Original Article

Hydroxychloroquine dosing and toxicity: A real-world experience in Saudi Arabia of 63 patients

Fadwa Al Adel, Samir S. Shoughy[1], Khalid F. Tabbara[1,2]

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Abstract:

PURPOSE: To assess the ocular toxicity in patients on high doses of hydroxychloroquine (HCQ) per weight, as per the latest American Academy of Ophthalmology (AAO) screening guidelines for HCQ toxicity.

METHODS: This is a multi-center study looking at consecutive patients attending the ophthalmology clinics at a tertiary hospital and a private clinic in Saudi Arabia. A data collection sheet was used to collect patient's information regarding the dose per body weight, duration of HCQ use and any risk factors associated with the use of the medication as per the latest AAO guidelines for HCQ screening. Ancillary testing including fundus photography, automated visual field (10-2) and spectral domain ocular coherence tomography were done. Further testing with fundus auto-fluorescence and multifocal ERG were done when needed. The presence or absence of toxicity was recorded.

RESULTS: A total of 63 patients were included in the study, 58 females and 5 males. The average patient age was 45 years (range 18–72). The mean dosage of HCQ was 3.9 mg/kg. Fourteen (22%) patients were on doses higher than 5 mg/kg. The duration of treatment ranged from 1-30 years (average 8.3). Thirty six (57%) patients were on the drug for more than 5 years. We found only one (1.58%) patient with HCQ toxic retinopathy over a mean of 8 years treatment period.

CONCLUSION: A significant number of our patients were found to be on doses of >5 mg/kg of HCQ, which may put them at a higher risk for retinal toxicity. Low dose HCQ such as 100 mg tablets should be made available to help physicians in adjusting the dose as per the latest reported guidelines by the AAO.

Keywords:

Chloroquine, cornea verticillata, hydroxychloroquine, screening, toxic retinopathy

Introduction

Hydroxychloroquine (HCQ) is an anti-malarial drug that is used to treat a variety of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, juvenile idiopathic arthritis and Sjogren's syndrome.[1,2] Novel indications for HCQ are also emerging including its potential use in cancer therapy, diabetes mellitus, heart disease, and pediatric inflammatory disorders.[1,2] Hydroxychloroquine is a less toxic metabolite of chloroquine.[2] Chloroquine has largely been replaced by HCQ. There is an ongoing increase in the number of patients who are using HCQ for prolonged duration because of the expanding indications and the relatively safe systemic profile.

Hydroxychloroquine can cause variable ocular adverse effects including corneal deposits, posterior sub-capsular cataract, ciliary body dysfunction and toxic retinopathy. Toxic retinopathy caused by HCQ has been recognized for many years. Patients with toxic retinopathy usually complain of blurry vision. The classical clinical picture of HCQ toxic retinopathy is a bilateral bull's-eye maculopathy, which is caused by a ring of parafoveal RPE depigmentation that spares the fovea. The exact mechanism responsible for the development of this pattern is not fully understood, however, it is believed that the primary damage is in the photoreceptors and

Department of Ophthalmology, College of Medicine, Princess Nourah Bint Abdulrahman University, [1]The Eye Center and The Eye Foundation for Research in Ophthalmology, [2]Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Address for correspondence: Samir S. Shoughy, The Eye Center, P.O. Box 55307, Riyadh 11534, Saudi Arabia. E-mail: samir.shawki@hotmail.com

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outer nuclear layer leading to secondary disruption of the RPE.[3] Dark skinned individuals may bind and store HCQ in the melanin of the RPE and this may predispose them for retinal toxicity.

