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Patient treated with antimalarial drug under the supervision of a rheumatologist and ophthalmologist

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HIGHLIGHTS

This paper describes the effects of chloroquine and hydroxychloroquine on the eye, used in the treatment of systemic lupus erythematosus and rheumatoid arthritis; risk factors for damage and possible screening tests.

ABSTRACT

Patients who come to see an ophthalmologist often have systemic diseases, the treatment of which can affect the condition of the eye. Such medications include the so-called antimalarial drugs chloroquine and hydroxychloroquine, which are used in the treatment of systemic lupus erythematosus or rheumatoid arthritis. During their use, regular ophthalmological follow-up is necessary.

In the early stages of antimalarial use, patients are usually asymptomatic, while advanced maculopathy or peripheral retinopathy can cause irreversible vision loss. The main risk factors for maculopathy are high doses (more than 5 mg/kg/24 h for hydroxychloroquine) and a long duration of use (greater than 5 years). Renal or liver impairment or concomitant use of tamoxifen increase the risk of ocular damage. Risk factors also include age and concurrent retinal disease.

Ophthalmic screening should include evaluation of visual acuity, colour vision, Amsler test, fundus and additional tests such as optical coherence tomography, electroretinogram, fundus autofluorescence, and visual field. The decision to discontinue the drug should be made jointly with the rheumatologist or attending physician, after taking into account the systemic effects of the drug.

Key words: hydroxychloroquine, chloroquine, adverse effects, eye

INTRODUCTION

Chloroquine and hydroxychloroquine have been used in clinical practice for many decades. Chloroquine was first synthesized in 1934, followed by hydroxychloroquine in 1946 [1]. Their primary indication was the treatment and prevention of malaria. In addition, chloroquine has been applied in the management of hepatic parasitic diseases, such as liver fluke infection and liver abscess caused by *Entamoeba histolytica* [2].

Hydroxychloroquine and chloroquine are used not only in acute infectious diseases but also in several chronic conditions. The beneficial effects of antimalarial drugs in reducing arthritis symptoms and improving skin lesions in rheumatic diseases were first observed in soldiers during World War II [3, 4]. Today, both agents are widely used in systemic lupus erythematosus (SLE) [5] and rheumatoid arthritis (RA) [6]. In patients with SLE, hydroxychloroquine has been shown to reduce disease activity, decrease the frequency of exacerbations, and improve long-term survival [7]. In SLE, hydroxychloroquine is recommended for all patients without contraindications, at a target dose of 5 mg/kg body weight/24 h (maximum 400 mg/24 h). The dose should be individualized according to the patient's risk of disease exacerbation and the potential for retinal toxicity. For patients in long-term remission, dose reduction to 200 mg/24 h may be considered [8]. Hydroxychloroquine remains the drug of choice; however, chloroquine can be used as an alternative [5].

For the treatment of rheumatoid arthritis (RA), hydroxychloroquine may be used in patients with early, mild disease (i.e., without poor prognostic factors), particularly when the other three conventional synthetic disease-modifying drugs (csDMARDs), i.e., methotrexate, leflunomide, and sulfasalazine, are contraindicated or not tolerated. Hydroxychloroquine is also frequently used as part of combination therapy [6]. In RA, it is administered once or twice daily at a dose of 200 mg (≤5 mg/kg body weight/24 h). Chloroquine, by contrast, is given once daily at a dose of 250 mg [9].

In both SLE and RA, hydroxychloroquine and chloroquine can be administered long-term, often for many months or even years [10, 11]. In Poland, hydroxychloroquine is available in 200 mg tablets, whereas chloroquine is available in 250 mg tablets. Chloroquine remains the less expensive option, with the cost of 30 tablets (250 mg) amounting to approximately PLN 20 (PLN 6 with reimbursement). In contrast, hydroxychloroquine is not reimbursed and costs approximately PLN 40 for a package of 30 tablets (200 mg) [2, 12].

The mechanisms of action of chloroquine and hydroxychloroquine are complex and not yet fully elucidated. Both agents are 4-aminoquinoline derivatives and weak bases that preferentially accumulate in acidic compartments, such as lysosomes and inflamed tissues. Their activity involves modulation of multiple pathways, including suppression of both innate and adaptive immune responses. Hydroxychloroquine and chloroquine increase the pH of endosomes, thereby disrupting lysosomal activity and autophagy, altering membrane stability, and modulating signaling pathways and transcriptional activity. These effects can suppress cytokine production and influence the expression of costimulatory molecules [13].

Hydroxychloroquine and chloroquine are well absorbed from the gastrointestinal tract and exhibit a large apparent volume of distribution. They accumulate in various tissues, including the liver, kidneys, lungs, and melanin-rich structures. Both drugs are slowly released from tissues and undergo hepatic metabolism. Their long elimination half-life, averaging 40–60 days, underlies the potential for tissue accumulation and delayed toxicity. Hence, both the slow onset of action and the prolonged effect after drug withdrawal are explained by their pharmacokinetics [2, 12, 13]. In the treatment of SLE, clinical improvement may not appear until 4–6 weeks after therapy initiation, while maximum therapeutic efficacy is typically achieved after 3–6 months [2, 12, 14].

