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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.

Chloroquine And Hydroxychloroquine Toxicity

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Last Update: June 4, 2019.

Introduction

Chloroquine (CQ) is used to prevent and treat malaria and amebiasis,[1] while hydroxychloroquine (HCQ), a less toxic metabolite of chloroquine, is used to treat rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren's syndrome.[2] Both medications can cause corneal deposits, posterior subcapsular lens opacity, ciliary body dysfunction, and most important, irregularity in the macular pigmentation in the early phase, a ring of macular pigment dropout in the advanced stage, and peripheral bone spicule formation, vascular attenuation, and optic disc pallor in the end-stage. Ocular symptoms of retinopathy include blurred and partial loss of central vision, side vision and in the later stage, night vision. Symptoms of corneal deposits include haloes and glare. Clinical research has resulted in precise screening protocols and safe dosing guidelines to prevent ocular toxicity and detect retinal damage at an early stage.

Etiology

Chloroquine and hydroxychloroquine bind to melanin in the retinal pigment epithelium (RPE) and cause damage to the macular cones outside of the fovea. The drugs inhibit RPE lysosome activity, reduce phagocytosis of shed photoreceptor outer segments causing an accumulation of outer receptor segments. In response, pigment-containing RPE cells migrate into the outer nuclear and outer plexiform layers of the retina resulting in irreversible photoreceptor loss and RPE atrophy.[3] HCQ has a long half-life (about one month) and takes about half a year to achieve full elimination from the body; this is significant when managing minor side effects such as itching and corneal deposits and major ones such as retinal toxicity and explains continued maculopathy even after discontinuation of the medication. Corneal deposits (called vortex keratopathy or corneal verticillata) result from binding to cellular lipids and deposition of the drug in the basal epithelial layer of the cornea. Discontinuation of the drug usually causes the deposits to disappear over time.

Epidemiology

The advance of spectral domain optical coherence tomography (SD-OCT) and multifocal electroretinography (mf-ERG) technology has allowed for better detection of retinopathy.[4] These advances, combined with the increased clinical availability of SD-OCT and, to a lesser degree mf-ERG, has increased reported incidence and prevalence of toxicity over the last decade.

The incidence of HCQ retinal toxicity was found to be 0.38% in a 2003 study of 526 patients.[5] A 2010 study of approximately 4000 patients found a higher overall incidence of toxicity of 0.68%. This study also found that the incidence increased sharply after 5 to 7 years of HCQ use from close to 0% to about 1%.[6] Based on this study the American Academy of Ophthalmology recommended new screening guidelines in 2011. The same study revealed that the most important predictor of toxicity was the duration of use (cumulative dose) and that age, the daily dose, and patient weight did not correlate significantly with HCQ toxicity. One reaches

a cumulative dose of 1000 grams (1 kilogram) at 7 years when taking the most commonly prescribed dose of 400 mg a day. A new study then focused on those patients that had taken HCQ over 5 years. This study revealed a much higher overall risk of 7.5% retinal toxicity among the 2361 patients studied.[7] A daily dose over 5 mg/kg body weight increased the odds 5.7 times and taking HCQ over 10 years increased the odds by 3.2 times of developing retinopathy. As long as patients received a dose of less than 5 mg/kg for less than 10 years, the incidence was still relatively low at 2%. However, this risk went up to 20% for those patients who had taken HCQ over 20 years. For those patients without retinopathy after 20 years of usage, the risk of developing toxicity in each subsequent year is around 4%. Therefore, this study revealed that dose matters as well. This study found that kidney disease and tamoxifen therapy increased the risk of retinopathy by 2.1 and 4.6 fold, respectively.

A report in 2015 described that pericentral maculopathy without the classic parafoveal (Bull's eye) retinopathy is common in Asian (50%) compared to Caucasian (2%) patients,[8] and Asian patients should, therefore, receive adapted screening tests such as a wider angle threshold visual field test.

