

The Royal College of Ophthalmologists



Hydroxychloroquine and Ocular Toxicity Recommendations on Screening

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Hydroxychloroquine and Ocular Toxicity
Recommendations on Screening
(Replacing the Royal College of Ophthalmologists Guidelines for Screening 2004
and 1998)

Background

Hydroxychloroquine is a quinolone used primarily by rheumatologists for rheumatoid arthritis and systemic lupus erythematosus, and by dermatologists for cutaneous lupus. Although its mechanism of action is not fully understood, it is thought to increase pH within intracellular vacuoles, which probably interferes with antigen processing in macrophages and other antigen-presenting cells, thereby down-regulating the immune response against auto-antigenic peptides¹. **Chloroquine** works in a similar way and is used for similar clinical indications although much less frequently. Its use in the prophylaxis and treatment of malaria is diminishing because of widespread resistance.

Systemic side effects of hydroxychloroquine and chloroquine include disturbances in hepatic and renal function. Ocular side effects include retinal toxicity (which can lead to permanent visual impairment) and deposition of the drug in the cornea. The mechanism of retinal toxicity is not well understood, though it appears that the earliest changes occur in the cytoplasm of ganglion cells and photoreceptors with later involvement of the retinal pigment epithelium², where it binds to melanin. Hydroxychloroquine has been used since the 1960s, and although it appears to be considerably less toxic to the retina than chloroquine, possibly because chloroquine crosses the blood-retinal barrier more easily³, a similar pattern of retinopathy has been observed with both drugs.

The incidence of clinically significant hydroxychloroquine retinopathy appears to be very low with only 50 cases identified in a literature review to May 2005⁴ and it has been estimated that at least one million patients have been treated with quinolones during the same time period⁵. In the largest single series, one patient out of 1207 developed retinopathy after 7 years⁶. In a prospective study of patients taking within the maximum recommended dose of 6.5mg per kg of lean body weight⁷, the incidence of irreversible hydroxychloroquine retinopathy was 2 cases in 400 patients, both of whom received treatment for over 6 years. Maximum daily dosage and duration of treatment appear to be more important determinants of the risk of toxicity than cumulative dosage^{6,9}

The risk of retinal toxicity with chloroquine appears to be significantly higher than with hydroxychloroquine, and the safe daily dose and cumulative dose is less clear^{6,7}. For this reason, chloroquine should only be considered if other drugs have failed to control the disease adequately. It is recommended that all patients taking chloroquine should be counselled on the risk of central visual field loss and ophthalmic examination should be arranged locally between the prescribing physician and the ophthalmologist.

Clinical features of ocular complications

Quinolones can precipitate in the corneal epithelium in a diffuse punctate or whorl-like pattern which can sometimes result in visual haloes. This is much less common with hydroxychloroquine than with chloroquine^{4,8}. The effect is reversible on stopping the drug.

The earliest sign of retinal toxicity is fine pigmentary stippling of the macula and loss of the foveal light reflex, sometimes referred to as premaculopathy. This may progress to the development of an annular zone of depigmentation of the retinal pigment epithelium surrounding the fovea ("bulls-eye" maculopathy) with a corresponding perifoveal visual field defect. If treatment continues, the pigment epithelial atrophy may become generalised with loss of visual acuity and peripheral visual field loss⁵. Even if treatment is stopped, areas of pigment epithelial atrophy may continue to increase for a time before stabilising⁷.

The appearances of premaculopathy and "bulls-eye" maculopathy are not specific to quinolone toxicity and can be seen in the "dry" form of age-related macular degeneration and in a number of retinal dystrophies.

Early detection of hydroxychloroquine retinopathy

By the time pigmentary changes at the macula are visible ophthalmoscopically, it is almost certain that some degree of irreversible damage will already have occurred. There has been considerable interest, therefore, as to whether it is possible to detect subtle effects of toxicity at a reversible stage.

Static perimetry of the central 10 degrees of vision (for instance the Humphrey 10:2 protocol) can detect small paracentral visual field defects, but is fairly time consuming to perform, is not widely available outside hospital eye clinics and it is a demanding test which depends on the subject maintaining steady fixation and concentration.

