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Review Article

Chloroquine and Hydroxychloroquine Toxicity

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ABSTRACT

Chloroquine and hydroxychloroquine have been used for decades as antimalarials and also as immunomodulating therapies for rheumatic diseases such as systemic lupus erythematosus and rheumatoid arthritis. They also have antiviral properties and are currently used empirically for the treatment of coronavirus disease 2019 (COVID-19). Retinal toxicity is a potential complication of these medications. Current ophthalmic screening and dosing recommendations aim to decrease the risk of developing retinopathy or prevent its progression. Baseline fundus examination is not currently recommended before initiating chloroquine or hydroxychloroquine for COVID-19 due to presumed very low risk of retinal toxicity. However, doses of the drugs used for the treatment of COVID-19 exceed the recommended doses, and patients often have additional risk factors. Research in the future is warranted to confirm the risk and incidence of toxicity with this novel use.

Keywords: Chloroquine, Coronavirus Disease 2019, Hydroxychloroquine, Retinopathy, Screening

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019. Since then, the virus has spread globally. As of April 2, there have been 962,726 cases and 49,186 deaths documented worldwide, and the number of people diagnosed with COVID-19 is increasing exponentially. Ongoing research centers on drugs effective against COVID-19. So far, the antiviral remdesivir and antimalarials chloroquine and hydroxychloroquine demonstrate promising inhibitory effects on SARS-CoV-2 *in vitro*.[1-3] Chloroquine has also been shown to be beneficial in the treatment of COVID-19 associated pneumonia in clinical studies of over 100 patients and has been added to the list of trial drugs in the Guidelines for the Diagnosis and Treatment of COVID-19 (seventh edition) published by National Health Commission of the People's Republic of China.[4,5]

Chloroquine is an anti-malarial therapy with documented antiviral properties against a number of viral infections, including the 2003 outbreak strain of SARS-CoV.[6] In addition to its antiviral properties, chloroquine has immune-modulating activity that may work synergistically to enhance its antiviral effect *in vivo*.[1] While commonly used in malarial prophylaxis, a narrow therapeutic window limits use outside of this scope. Failure to properly dose the drug leads to acute poisoning and even death secondary to cardiac toxicity and arrest.[7] Hydroxychloroquine sulfate, a hydroxylated derivative of chloroquine, exhibited less toxicity than chloroquine in animals while providing similar therapeutic benefits. For this reason, it is commonly used in managing autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[8] Multiple clinical trials

investigating hydroxychloroquine as a therapy for COVID-19 are already underway.[3] Meanwhile, in the absence of data and better alternatives, hydroxychloroquine is empirically administered to hospitalized COVID-19 patients in multiple countries, including the United States.[9]

Both chloroquine and hydroxychloroquine have concerning side effects. One significant adverse drug event is ocular toxicity, including retinopathy that can lead to end-stage irreversible vision loss if undetected. Clinical research to date, primarily with hydroxychloroquine, has provided ocular screening protocols and safe dosing guidelines for long-term use in antimalarial prophylaxis and rheumatological diseases. Given the increased and often empiric usage of chloroquine and hydroxychloroquine against COVID-19, it is important to review ocular toxicities, screening recommendations, and safe use in this novel setting.

EPIDEMIOLOGY

Hydroxychloroquine is preferred over chloroquine due to the lower incidence of gastrointestinal adverse reactions and lower risk of ocular adverse reactions, particularly in long-term treatment of rheumatologic disease.[10] In one 2010 study of 3995 patients who had taken or were taking hydroxychloroquine for RA or SLE, the incidence of documented toxicity was 0.65%.[11] While low, the risk of toxicity increased five-fold after 7 years of usage, with incidence exceeding 1% after 5–7 years. Duration of use was the most important predictor of toxicity, while age, daily dose, and patient weight did not correlate significantly with toxicity. In a more recent study done in 2014 of 2361 patients who used hydroxychloroquine for at least 4 years, the overall prevalence of retinopathy was 7.5%.[12] The risk of developing toxicity was greater for patients with daily consumption of >5.0 mg/kg of real body weight. In addition, the prevalence of retinal toxicity was <2% within the first 10 years of use in those with daily consumption of 4.0–5.0 mg/kg, but increased to nearly 20% after 20 years of use. This demographic study revealed a much higher overall risk of toxicity among the patients studied, which could be due to both the long duration of hydroxychloroquine use in the study population and advance of imaging technologies that enable for better detection of retinopathy.[13] The study revealed that in addition to duration of use, risk was also associated with daily dosage. That information forms the basis for the most recent screening guidelines for chloroquine and hydroxychloroquine toxicity by the American Academy of Ophthalmology published in 2016.[14]