In addition to their use in the above-mentioned diseases, antimalarials are also registered for the treatment of lupus erythematosus, while hydroxychloroquine is additionally approved for photodermatoses and, in combination with other therapies, for juvenile idiopathic arthritis [2, 12]. During the COVID-19 pandemic, hydroxychloroquine was also investigated as a potential treatment for SARS-CoV-2 infection [15].

For many decades of chloroquine and hydroxychloroquine use, ophthalmology lacked the diagnostic tools to detect early ocular changes. The toxic effects of long-term chloroquine therapy for malaria on the retina were first reported in 1959 by Hobbs et al. [16].

OCULAR CHANGES

Antimalarial drugs are eliminated very slowly and tend to accumulate in melanin-rich tissues such as the retinal pigment epithelium and choroid. While toxic retinal damage is most often localized perifoveally, in Asian patients extramacular involvement is more frequently observed. The risk of toxicity is further increased in the presence of liver or kidney dysfunction [17].

It was once believed that obesity could lead to misjudgment of the safe dose of antimalarials [18]. However, according to the 2016 recommendations of the American Academy of Ophthalmology, the maximum daily dose of hydroxychloroquine should not exceed 5 mg/kg of actual body weight, as this parameter correlates more reliably with toxicity risk than ideal body weight. For chloroquine, no comparable demographic data exist, but older studies suggest a safe daily dose of approximately 2.3 mg/kg actual body weight. Importantly, calculating cumulative chloroquine dose to estimate toxicity risk is no longer recommended [19].

Since the introduction of the safer alternative hydroxychloroquine, the use of chloroquine has steadily declined. Retinal toxicity associated with chloroquine is closely linked to the total cumulative dose. The risk increases significantly once the cumulative dose exceeds 300 g, although individual susceptibility to toxicity may vary considerably [2, 12].
Hydroxychloroquine is considered much safer than chloroquine. The risk of retinal toxicity increases significantly (exceeding 1%) once the cumulative dose surpasses approximately 1,000 g, which corresponds to about 7 years of treatment at a standard dose of 200 mg twice daily [18]. Nonetheless, the overall incidence of true hydroxychloroquine retinopathy remains extremely low [20].
Ocular toxicity of antimalarial drugs may manifest as keratopathy, ciliary body dysfunction, lens opacities, and retinopathy. Among these, retinopathy represents the most serious complication, while the other lesions are more frequent but usually benign and reversible. Clinical symptoms may include difficulty with reading, reduced visual acuity, central scotoma, accommodative disturbances, glare, blurred vision, photopsias, metamorphopsia, or headache. However, retinal changes can also remain asymptomatic for a long time [16, 20, 21].

Effects on the ciliary body

Long-term use of antimalarials may, albeit rarely, lead to accommodative dysfunction. In some patients, difficulty with rapid changes in focus can appear shortly after chloroquine administration, and in bothersome cases dose reduction may alleviate symptoms. Earlier studies reported no impairment of accommodation in patients treated with hydroxychloroquine [20].

Corneal lesions

Antimalarial drugs in salt form may deposit in the corneal epithelium, producing corneal deposits. Their appearance varies from scattered, pinpoint opacities to radial and whorl-like aggregations that converge beneath the central cornea, creating the characteristic picture of vortex keratopathy. Although visual acuity is typically preserved, patients may report halos around light sources and photophobia. Keratopathy occurs in up to 90% of patients receiving therapeutic doses of chloroquine but is very rare in those treated with hydroxychloroquine. Vortex keratopathy is not dose- or duration-dependent, and the corneal changes are usually reversible after discontinuation of therapy. In some cases, however, they may also resolve spontaneously despite continued treatment [20].

Cataracts

Cataracts associated with chloroquine therapy have been reported in over 20% of patients. They appear as small, white, flake-like opacities located axially beneath the posterior lens capsule and differ from the central posterior subcapsular plaques characteristic of glucocorticosteroid-induced cataracts. However, differentiating these opacities from age-related changes can be challenging. Notably, such cataract changes have not been observed in patients receiving hydroxychloroquine [20].