Certain risk factors have been found to increase the risk of HCQ toxic retinopathy. The American Academy of Ophthalmology (AAO) listed the major risk factors for HCQ toxic retinopathy in their 2016 recommendations.[2] The most significant risks are high dose (HCQ dose >5.0 mg/kg of real body weight) and long duration of use (>5 years). As well as other factors such as concomitant renal disease, use of Tamoxifen and macular disease.[2]

Proper screening for HCQ retinopathy may help in early detection of structural or functional changes in the macula prior to the development of irreversible visual loss and end stage maculopathy. The screening tests include automated visual fields, spectral-domain optical coherence tomography (SD OCT), multifocal electro-retino-gram (mf-ERG) and fundus auto-fluorescence (FAF).

The overall prevalence of toxicity was estimated to be 7.5% in a study that included 2361 patients[4], although it varies greatly with the daily dose and duration of use. Recent advances in imaging such as in SD-OCT and mf-ERG technologies has allowed for better and earlier detection of retinopathy.[5] Comparison of the incidence of HCQ toxic retinopathy among different populations may be challenging. This may be explained by variations in the definitions of HCQ toxic retinopathy, imaging techniques used to detect retinopathy and the study population characteristics.[6]

The aim of this study was to report the percentage of patients on high daily doses per weight (>5mg/kg) of HCQ, as per the latest American Academy of Ophthalmology (AAO) screening guidelines for HCQ toxicity and look at the percentage of retinal toxicity.

Methods

The institutional review board approval was obtained from King Khalid University Hospital and The Eye Center clinics. The study was adherent to the tenets of the declaration of Helsinki and was registered at clinicaltrials.gov (registration number is NCT04010110). This was a multi-center study looking at a consecutive sample of sixty-three consecutive patients attending the ophthalmology clinics at King Khalid University Hospital and The Eye Center in Riyadh, Saudi Arabia. Consent was obtained from each patient. The period of data collection was from June 2017 until June 2018. We included patients on HCQ therapy who came for their ophthalmology screening appointment irrespective of the duration of use of the medication. We excluded patients who have stopped their HCQ medication. A data collection sheet [Figure 1] was used to collect patient's information. The following data were collected: demographic data (age, gender, race), dose of HCQ per body weight, duration of use, reason for use and risk factors associated with the use of HCQ such as renal disease (abnormal glomerular filtration rate), Tamoxifen use, and preexisting macular disease. All patients underwent a complete ophthalmic examination including assessment of visual acuity, anterior segment examination looking for corneal verticillata and a dilated fundus examination looking for retinal pigment epithelium (RPE) depigmentation either in a para-foveal or extra-macular distribution within the retina. Ancillary tests were done which included: fundus photography, automated visual field testing (10–2), spectral domain ocular coherence tomography (SDOCT). Fundus auto-fluorescence (FAF) and mf-ERG were done if further ancillary testing was needed in doubtful cases or to confirm findings. The diagnosis of toxic retinopathy was based on the positivity of at least two objective tests to confirm the subjective findings. The presence or absence of toxicity was recorded.

Results

A total of 63 patients were included in this study. There were 5 male and 58 female patients. All patients were from Saudi Arabia [Table 1]. The average age was 45 years (range 18–72). There were 43 patients with Systemic Lupus Erythematosus, 17 with Rheumatoid Arthritis, one with scleroderma, one with Sjogren syndrome and one with antiphospholipid syndrome. The dose of HCQ ranged from 1.7 to 8.9 mg/kg (average 3.9 mg/kg). Surprisingly fourteen patients (22%) were on doses of >5 mg/kg. The duration of treatment ranged from 1-30 years (average 8.3 years). Thirty-six patients (57%) were on the drug for more than 5 years. Seven patients (11%) had renal impairment (abnormal glomerular filtration rate) and one of them was on dialysis. 6 patients (9.5%) had preexisting macular pathology, i.e., drusens, retinal pigment epithelium (RPE) changes. None of the patients were ever on Tamoxifen. None of the patients had corneal verticillata on anterior segment examination. The dilated fundus examination of all patients was normal except for 6 patients who had drusens and RPE changes consistent with macular degeneration that was further confirmed by ancillary testing, i.e., SD OCT, FAF. One patient had para-foveal RPE depigmentation on funduscopic examination. On further testing with SD OCT, the patient had a para-foveal outer segment loss