MECHANISM OF ACTION

Chloroquine and hydroxychloroquine mediate their antimalarial effects through increasing the pH of acidic food vacuoles within parasites, which then interferes with their vesicle function and reproductive cycle.[15] One mechanism for their immune-modulating effects is suppressing activation of toll-like receptors by binding directly to nucleic acids in the activation cascade. Toll-like receptors are necessary for the expression of interferon-regulated genes and production of tumor necrosis factor alpha, and their inhibition blunts the body's primary cell-mediated inflammatory response.[16] While the exact mechanisms for its antiviral properties have yet to be completely elucidated, chloroquine was found to increase the pH within endosomes and at the surface of the cell membrane, thereby blocking fusion of the virus to the cell membrane. The drug also interferes with glycosylation of SARS-CoV spike protein and its receptor, angiotensin-converting enzyme 2, resulting in reduced binding affinity and cell entry.[6] The amino acid sequences for receptor binding between SARS-CoV and SARS-CoV-2 are conserved, suggesting that the two strains use the same host receptors for entry.[3]

MECHANISM OF TOXICITY

Once within the systemic circulation, chloroquine and hydroxychloroquine have binding affinity toward melanin containing tissues, such as the eye. Although the link between chloroquine accumulation within the eye and retinopathy is established, the exact mechanism remains unknown. Several theories have emerged. Chloroquine is known to inhibit protein synthesis within the retinal pigment epithelium (RPE), which has been proposed to lead to retinopathy over time.[17] An alternative hypothesis is that by binding to melanin, chloroquine undermines the protective role of melanin as a free radical scavenger, thus leading to retinal damage and toxicity.[18] Hydroxychloroquine was demonstrated to have lower tissue accumulation and binding affinity for melanin compared to chloroquine leading to less ocular toxicity, which substantiates the idea that drug toxicity is mediated through binding melanin rich tissues.[19]

PHARMACOLOGIC PROPERTIES

Hydroxychloroquine and chloroquine are metabolized by cytochrome P450 enzymes in the liver and then cleared to a large degree by the kidneys. With a half-life elimination of 40–50 days, it takes about 6 months of therapy for the drug to reach its steady state concentration.[20] Therefore, short-term changes in dose or duration of use, such as the recommended 5–6 days regimen for the treatment of COVID-19, should have little effect on basic tissue stores and blood levels. Although oral bioavailability of hydroxychloroquine is estimated as 75%, individual pharmacokinetics lead to great variability of blood concentrations in patients taking similar doses.[20] A recent study of 537 patients found that higher

blood levels of hydroxychloroquine were predictive of the development of retinopathy.[21] As such, monitoring serum drug levels to assess for toxicity risk may be productive.

CLINICAL PRESENTATION

Anterior eye

Long-term use of hydroxychloroquine and chloroquine can cause drug precipitation in the cornea.[22] The corneal epithelium alters its structure into whorl-like patterns that resolve with drug cessation and does not generally cause visual impairment, although some patients reported seeing haloes. Cornea verticillata occurs more commonly with chloroquine than hydroxychloroquine, but its presence does not correlate with retinal toxicity. Chloroquine has also been associated with cataracts in about 20% of patients, which present as small, white flecks below the posterior lens capsule.[22] This finding has not been observed in patients taking hydroxychloroquine.

Retinopathy

The risk of developing retinopathy, while low, is a major concern expressed by patients and clinicians using hydroxychloroquine. The earliest fundoscopic findings of hydroxychloroquine retinopathy are subtle changes at the macula, including pigmentary stippling and RPE depigmentation that usually starts at the inferior zone of the macula. Because the early changes progress in a parafoveal pattern with sparing of the central fovea, patients are usually asymptomatic with intact central visual acuity. The standard visual acuity tests, such as Snellen distance acuity, are unlikely to detect early changes. However, formal central visual field testing by 10–2 Humphrey visual field may detect decreased sensitivities in the upper visual field corresponding to inferior parafoveal area of depigmentation [Figure 1a].[23] Notably, patients of Asian descent tend to present with pericentral toxicity with an extramacular pattern that could be missed with the 10–2 Humphrey visual field test.[24] Spectral domain optical coherence tomography (SD-OCT) can further characterize structural changes [Table 1]. In early stages, the RPE layer is intact. As the disease progresses, downward displacement of inner retinal layers, thinning of outer retinal layers, or loss of the ellipsoid zone can be observed.[25,26]

In its advanced stage with continued drug exposure, hydroxychloroquine retinopathy progresses to a clear zone of depigmentation around the fovea, described as bull's-eye maculopathy, and even overt RPE and retinal degeneration [Figure 1b]. Patients may gradually develop symptomatic disturbances in vision with central extension of disease, including photopsia, metamorphopsia, reduced color vision, and peripheral field loss.[27,28] The pattern of retinopathy is similar in both hydroxychloroquine and chloroquine. Patients with chloroquine retinopathy may also exhibit diffuse chorioretinal atrophy and sharp demarcation between the posterior pole and retinal periphery.[29]