The Amsler Chart is a grid of squares printed on paper with a central fixation dot. It is viewed monocularly at 30cm (with reading glasses if required) and a visual field defect within the central few degrees of vision may be seen as a blank or distorted area superimposed on the grid, where it can be plotted. The attraction of the test is that it is cheap to perform and can easily be self-administered. The most commonly used Amsler chart is a black grid printed on white paper, but a red grid printed on black paper is also available and may be more sensitive. One study reported that 25 of a sample of 56 patients taking hydroxychloroquine had one or more detectable scotomata when viewing the Amsler chart under conditions of reduced illumination using cross-polarizing filters (of which 5 were detected with the red Amsler chart and 2 with the standard Amsler chart)¹⁰. However, it is not clear whether these apparent field defects were reproducible by other means or whether any progression of the field defects occurred subsequently, and there was no estimate of the specificity of the test¹¹.

Multifocal electroretinography (mfERG) involves the projection of an array of hexagonal light sources onto the retina. Each hexagon flashes on and off independently of the others in a pseudo-random binary sequence and the electroretinographic signal from the area of the retina stimulated by each hexagon is extracted by the mathematical technique of kernel analysis. In a cohort of 12 patients receiving hydroxychloroquine, mildly reduced mean mfERG amplitudes were found when compared to age-matched controls. Three patients who stopped treatment appeared to show some recovery in responses.¹² However, no patient had clinical evidence of maculopathy and the reduction in mfERG responses was small in comparison to the inter-test variability of the mfERG¹³. It has not yet been established whether changes in the mfERG predict the development of clinically significant hydroxychloroquine retinopathy.

The property of lipofuscin in the retinal pigment epithelium to fluoresce when stimulated with monochromatic light at a wavelength of 488nm is used in the technique of fundus autofluorescence (FAF) imaging. The fundus is imaged with a scanning laser ophthalmoscope through a barrier filter which blocks wavelengths below 495nm. FAF provides an indirect measure of the activity of the photoreceptors and the retinal pigment epithelium. A cohort of 25 patients on long term quinolones was examined using FAF. 10 of 19 patients taking chloroquine for 2-20 years had abnormalities of FAF, whereas 6 patients taking hydroxychloroquine for 1.3-19 years all had normal FAF appearances¹⁴, providing additional evidence that hydroxychloroquine is safer than chloroquine.

Is there a case for systematic screening for ocular toxicity?

To justify a systematic programme of screening for hydroxychloroquine toxicity, it is necessary to demonstrate:

1. That there is a causal relationship between the drug and the adverse effect
2. That a test or a combination of tests is capable of detecting toxicity at a reversible stage with acceptable levels of sensitivity and specificity
3. That an intervention (e.g. stopping the drug) prevents the development of irreversible retinal damage
4. That the process of screening is acceptable to patients and that the benefits of screening outweigh any risks.

If all four conditions are met, it is also necessary to introduce an economic evaluation (the cost of one case of visual loss prevented). Possible risks of screening include causing unnecessary anxiety to patients, a burden of unnecessary appointments on the health economy and lost opportunity to benefit from treatment for patients incorrectly identified as being at risk¹⁵.

Although the reviewing group accepts that there is a link between hydroxychloroquine use and retinal toxicity, it does not believe that the available evidence supports the introduction of a programme of systematic screening for hydroxychloroquine toxicity at the present time because clinically significant maculopathy is very rare and there is currently no reliable test for detecting it at a reversible stage.

Recommendations for good practice in rheumatology and dermatology clinics

- The maximum dosage of hydroxychloroquine should not exceed 6.5mg / kg lean body weight (typically 200-400 mg daily); if the patient is overweight, check lean body weight with a body mass index calculator.
- Establish renal and liver function at baseline assessment
- Enquire about any visual impairment which is not corrected with spectacles (at baseline and at annual review)
- Record reading performance with each eye with a reading spectacle correction if worn, using a near vision test type, at baseline and at annual review (see Appendix 1).
- If the patient can read a small print size such as N8 or N6 at baseline assessment, treatment with hydroxychloroquine can be commenced.

Although the use of Amsler Charts has not been validated in rheumatology and dermatology clinics, the specimen patient information chart in Appendix 2 contains instructions for self-administration of the Amsler test and the patient may be issued with the instructions and an Amsler Chart (either black on white or red on black).

If visual impairment is suspected, the patient should be advised to consult an optometrist in the first instance. If any apparent impairment is correctable with refraction, treatment may then commence. Any relevant abnormality detected by the optometrist would be referred to an ophthalmologist in the usual way.