Table 1: Demographic characteristics of participants, *n*=63

Variables	*n* (%)
Mean age±SD	45±13.5
Females	58 (92%)
Males	5 (8%)
Ethnicity	
Arabs (Saudi Arabian)	63
Duration of treatment	
_5 years	27
>5-10 years	16
>10 years	20
Reason for HCQ therapy	
Systemic lupus erythematosus	43
Rheumatoid Arthirtis	17
Scleroderma	1
Sjogren syndrome	1
Antiphospholipid syndrome	1

PROPOSED HYDROCYCHLOROQUINE / CHLOROQUINE TOXICITY SCREENING PROTOCOL

HISTORY :

Name : _____
Medical Record Number : _____
Age : _____
Gender : Male Female
Date of examination : _____
Race : Asian European Middle Eastern African
Body weight : _____ Daily Dose : _____
Duration of Use : _____ Reason for Use : _____
Comorbidities : _____

RISK FACTORS :

HCQ Dose > 5 mg/kg YES / NO (Specify : _____ mg /kg)
CQ Dose > 2.3 mg/kg YES / NO (Specify : _____ mg /kg)
Duration > 5 years YES / NO (Specify : _____ years)
Renal Disease (Abnormal GFR) YES / NO (GFR : _____)
Tamoxifen Use YES / NO
Macular Disease YES / NO (Specify : _____)

EXAMINATION :

Visual Acuity (corrected) : OD _____ OS _____
Corneal Verticillata YES / NO
Parafoveal RPE depigmentation YES / NO
Extramacular RPE depigmentation (Asians) YES / NO
Others findings : _____

ANCILLARY INVESTIGATION :

Visual Field (10-2) (24-2/30-2 in Asians) : Normal / Non Specific Changes / SuperoNasal Defect / Partial Bull's Eye Scotoma / Complete Bull's Eye Scotoma / Others _____
SDOCT : Normal / Loss of Inner Segment - Outer Segment Line
Fundus Autofluorescence : Normal / Increased Parafoveally / Decreased Parafoveally
Multifocal Electroretinogram : Normal / Weak Parafoveal Responses / Severely Attenuated

IMPRESSION :

No Toxicity **Possible Toxicity** **Probable Toxicity**

PLAN :

Continue Medication Repeat Testing _____
D/C Medication Follow Up_____

Figure 1: Data collection sheet for patients on hydroxychloroquine

and disruption of the inner segment-outer segment line [Figure 2]. Visual field testing was normal in 30 cases (48%) and had nonspecific changes in 31 cases (49%). One patient had a bitemporal hemianopia and was referred to neurology for further evaluation, and one patient (the patient with para-foveal RPE depigmentation) had a superonasal defect on visual field testing. Further testing with mf-ERG was done to the patient with para-foveal RPE depigmentation (suspicious of HCQ retinopathy) that had results of depressed retinal sensitivity and confirmed the diagnosis of HCQ toxicity. There was only one patient out of our cohort who was found to have HCQ toxicity.

Discussion

HCQ is an excellent medication in controlling rheumatological diseases with much fewer side effects than other alternative

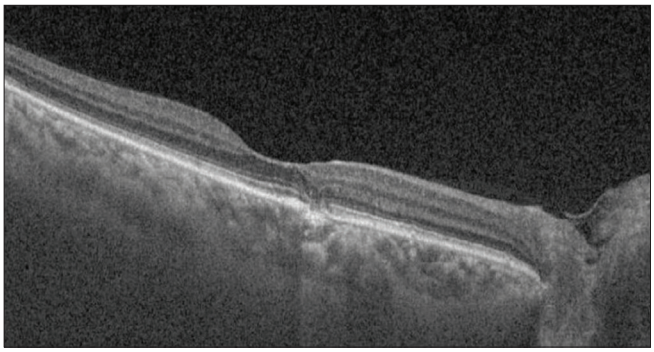

Figure 2: SD OCT of the right eye showing a para-foveal outer segment loss and disruption of the inner segment-outer segment line

