ORIGINAL RESEARCH

Toxic Effects of Hydroxychloroquine on The Retina: The Incidence in An Ophthalmology Hospital

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ABSTRACT
Hydroxychloroquine is extensively used by rheumatologists in the management of many medical conditions, including systemic lupus erythematosus and rheumatoid arthritis, owing to its favorable safety profile and cost-effectiveness. Nevertheless, it has the potential to induce retinal defects. Currently, there is a lack of an established Indian methodology for the screening of retinal abnormalities in individuals of this nature. In this study, we conducted a comprehensive analysis of the medical records and optical coherence tomography (OCT) data of all individuals who sought treatment at the Hychloroquine Ambulatory of the VSSIMSAR, Burlaover a one-year period.

Keywords: Retina/drug effects, Hydroxychloroquine/toxicity; Rheumatic drug therapy

INTRODUCTION

Chloroquine was primarily used as an anti-malarial agent. However, chloroquine and hydroxychloroquine have also been indicated for various other diseases for a long time now. Hydroxychloroquine is indicated for rheumatoid arthritis, lupus erythematosus, cutaneous lupus, and other disorders related to connective tissue. Hydroxychloroquine is widely used owing to its better safety profile compared to chloroquine. The mechanism of action of both drugs is not certain, but they act on the lysosomes and certain other parts of the immune system. [11]

Recently, hydroxychloroquine has proven to be useful as an auxiliary treatment for diabetes, and cancer adjuvant. Its prescription rate has increased by 30%. [4,5]

Hydroxychloroquine is associated with collateral damage to the retina. This happens due to macular alteration, which can lead to vision loss in mild to severe cases. The clinical symptoms of it include lesions like the bull's eye and central scotomata. Patients usually complain about reading difficulties and loss of vision. The risk of renal toxicity is much lower in hydroxychloroquine compared to chloroquine, yet it is significant. The risk factors are also subjective and depend on the following factors: a) obesity b) preexisting retinal disease; c) liver or kidney impairment; d) dose greater than 6.5 mg/kg; and e) chronic use of the drug. [12]

The abnormalities in the retina due to drug toxicity can be detected early using fundus autofluorescence, optical coherence tomography, and multifocal electroretinography. The structural and functional abnormalities in the retina can be detected and monitored using the ten mentioned Early detection of the abnormalities helps to decide the further course of treatment, where medication in the dosage or cutting off the drug completely can slow down the macular damage. This study aims to evaluate macular degeneration by using optical coherence tomography in patients who developed secondary retinal toxicity due to the use of hydroxyl chloroquine at VSSIMSAR, Burla.

METHOD

A retrospective database and medical reviews of the patients were used for this cross-sectional study. The patients taken in the study were who took hydroxychloroquine or chloroquine. They attended the hydroxychloroquine ambulatory of Department of Ophthalmology, VSSIMSAR, Burlafor a period of a year, following hospital protocol. During the mentioned period, 200 patients visited the ambulatory.

Optical coherence tomography was performed using Heidelberg Spectralis.

RESULTS

Out of the 200 patients evaluated 188 (94%) were women and 12(6.%) were men. All the patients were above 19 years and below 82 years old, the mean age was 48 years old. The dose range of hydroxychloroquine was 2.32 to 7.5 mg/kg/day, mean dose was 5.33 mg (sd:0.92). The patients were treated for systemic lupus erythematosus with hydroxychloroquine. The patients were not using chloroquine during the course of the study, however, in some patients there was a history of chloroquine usage. In the optical coherence tomography no abnormalities were observed for 191 patients, amongst these 10 (5.2%) were males and 181 (94.7%) were female. The mean dosage of hydroxychloroquine in the 191 patients was 5.3 mg/kg/day, the dosage of the drug varied from 2.32 to 7.5 mg. The mean age of the patients was 47.51 years (SD: 13.22)

Eight (4%) patients showed abnormalities in their OCT results. Out of the eight patients, six (75%) were female, and 2 were male (25%). The time period of their systemic lupus erythematosus diagnosis in these patients ranged from 7 to 32 years, the mean time period was 17.37 (6.78). The abnormalities were collateral to the use of hydroxychloroquine, the mean dosage of it was 5.0 mg/kg/day (SD: 1.25), ranging from 3.09 to 6.7mg. The patients were above 42 years and below 72 years, the mean age was 56.72 years (ds: 8.65). Among the 8 patients, 3 (37.5%) reported previous use of chloroquine, and 3 (37.5%) of them did not have a history of chloroquine usage. The histories of the remaining 2 (25%) patients were not reported.