Referral to an ophthalmologist

This is appropriate if any patient:

- Has visual impairment or eye disease detected at baseline assessment (confirmed by an optometrist). It should be noted that in elderly patients there is often coincidental ocular morbidity from cataract, glaucoma and age-related maculopathy.
- Notices reduced vision (particularly for reading), patchy central vision or distorted central vision whilst on treatment. Patients should be warned to seek advice from the prescriber (as abrupt withdrawal of treatment may provoke a flare-up of their inflammatory disease) and to have their vision checked by an optometrist.

Although quinolones are not licensed for children, they are used in specialist units particularly in the management of juvenile idiopathic arthritis, systemic lupus erythematosus and fibrosing alveolitis. Some of these children will already be attending an ophthalmologist for monitoring for the development of uveitis. Little is known about ocular toxicity of hydroxychloroquine in children, and it is recommended that locally agreed protocols should be established between the prescriber and ophthalmologist for such children.

Examination by the ophthalmologist

The assessment should include:

- Enquiry about any disturbance of central vision
- Visual acuity and reading acuity
- Central visual field, using an Amsler Chart (preferably red on black) or automated perimetry (e.g. Humphrey 10-2 protocol).
- Slit lamp examination of the cornea
- Stereoscopic slit lamp examination of the retina (e.g. with a 90D or 78 biconvex lens)

Evaluation may need to be extended according to signs and symptoms to include retinal photography, ocular coherence tomography (OCT), fundus autofluorescence (FAF) imaging and visual electrophysiological tests.

Subsequent examinations should be at the discretion of the ophthalmologist, but indefinite follow up is not likely to be required for most patients. For patients who have received continuous treatment for more than 5 years, an individual arrangement should be agreed with the local ophthalmologist.

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Conflicts of interest

None declared.

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Appendix 1. Reading Chart

READING CHART

Use the texts below to test each eye separately with glasses when appropriate. Record the smallest text that can be read at a distance most comfortable to the patient

N.8

He moved forward a few steps: the house was so dark behind him, the world so dim and uncertain in front of him, that for a moment his heart failed him. He might have to search the whole garden for the dog.

N.10

The camp stood where, until quite lately, had been pasture and ploughland; the farm house still stood in a fold of the hill and had served us for battalion offices; ivy still supported part of what had once been the walls of a fruit garden;

N.12

And another image came to me, of an arctic hut and a trapper alone with his furs and oil lamp and log fire; the remains of supper on the table, a few books, skis in the corner;

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Appendix 2 Information for patients taking hydroxychloroquine

Hydroxychloroquine is used to treat a number of conditions which cause inflammation of the skin, joints or soft tissues. It has been used in a very large number of people since the 1960s and has a very good safety record.

It can very occasionally cause problems with the vision, which usually take the form of small areas of reduced vision or distortion near the centre of the vision. This is a very rare side effect of the drug, but where it has occurred, the effects have usually been permanent. It is extremely rare for a problem with the vision to occur in people who have been taking hydroxychloroquine for less than 5 years.

If you suspect that hydroxychloroquine is starting to cause problems with your vision, you should first of all ask for advice from the doctor who is treating you with the drug. It may be necessary to stop hydroxychloroquine, but you may need to start an alternative treatment to prevent the condition for which you are being treated from flaring up. You should also consult an optometrist (optician) who will be able to check that there is not another explanation for the problems you have noticed with your vision. The optician may recommend that you see an ophthalmologist (eye doctor) if further tests are required.

You can monitor your vision yourself at home. Any problems caused by hydroxychloroquine may be apparent when you read newspaper print – for instance by causing patches of print near the print you are actually reading to go missing.

You may be issued with a special chart called an Amsler Chart with which to test your vision. The Amsler Chart is a grid of squares with a dot at the centre printed on a piece of paper. You should hold this at a comfortable reading distance (about 30cm or 1 foot) and view it with your reading glasses (if you wear any), testing one eye at a time. You should look steadily at the dot in the centre of the chart. When you do this, if the squares around the central dot appear even with no patches missing, all is well. You should test each eye about once every month.

If you notice a change in your vision using either of these tests, you should repeat the test a few days later and if there is still a problem, report it to the doctor who is treating the condition for which you are taking hydroxychloroquine and arrange a sight test with your optician.

Remember, it is very unlikely that you will experience an eye problem with hydroxychloroquine and even if you do experience an eye problem while you are taking it, it is much more likely that there will be another explanation for it.