Early discontinuation of chloroquine and hydroxychloroquine before advanced toxic effects can lead to functional visual improvement or preservation. However, late detection following loss of ellipsoid zone and RPE atrophy has been associated with progression of structural and functional visual deterioration even after cessation of drug.[30,31]

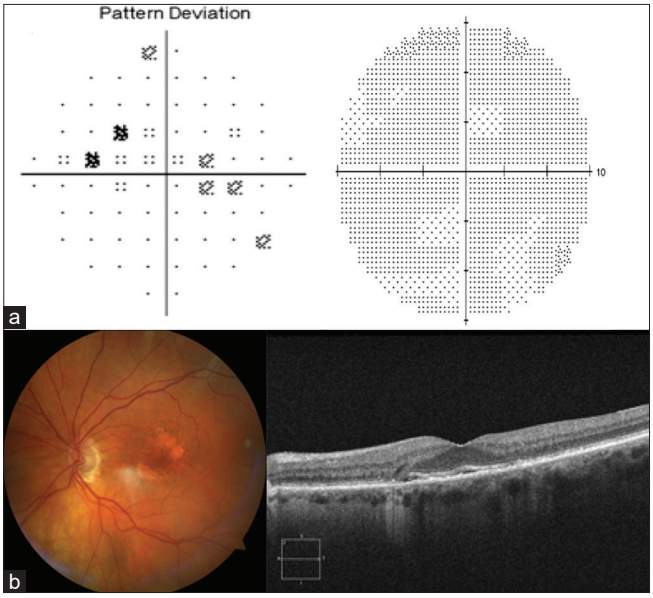

Figure 1: (a) Mild toxicity; 10-2 white target visual fields (pattern deviation plot and threshold plot) showing fragments of ring scotoma and decreased sensitivities in upper visual field. (b) Severe toxicity; bulls-eye maculopathy on fundus image (left) and disruption of retinal pigment epithelium and ellipsoid zone on SD-OCT (right).

Table 1: Screening modalities with associated early changes of hydroxychloroquine retinopathy.

Screening modality	Findings
Fundoscopy	Macular pigment changes, pigmentary stippling, and depigmentation
Visual fields	Paracentral defects[23]
SD-OCT	Perifoveal ellipsoid zone disruption with intact outer retina directly under the fovea – "flying saucer" sign[25]
MfERG	Increased R(1)/R(2) ring ratio[42]
FAF	Pericentral ring of increased fluorescence that progresses to mottled loss of FAF with increased FAF in adjacent retina[35]

SD-OCT: Spectral-domain optical coherence tomography, MfERG: Multifocal electroretinography, FAF: Fundus autofluorescence

RECOMMENDATIONS FOR SCREENING

Hydroxychloroquine and chloroquine retinopathy is irreversible. For this reason, identifying toxicity before RPE involvement allows prompt discontinuation of the medication thereby limiting progression of the disease. Proper screening is important in catching patients at an early stage before vision is significantly affected.

The most recent update on recommendations for screening for chloroquine and hydroxychloroquine toxicities was published by the AAO in 2016 [Table 2].[14] The AAO recommends that every patient should have a baseline examination before starting the drug and annual screening after 5 years of use in patients with no additional risk factors. The primary purposes of the baseline examination are to document the fundus appearance and rule out any underlying disease of the macula. Annual screening should begin earlier in the at-risk population: Those on a dose >5 mg/kg based on real weight, taking for longer than 5 years, possess renal or hepatic impairment, concurrently take tamoxifen, or have pre-existing retinal and macular disease. The recommendation to dose based on real weight represents a shift from prior guidelines advocating ideal weight use. It was made based on studies showing that real weight correlated more closely with risk of developing toxicity and prevented over-dosage in thin individuals.[12] Although there are no demographic studies of dosages for chloroquine toxicity, the previous literature estimated that risk of toxicity with 3.0 mg of chloroquine approximately equated risk of toxicity with 6.5 mg of hydroxychloroquine.[32] Based on this estimation, 5.0 mg/kg of hydroxychloroquine should be equivalent to about 2.3 mg/kg of chloroquine, which is the dosage of chloroquine that the AAO recommends.

