plasma concentration of Amiodarone, identified explicitly by the HPLC method, it can be concluded that significant corneal deposits from 1st to 3rd degree occur in 5.7% of the patients (7 people) whereas the percentage is 2-3 % when only the oral dosage is taken into consideration (Figure 3).

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CONCLUSIONS

The results of the study indicate that the consistent monitoring of the anterior eye segment and cornea is justified for cases of 6-9 months of Amiodarone therapy, which is much more accessible and requires less resources compared to the HPLC analysis.

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