Retinopathy

Retinal and macular damage can vary in severity, ranging from changes confined to the macula to lesions that extend beyond it.
Premaculopathy is a condition in which early structural and functional changes in the retina occur, but are not yet visible on routine fundus examination. The purpose of performing additional tests is to detect subtle changes before irreversible damage develops. In optical coherence tomography (OCT), hydroxychloroquine and chloroquine increase the pH in endosomes, thereby interfering with lysosomal activity and autophagy, affecting membrane stability, and altering signaling pathways and transcriptional activity, which can inhibit cytokine production and modulate some costimulatory molecules [13]. Hydroxychloroquine and chloroquine are well absorbed from the gastrointestinal tract. They are characterized by a large apparent volume of distribution and accumulate in the liver, kidneys, lungs, and melanin-containing tissues, among others. They are slowly released from the tissues and metabolized, with a long half-life of about 40–60 days. Hence the slow onset of action and the prolonged effect after the drug is discontinued. Macular disruption of the ellipsoid zone is evident – a reduction in pigment density in the macula may be seen at the junction of the inner and outer segments of the photoreceptors in fundus autofluorescence studies. Minor central visual field abnormalities can be detected in the macular visual field test (10-2) or the Amsler test. Subtle color vision abnormalities may occur but can go undetected using Ishihara plates due to their low sensitivity [22].
In **early maculopathy**, a slight decrease in visual acuity is noticeable, to a level of 0.7–0.5. On fundus examination, the macula shows subtle changes that may be more apparent on autofluorescence [22].
Progression of maculopathy results in a moderate-to-severe decrease in visual acuity, down to 0.2–0.1, with characteristic bull's-eye maculopathy – a central, fovea-located island of pigment within a discolored zone of retinal pigment epithelium (RPE) atrophy, surrounded by a ring of excessive pigmentation. Further progression leads to extensive atrophy of the RPE surrounding the fovea. Arterioles may become attenuated, and clusters of pigment may form in the periphery. All patients develop visual field defects, including paracentral, pericentral, central, and peripheral field loss. Color vision is typically impaired [20, 22].

Retinopathy is irreversible, and there is currently no treatment for it. Early diagnosis (before any loss of the retinal pigment epithelium) is crucial for preventing central vision loss. However, questionable test results should be repeated or verified with additional procedures to avoid unnecessary discontinuation of valuable medications [17]. Discontinuation of the drug is the only effective treatment for toxicity [20].

PREVENTION

Patient education is essential, with emphasis on awareness of potential drug-related ocular effects and the need for regular ophthalmologic follow-up [17].

To minimize the risk of vision loss, baseline screening should be performed prior to or shortly after treatment initiation to allow comparison with subsequent examinations and to exclude pre-existing maculopathy [17].

The primary screening modalities include standard automated perimetry and spectral-domain optical coherence tomography (SD-OCT). In patients of Asian descent, testing should extend beyond the central macula due to the higher prevalence of extramacular involvement. Multifocal electroretinography (mfERG) provides an objective measure for confirming visual field defects, while fundus autofluorescence (FAF) enables topographic assessment of retinal damage. Modern screening protocols should allow for the detection of retinopathy prior to the appearance of funduscopic changes [17].

Follow-up examinations should be performed annually after five years of treatment, or after 12 months in patients classified as high risk. Chloroquine is associated with a less favorable safety profile compared to hydroxychloroquine; therefore, all patients receiving chloroquine require baseline and at least annual ophthalmic monitoring. In cases where signs of drug-related toxicity are detected, discontinuation of therapy should be considered in consultation with a rheumatologist [23, 24].

RISK FACTORS

The principal risk factors for the development of antimalarial-induced maculopathy include a high daily dose (>5 mg/kg/24 h) and prolonged treatment duration (>5 years). Additional risk factors comprise impaired renal or hepatic function and concomitant use of tamoxifen, which further increase susceptibility to ocular toxicity [23, 25]. Age and pre-existing retinal disease have also been identified as potential contributors [20].

ANTIMALARIAL DRUGS AND AGE-RELATED MACULAR DEGENERATION

A potential challenge for ophthalmologists is the presence of coexisting macular pathology, such as dry age-related macular degeneration, which is frequently encountered in this patient population. In such cases, certain diagnostic tests may be of limited value in differentiating disease-related changes (e.g., progressive visual acuity loss) from drug-induced toxicity. This raises an important clinical question: should initiation or continuation of antimalarial therapy be reconsidered in patients already receiving treatment? Despite the long-standing use of antimalarial drugs in medicine, consensus remains limited regarding several aspects of toxicity, including nomenclature, the most appropriate ophthalmic test(s), and the recommended frequency of screening. Current guidelines also vary between European-American and Asian medical systems [17, 20]. Advances in ophthalmology, particularly in imaging techniques, now allow for the early detection of ocular changes. However, limited availability of additional ophthalmic testing – especially electrophysiological examinations – remains a significant constraint.

CONCLUSIONS

Patients with systemic diseases often require periodic or long-term ophthalmic evaluation, as ocular complications may result from the underlying systemic disease and its treatment. This is particularly relevant for individuals with SLE or RA receiving chloroquine or hydroxychloroquine, which are associated with the risk of toxic retinopathy. Regular ophthalmic screening in this patient population is therefore essential to enable early detection and prevention of irreversible retinal damage. Ophthalmologic evaluation should include assessment of visual acuity, fundus examination, color vision testing, and Amsler grid testing, supplemented by additional diagnostic modalities such as OCT, electroretinography, fundus autofluorescence, and visual field testing. The decision to discontinue therapy should be made collaboratively with a rheumatologist or the treating physician, taking into account both ocular findings and the systemic benefits of the drug.

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