Pathophysiology

In malaria, chloroquine and hydroxychloroquine act as chemotherapeutic agents against erythrocytic forms of the *Plasmodium* parasites. Absorption of the drug increases the pH of the acidic food vacuoles of the parasite while it is inside the erythrocyte, which interferes with vesicle function and the development and asexual reproduction of the parasite.[9] The drugs also inhibit parasite growth by interfering with the conversion of toxic heme, released from the parasite digestion of hemoglobin to the non-toxic hemozoin.[10] As a treatment for rheumatic disease, HQ/HCQ increases the pH in the lysosomes of antigen-presenting cells. This blocks toll-like receptors (TLR) on dendritic cells, reduces the activation of these cells and reduces inflammation by inhibiting the production of rheumatoid factor and acute phase reactants. The drugs also accumulate in white blood cells, and by stabilizing lysosomal membranes inhibit the activity of enzymes that cause cartilage breakdown such as collagenase and protease. TLR 9 recognizes DNA-containing immune complexes and inhibition by CQ/HCQ leads to inhibition of anti-DNA auto-inflammatory processes, such as occur in SLE.[11]

Histopathology

SD-OCT testing visualizes the retinal layers in as much detail as microscopic examination and in CQ/HCQ retinopathy a loss of the photoreceptor inner-outer segment junction (the IS/OS line, also called the ellipsoid zone or the photoreceptor integrity line (PIL)) and a thinning of the outer nuclear layer of the retina are observed.[12]

Toxicokinetics

Both chloroquine and hydroxychloroquine have excellent oral absorption and bioavailability. Both have a long and variable plasma elimination half-life because of a high volume of distribution, an extended mean residence time (HCQ 1300 hours and CQ 900 hours) and with about half the drug metabolites undergoing unmodified renal clearance. Both drugs are modified by cytochrome P450 in the liver.[13] chloroquine and hydroxychloroquine can pass through the placenta, but do not appear to cause harm to the baby and likely is beneficial to both mother and baby by an improved pregnancy outcome.[14] Both drugs are excreted in breast milk. Studies of pregnant mice revealed that the drug accumulates in the fetal retina. However, this accumulation is not permanent, and no reports of permanent harm exist.[15]

History and Physical

History should include the medical condition(s) that prompted CQ or HCQ therapy, the time since the start of therapy and the daily dose in mg per kilogram of the patient's actual weight. Ideal weight was the preferable measure in the past but can cause overdosing of thin patients, and the patient's actual weight is now the preferred measure.[16] Record whether the patient is Asian as it increases the risk for peripheral retinopathy.[8] Perform a review of systems with specific questions about kidney and concurrent liver disease. A comprehensive medication review should emphasize the following concurrent medications: tamoxifen therapy increases the risk for retinal toxicity, antacids, and kaolin clay reduce the activity of CQ/HCQ, and the patient should take the medicines 4 hours apart. CQ/HCQ reduces ampicillin activity and increases cyclosporin activity. CQ/HCQ increases the risk of convulsions in patients taking mefloquine (another drug to treat malaria).[17] An ocular history should include specific questions regarding any pre-existing retinal disease. Ask questions regarding central acuity and whether the patient has noticed fading out of the region right next to fixation. Ask questions regarding the ability to focus on near objects and glare as well. One may use a questionnaire such as the systemic lupus erythematosus disease activity index to measure the effectivity of the therapy.[18] Ask questions about non-ocular side effects as well. Only two third of patients comply with therapy,[19] and most non-adherence to therapy are in patients under 80 kilograms in weight, likely because of an increased incidence of side effects. Common, nonocular, side effects of chloroquine and hydroxychloroquine include pruritus, headaches, dizziness, and gastrointestinal upset. Less frequent side effects include discoloration of the oral cavity, nails, skin and hair and rash. HCQ myopathy is uncommon and presents with proximal muscle weakness and rarely ventilatory failure. In these cases, a muscle biopsy can determine characteristic pathological findings.[20]