The patients who showed abnormalities in the OCT were further divided into three groups according to the stages of the abnormalities. First were the patients who showed early signs in the inner and outer segments of the photoreceptors, characterized by an ellipsoidal line. Second, were the patients who showed thinning of the perifoveal outer nuclear layer, which looked like a typical flyer saucer. The last group of patients were in the later stage, and foveal atrophy was seen in the OCT.

Among the eight patients with abnormalities, 3 belong to the first group and had an ellipsoidal line in their OCT. 4 patients belonged to the second group and showed an image like a flyer saucer in their OCT, and only 1 patient reached the later stage of foveal atrophy.

The mean age of the patients in the early stage was 53.16 years, the mean duration of hydroxychloroquine usage was 6.6 years, with a mean dose of 5.13mg/kg/day, and the mean period of SLE diagnosis was 15.8 years. Whereas the second group of patients who showed a flyer saucer in their OCT had a mean age of 57.88 years, the mean duration of hydroxychloroquine usage was 12.25 years, with a mean dose of 4.83mg/kg/day, and the mean time period of SLE diagnosis was 16.77 years. The patient who had a later stage of abnormality was 59 years old, he used hydroxychloroquine for the duration of 10 years at a dose of 5.5 mg/kg/day, and he was diagnosed with SLE 24 years ago.

Table no. 1: Summary of the data of the patients having abnormalities detected in the optical coherence tomography

Stage of abnormality	Mean age (years)	Mean SLE diagnosis time period (years)	Mean dose of HCQ mg/kg/day	Mean duration of HCQ (years)
First	53.16	15.8	5.13	6.6
Second	57.88	16.77	4.83	12.25
Third	59	24	5.5	10

DISCUSSION

The posterior degeneration of the external nuclear layer is the reason for the damage of the photoreceptors, it usually affects the macula [6]. Although other studies suggest that etiology also includes the cone's metabolism which is the cause of the lesions [1]. Some studies report that the drug can connect with melanin which is the reason for depigmentation parafoveally.[9].

Other HCQ-related damage include anterior uveitis, cornea vercilatta, optic neuropathy, and subcapsular cataract.[10]

The American Academy of Ophthalmology states screening recommendations for patients using HCQ [1]. **The most important risk factors that can lead to retinal toxicity include the following**

1. Duration of use of HCQ- more than 5 years. In a study of 3995 patients, the mean retinal toxicity was 6.5 cases per 1000 cases when the usage is more than 5 years. This mean increases 20/1000 cases when the usage is for 10 years. It decreases significantly to 3/1000 cases when the usage is for less than 5 years
2. A daily dose greater than 5mg/kg/day of HCQ and a dose greater than 3mg/kg/day of chloroquine. It is important to understand that the dose refers to the real weight and not the ideal weight as the consideration of ideal weight might lead to overdosage in leaner individuals
3. Tamoxifen use- it has been reported that the concomitant administration of tamoxifen and HCQ results in an increased risk of retinal damage that is 5 times more than usual. However, the reason for this is not known.
4. Renal disease- both HCQ and chloroquine have renal clearance so if the renal function is impaired

it will increase the amount of the drugs in the blood circulation

5. Previous retinal disease- risk factors such as genetic conditions, elderly patients, and liver disease

The academy recommends that the first evaluation should be done in the first year of drug use. This helps in establishing the record of functional status and the appearance of the fundus. OCT is not indispensable at this point in time.

The later screening is done on the basis of whether the patient has a major risk factor. If the patient has a major risk factor the evaluation should start earlier compared t the patient who does not have any risk factor, such patients can be evaluated annually starting after 5 years of starting HCQ. **In both cases, the evaluation is one time per year with the following tests:**

1. Automated visual field- pattern 28-2 field
2. Spectral-domain coherence tomography- this is done to show the thickening of the photoreceptors

Other examinations that are proven to be useful are as follows:

1. Fundus autofluorescence- it reveals photoreceptor damage even before OCT
2. Multifocal electroretinogram: same sensitivity as in the automated visual field.

Academy [1] does not recommend time-domain optical coherence tomography, electrooculogram, Amsler grid, and fundus examination. At 'ABC' hospital we have our protocol, which recommends fundus examination primarily for baseline and later annual screening with SD-OCT.

CONCLUSION

Hydroxychloroquine has been indicated in a variety of systemic diseases as well as the cost/benefit ratio of the drug and its high tolerance is the reasons for its rising prescription. Retinal toxicity is the secondary development when HCQ is used. It can range from mild cases to the greater loss of vision which can affect a patient's autonomy. However, if the abnormalities are detected earlier the progression can be slowed and usage can be stopped. In VSSIMSAR, Burlawe modified the AAO recommendation to screen for the retinal damage in the patients using HCQ.

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