medications. Ophthalmologist should be aware of the risk factors for HCQ retinopathy. The recent AAO guidelines published in 2016, better guided ophthalmologists to properly screen patients for HCQ toxicity and pay special attention to particular patients that are at risk of toxicity. It also emphasized that the most significant risk factor for toxicity was daily dose per weight and that the risk was much higher when the daily dose was >5 mg/kg.[2] Adhering to doses of <5 mg/kg was associated with a relatively acceptable risk of toxicity for patients being screened annually.[4] Surprisingly, 22% of our sample were on daily doses of >5 mg/kg of HCQ, which puts them at a higher risk for toxicity. Since rheumatologists usually prescribe HCQ to their patients they should be aware of the importance of properly dosing patients in a way that controls their disease and lessens the possibility of toxicity in the future. The challenge that rheumatologists have is that HCQ is only available in a 200 mg tablet. Intermediate doses can be achieved by taking it on alternative days of the week or simply by splitting the tablet.[2] In theory, checking HCQ blood levels would seem helpful in dosing or evaluating cases of poor clearance of the drug.[2] However, literature on the measurement of HCQ blood levels indicates that it is inconsistent and doesn't reflect medical effectiveness nor toxicity.[7-9] HCQ is metabolized by cytochrome P450 enzymes, which can be affected by a variety of other drugs and consequently affect blood levels.[10,11]

Previously the prevalence of HCQ retinopathy was dependent on the presence of classic bull's eye maculopathy, which happens in late stages of toxicity. This should no longer be seen with the recent advances in more sensitive diagnostic test modalities, which detects toxic retinopathy at much earlier stages. Recently, implementation of new diagnostic test modalities has permitted more sensitive detection of HCQ retinopathy before the development of the classic fundus changes.

The incidence of HCQ retinopathy ranged from 0% to 4% according to a meta-analysis that was conducted in 2006.[12] However, the use of high-dose HCQ is associated with higher incidence of toxicity. In patients receiving HCQ at 800 to 1000 mg/day (up to 20 mg/kg) for non-rheumatoid diseases, the incidence was found to be 25% and 40% in 2 separate studies.[13,14]

Among our 63 patients, one patient was found to have HCQ retinopathy. Of note, this patient had renal failure and was on dialysis. In this case, parafoveal inner segment-outer segment line loss was detected on SDOCT. The mf-ERG generated corresponding depression in the parafoveal area. The overall percentage of HCQ toxicity in our study was 1.6% for an 8 years average duration of treatment.

The low percentage of HCQ toxicity found in our study population, maybe due to screening patients irrespective of the duration of use of the medication. According to the most recent AAO recommendations, a baseline screening should be done initially followed by an annual screening after 5 years of starting the medication for patients on acceptable doses and without major risk factors.[2]

Our small sample size is a limitation in our study. However, there is a lack of studies about the percentage of HCQ toxic retinopathy in our region. Further studies with a larger sample size are needed.

In conclusion, a significant number of patients were found to be on doses of >5 mg/kg of HCQ which may put them at a higher risk for retinal toxicity as per the recent AAO guidelines. A better dosing should be suggested to rheumatologists to prevent retinal toxicity in the future. Regular annual screening should be emphasized for those at risk. We propose using a data sheet, similar to the one used in our study that has all risk factors for toxicity listed, which helps in proper assessment of the possibility for HCQ retinal toxicity. The lack of availability of low dose HCQ tablets makes it difficult for physcians and patients to adjust the dose as per the latest reported guidelines by the AAO. We suggest making low dose HCQ available in tablets such as 50 and 100 mg tablets.

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Conflicts of interest

There are no conflicts of interest.

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