Vortex keratopathy (corneal verticillata) rarely causes vision complaints. In some advanced cases, patients may notice haloes and glare. The deposits occur within the sub-epithelium, do not stain, and are non-irritating. Verticillata appears as bilateral fine, golden-brown or gray opacities in the inferior cornea that branch out from a central whorl.[21]

Evaluation

Three reports from the American Academy of Ophthalmology (AAO) in 2002, 2011, and 2016 have provided clinicians with evidence-based guidelines for screening patients on CQ/HCQ therapy.[22] Baseline testing within the first year of starting therapy should include a dilated fundus exam to document pre-existing retinal pathology. While the latest recommendations do not require it, automated visual field (VF) testing and spectral domain optical coherence tomography (SD-OCT) are often done at this visit as well. Guidelines recommend a 10-2 threshold VF except for Asian patients where a wider angle test such as a 24-2 or 30-2 VF protocol will pick up the 50% that develop retinopathy outside the central 20 degrees of VF. Additional recommended screening tests include SD-OCT, fundus autofluorescence (FAF), and the most sensitive test of all, multifocal electroretinography (mf-ERG). For Asian patients, wide-field SD-OCT and FAF should be performed. Tests no longer recommended include baseline retinal photography, time-domain OCT, full-field ERG, electro-oculography, fluorescein angiography, color vision, and Amsler grid tests.

The guidelines recommend starting annual screening after 5 years unless additional risk factors are present that include small stature, obesity, liver or kidney disease, and retinal disease. In these cases, test on an annual basis from the start. Since mf-ERG, is the most sensitive test but not as readily available, some protocols recommend introducing it at a later stage.[22] These guidelines recommend doing SD-OCT/FAF and VF tests first and to introduce mf-ERG only when these tests suggest retinopathy.

Interpretation of results is:

- Visual field: defects are most likely to occur at 5 degrees from the center, except in Asian patients where the defect may be over 10 degrees from the center. Use statistical analysis to determine the significance of the data.
- SD-OCT: will reveal parafoveal thinning of the photoreceptor integrity line and the outer nuclear layer of the retina; this results in a "flattening" of the foveal depression and the "flying saucer sign" where the outer nuclear layer in the fovea's center is unaffected, and just around it this layer is much thinner (the edge of the saucer).
- FAF: reveals in early maculopathy, a ring of hyperfluorescence (caused by the accumulation of lipofuscin) and in later stages, a ring of hypofluoresence (caused by the loss of photoreceptor and retinal pigment epithelial layers).[23]
- mf-ERG: amplitude reduction is most common in ring 2, followed by ring 3, 4 and 1. Delayed implicit times are less common.[23]
- The dilated fundus exam: 2016 recommendations indicate that with better dosing guidelines and earlier detection, end-stage bull's eye maculopathy presents less often. However, the clinician should have familiarity with the fundus appearance of irregularity in the macular pigmentation in the early phase, a ring of macular pigment dropout in the advanced stage, and peripheral bone spicule formation, vascular attenuation, and optic disc pallor in the end-stage.

Treatment / Management

The clinician needs to be well-versed in the reasons to prescribe chloroquine and hydroxychloroquine and dosing recommendations to detect those patients at increased risk.

Chloroquine has a long history in the treatment of malaria caused by *Plasmodium vivax*, *ovale*, *malariae*, and *falciparum* in regions where *P. falciparum* has not developed resistance to it (mainly in North Africa). It also has utility in treating amebiasis, especially the extra-intestinal forms. For malaria prophylaxis in adults, start 500 mg CQ phosphate once a week from 2 weeks before until 8 weeks after travel to an endemic area. The adult dose for active infection of malaria is a total dose of 2500 mg divided over 3 days for patients over 60 kg and for those less than 60 kg, 41.7 mg/kilogram of divided over 3 days. Give patients with amebiasis a 1 gram loading dose for two days followed by 500 mg of CQ phosphate for 2-3 weeks. Chloroquine is often part of a multi-drug regimen with other anti-parasitic medications. A cumulative dose of over 460 g or a daily dose of 2.3 mg/kg body weight/day is high risk.[24][25] The latest studies show that using the patient's real weight instead of ideal weight correlates better with safe dosing. Chloroquine is rarely an option for rheumatic diseases over hydroxychloroquine.