RECOMMENDED SCREENING MODALITIES

Screening visits should include a detailed ophthalmic examination, automated visual field test, and at least one objective test (SD-OCT, Multifocal Electroretinogram [mfERG], or fundus autofluorescence) [Table 1]. Any abnormalities detected on automated visual field test, which has high sensitivity but low specificity, should be retested or evaluated by additional objective tests. 10–2 Humphrey visual field pattern may be used for non-Asian patients, while Asian patients should receive wider test patterns (24–2 or 30–2) due to findings of early extramacular involvement. Similarly, wider-angle SD-OCT scans are recommended for Asian eyes to evaluate for thinning of photoreceptor layers near the vascular arcade region. In non-Asian eyes, SD-OCT may show thinning of the photoreceptor layer in the parafoveal region or distinct focal interruption of the photoreceptor outer segment structural lines.[14] SD-OCT is more accessible but not as sensitive as the mfERG, which can detect parafoveal or extramacular electroretinogram depression in early retinopathy.[42] The mfERG can provide objective confirmation of suspected field loss detected on visual fields and detect functional abnormalities before there are clinically evident structural changes.[30] Finally, fundus autofluorescence may identify early photoreceptor damage and accumulation of lipofuscin granules as areas of increased autofluorescence that correlate with abnormalities detected on SD-OCT.[33-36]

Table 2: Screening guideline with risk factors.

	Recommendation
Dosing	HCQ: ≤ 5 mg/kg/day CQ: ≤ 2.3 mg/kg/day
Initial screening	Fundus examination within 1st year of use Add visual fields and SD-OCT if maculopathy is present
Repeat annual screening	After 5 years of therapy in low-risk patients, earlier in patients with risk factors*

*Dose >5 mg/kg/day for HCQ, decreased renal function, tamoxifen use, and underlying macular disease. HCQ: Hydroxychloroquine, CQ: Chloroquine, SD-OCT: Spectral-domain optical coherence tomography. Based on information in reference 28

USE OF CHLOROQUINE AND HYDROXYCHLOROQUINE FOR COVID-19

In regard to the use of chloroquine and hydroxychloroquine in the treatment of COVID-19, the AAO states that baseline fundus examination is not needed before initiating therapy. Given the short duration of treatment (weeks to months), there is very low risk of ocular toxicity if patients receive dosages that were previously determined to be safe for the retina (≤5 mg/kg of real weight for hydroxychloroquine, and ≤2.3 mg/kg of real weight for chloroquine).[37] While optimal dosing and duration for treatment of COVID-19 have yet to be established through clinical trials, real world doses are being reported.

In the United States a regimen of 400–600 mg BID on day 1, then 400 mg daily on subsequent days is used. Under this dosing schedule patient under 80 kg would be receiving higher doses than the recommended 5 mg/kg. Within the Guidelines for the Diagnosis and Treatment of COVID-19 (seventh edition) published by National Health Commission of the People's Republic of China, chloroquine is dosed at 500mg BID for 7 days in patients over 50 kgs. This far exceeds the recommended chloroquine dosing of 2.3 mg/kg based on real weight. Although for a short duration, these doses are notably high. Reports of acute kidney dysfunction and acute kidney injury with severe COVID-19 infections raise concern that the drug may persist in the system due to poor elimination.[38]

There is cause for concern. Reports of accelerated retinopathy – within a few months – have emerged in patients with no risk factors apart from higher dosage. One case reported bilateral bull's-eye retinopathy in a 42-year-old woman who had been taking hydroxychloroquine for 2 months, on 400 mg/day (above ideal dose) for the 1st month, and 200 mg/day for the 2nd month. Apart from exceeding the recommended dose for 1 month, the patient did not have any of the other risk factors.[39] In another case report, a 56-year-old woman on 400 mg/day of hydroxychloroquine for 48 months presented after 6-month history of worsening vision with bilateral bull's-eye lesions on exam. She also did not have any risk factors apart from taking a greater dose than recommended.[40] Finally, a 61-year-old woman on an appropriate dosage and no risk factors developed bull's-eye retinopathy after taking the drug for 2 months.[41] Although these reports may be due to underlying genetic predisposition, there is concern for iatrogenic injury.[39-41] As such, studies in the future may be warranted to confirm that there is no increased risk of retinopathy in COVID-19 patients. Until that time, the minimal but unpredictable risk of retinopathy with short-term use of high drug dosages must be weighed against patient status and benefits of a potentially life-saving treatment.

CONCLUSION

There are no medical therapies available to treat hydroxychloroquine or chloroquine retinopathy once it develops. The only available intervention is cessation of the drug, although this does not prevent progression of disease and subsequent vision loss.[30] The risk of vision loss is minimal if retinopathy is detected early before there is RPE damage, but significant in patients who already present with a bull's-eye lesion since the damage can continue for years after cessation of drug.[14]

The current literature forms a strong basis for the current recommendations of maintaining a dose ≤5 mg/kg/day and timeline for screening in patients with and without risk factors. The rationale for screening is to detect retinal changes and intervene early on to avoid irreversible progression of disease. While there is no single preferred screening modality for identifying early retinopathy, there are a number of tests that may detect structural and functional changes before visual symptoms. At present, it is not recommended to screen patients receiving chloroquine or hydroxychloroquine for the treatment of COVID-19 due to short duration of therapy, although studies to confirm risk and incidence of toxicity in this population may be warranted.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

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