HCQ treats rheumatic conditions as mentioned previously in this article. It also has utility in the treatment or prevention of malaria. For malaria prophylaxis in adults, start 400 mg HCQ once a week from 2 weeks before until 8 weeks after travel to an endemic area. The adult dose for the treatment of malaria is a total dose of 2000 mg divided over 3 days for patients over 60 kg and for those less than 60 kg, 25 mg/kilogram divided over 3 days. For rheumatic diseases, the most common dose is 400 mg per day. In 2016, the previous guideline to keep the daily dose of HCQ under 6.5 mg/kilogram of ideal bodyweight was adjusted to 5 mg/kilogram of the actual body weight to keep the risk of retinopathy within acceptable levels.

Previous guidelines using ideal weight protect short stature, obese patients, while the new guidelines using actual weight appear to protect short stature thin patients from receiving a dose

that is too high.[26] While overdose is a concern for maculopathy, it also results in poor medication compliance because of immediate side effects. Ask patients about common side effects of CQ/HCQ therapy that include pruritus, headaches, dizziness and gastrointestinal upset to detect those that are non-compliant and those that are receiving a dose that is too high. Non-compliance significantly increases the risk for morbidity from the disease the CQ/HCQ treats and several tools have been tested to improve compliance.[16] These tools include patient access to online blood results and web-based education.[27]

Convincing evidence of toxicity should result in the drug's discontinuation in consultation with the prescribing physician. Because of the long half-life of both drugs, retinopathy can continue for over 6 months, and studies have shown ongoing changes for up to 20 years after cessation of the drugs.[28] The goal is to detect early indications of retinal toxicity while the patient is still asymptomatic.

Differential Diagnosis

The differential diagnosis for CQ/HCQ vortex keratopathy (VK, also called corneal verticillata) includes:

- Sub-epithelial deposition of other medications: A good medical history should reveal the medication responsible. Amiodarone most commonly is the cause of vortex keratopathy, followed by CQ, HCQ, indomethacin, and phenothiazines. The appearance of the verticillata caused by these different medications is similar in appearance.[29]
- Fabry disease: Verticillata from Fabry disease is similar in appearance to those caused by medications. Fabry disease presents with retinal vessel tortuosity and cataracts as well. Other findings include pain of the extremities and angiokeratomas of the skin. Cardiovascular, renal and cerebrovascular disease are late manifestations.[30]
- Iron lines: Caused by iron deposition from the tear film into the basal epithelium layer.[31]
- Hudson Stahli line: Tends to be more linear and usually horizontal and at the junction of the lower one third and upper two-third of the cornea.
- Fleisher ring: This is present in moderate to advanced cases of keratoconus. The inferior portion of the ring may be present in less advanced cases and can be confused with VK.
- Corneal irregularity from refractive procedures such as radial keratotomy: The deposits are within the irregularities caused by the surgery (for example, within the radial keratotomy incisions).
- Stocker's line: The iron line is found next to the head of a pterygium.
- Ferry's line: The iron line is found next to a glaucoma filtering bleb.
- Gout: Uric acid crystal deposition in Bowman's membrane appears as a dust-like brown type of band keratopathy. In an early stage, it can be confused with VK.[32]
- Corneal chrysiasis: Caused by deposition of gold in the corneal stroma. A good medical history should reveal a history of treatment with intramuscular injections of gold salts. The deposition is more granular in appearance and more diffusely distributed throughout the surface of the cornea.[33]

The differential for CQ/HCQ retinopathy includes:

Age-related macular degeneration: Geographic atrophy (GA) in the absence of drusen and choroidal neovascularization and CQ/HCQ retinopathy can present similarly. Both present with thinning of the photoreceptor integrity line and the outer nuclear layer of the retina and atrophy of the choriocapillaris on SD-OCT.[34] However, GA does not appear in a parafoveal ring (bull's eye) pattern. Conversely, especially in Asian patients, CQ/HCQ retinopathy does not present in the typical bull's eye pattern either, and the clinician will need to use other clinical criteria to differentiate the two conditions. One study revealed that reticular drusen are visualized in all patients with GA by SD-OCT and FAF and their presence can be a valuable tool to differentiate GA from CQ/HCQ retinopathy [35] mf-ERG reveals a typical paracentral reduction in CQ/HCQ retinopathy that is not present in GA.

Central areolar choroidal dystrophy (CACD): CACD can appear in a bull's eye pattern. However, it develops between age 20-40 years old, usually too young of an age to have been on CQ/HCQ for over 20 years and to be at high risk of CQ/HCQ retinopathy. It progresses through 4 stages, each associated with characteristic retinal and choroidal findings. A speckled FAF pattern is present in 85% of patients with CACD and can be used to differentiate CACD from GA and CQ/HCQ retinopathy.[35]

Stargardt disease: Presence of irregular, pisciform, yellow flecks, at the RPE level in the macula with a possible extension into the periphery differentiates Stargardt disease from CQ/HCQ maculopathy. The commonest age of onset is in the 2nd decade of life; the classic "beaten bronze" appearance and positive genetic testing for the *ABCA4* mutation are additional ways to differentiate the two conditions. Finally, the classic "silent choroid" found in patients with Stargardt disease when tested with fluorescein angiography is not present in patients with CQ/HCQ retinopathy.[36] Conversely, a recent study of eight patients with Stargardt disease revealed an almost complete overlap of SD-OCT, FAF, mf-ERG, and fundus findings with CQ/HCQ retinopathy.[37]

Cone-rod dystrophy (CRD): CRD can present with bull's eye maculopathy. CRD occurs in childhood and causes loss of central vision and photophobia in the early stage, followed by central scotomas, loss of color vision, and peripheral vision. Night blindness is a present in the early stage. Photopic and scotopic ERG testing is precise in differentiating CRD from CQ/HCQ retinopathy.[38]

Benign concentric annular dystrophy (BCAD): This rare disorder is characterized by a bull's eye macular pigmentary change while visual acuity is well-preserved.[39]

Prognosis

When the clinician that detects early retinopathy does not discontinue CQ/HCQ therapy, the prognosis is a progressive loss of paracentral vision followed by loss of central vision and night blindness. Even when the clinician discontinues therapy, retinopathy can progress for many years. Progression of vortex keratopathy (VK) causes increasing haloes and blur but is fully reversible upon discontinuation of therapy.

Complications

Even when the clinician and patient adhere to screening guidelines and retinopathy is detected in a sub-clinical stage, discontinuation of chloroquine or hydroxychloroquine therapy may not stop the progression of retinopathy to a stage where the patient loses vision.

Deterrence and Patient Education

As discussed in previous sections, a thorough knowledge of the latest screening guidelines, last amended in 2016, and clear communication on the risks and benefits of CQ/HCQ therapy are essential in reducing toxicity while maintaining the extensive benefits of CQ/HCQ treatment of certain parasitic and rheumatic diseases.

Enhancing Healthcare Team Outcomes

To reduce the incidence of chloroquine and hydroxychloroquine toxicity, health care providers (HCP's) that prescribe these medications and those that screen for ocular toxicity have developed clear dosing and screening protocols that have reduced the risk of end-stage disease; bull's eye maculopathy and central vision loss (Level I).

The best approach to maintaining excellent patient care and minimizing risk is a team approach involving nurses, nurse practitioners, physician assistants, and physicians. [Level V]

Questions

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