Visual function and long-term chloroquine treatment

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Abstract **Ophthalmic examinations and selected tests of visual function were performed on 64 patients with rheumatoid arthritis who had received daily doses of 200 mg chloroquine sulphate for periods ranging from 3 to 11 months. Visual fields were determined by Humphrey automated perimetry and Amsler grids and a further battery of four tests of macular function (visual evoked potentials, critical flicker fusion threshold, Cambridge contrast sensitivity and the macular dazzle test) were administered. No case of retinal pigmentary abnormalities plus visual loss was found, but 2 patients were advised to cease chloroquine therapy on the basis of funduscopic findings. A small group of patients with relatively poor scores on one or more tests had normal visual fields and ophthalmic findings. There were no significant partial correlations between test results and the cumulative dose of chloroquine. These results support the opinion that currently recommended doses of chloroquine pose a minimal risk of retinal toxicity.**

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Chloroquine and its derivatives are being used increasingly in the treatment of connective tissue diseases.[1] Ocular side-effects of prolonged chloroquine use, especially corneal deposits, which are generally associated with either no or only minor visual symptoms, are common. Diplopia and defects in convergence and accommodation may occasionally be reported. However, the risk of serious retinal disease and visual deficits, even if these are very infrequent,[2] is of paramount importance.

Various tests have been suggested as potential markers of impending retinal dysfunction and their application may permit the withdrawal of chloroquine before permanent damage is caused.[3] While the Amsler grid has been advocated as an ideal screening test,[4] some other relatively easily administered tests have not been evaluated thoroughly.

This study involved the screening of rheumatoid arthritis patients for retinal toxicity by detailed ophthalmological examinations and assessment of visual fields and colour vision. In addition, a battery of selected tests of macular function was administered.

Patients and methods

Patients with rheumatoid arthritis were referred by one of two physicians. Sixty-four patients who complied with the physical requirements of the test battery were entered into the study. All were receiving daily doses of 200 mg chloroquine sulphate, and most took additional medication. The patients ranged in age from 12 to 73 years and there were 15 males and 49 females.

Clinical information regarding diagnosis, duration and extent of disease, and medication was provided by the referring physician.

A detailed ophthalmic examination was performed on each patient according to protocol and the findings were classified into five categories: refraction, eye motility, pupil reactions, slit-lamp microscopy and funduscopy. Colour vision was assessed by the first 15 plates

of the Ishihara Colour Blindness Test. Visual fields were determined for each eye by means of a Humphrey automated perimeter, using the 10 - 2 white programme, and by Amsler grids.

A further battery of specialised laboratory tests included:

1. Pattern reversal visual evoked potentials (VEPs), elicited by reversing a checkerboard pattern at a rate of 1,9 stimuli per second on a television monitor with a field size of 15° × 12° (individual squares subtended 28′ of arc). Monocular stimulation was used and the major P100 potential recorded from a mid-occipital to a mid-frontal electrode derivation was assessed.

2. Critical flicker fusion frequency for each eye, using an apparatus consisting of red light emitting diodes seen through an artificial pupil in Maxwellian view at optical infinity. Flicker threshold was determined by a computer-based system using a combination of the method of limits and a two-alternative forced-choice strategy.

3. Contrast sensitivity for each eye, by means of the Cambridge Low Contrast Gratings.

4. Macular dazzle (photostress), by directing the light of a direct ophthalmoscope, from a distance of 3 cm, through undilated pupils at each macula for 10 seconds and recording the time to the recovery of pretest visual acuity.

The clinical findings were coded for analysis. Test results were correlated with the duration of chloroquine therapy after correcting for age.

Results

The duration of therapy at the time of testing ranged from 3 to 111 months. The total cumulative dose of chloroquine ranged from 18 to 671 g, with a group mean of 136 g.

Eye motility and pupillary reactions were normal in all patients. Findings on slit-lamp microscopy of the cornea, anterior chamber, vitreous humour and iris were normal in 95% of patients. Lens abnormalities consisting of cataracts were present in 14%.

Findings on funduscopic examination of the maculae were normal in 91% of patients. In 2 patients pigmentary changes suggestive of chloroquine toxicity were encountered; the cumulative chloroquine doses in these cases were 90 and 126 g. These patients were advised to stop chloroquine therapy. A further 3 patients had macular changes unrelated to the clinical appearance of chloroquine maculopathy — 2 had unilateral pigmentary changes, and a further patient had bilateral drusen and a small haemorrhage in the right fovea.

Visual acuity was 6/12 or better in 97% of patients and cataracts accounted for the reduced visual acuity.

Colour vision was normal in 61 of 63 patients; 2 had red-green colour blindness.

Visual fields as determined on Amsler grids were normal in 59 of 64 patients and the findings were unreliable in 1. A bilateral abnormality consisting of faded or missing squares is regarded as particularly important for assessing the side-effects of chloroquine[4] and was detected in 2 patients; 1 of them had bilateral cataracts, while the other had normal ophthalmic findings. Both patients had normal results on Humphrey perimeter and colour vision testing. A further 2 patients had unilateral Amsler grid abnormalities.

The findings of the specialised tests of visual function are summarised in Table I and the correlations between test performance and the duration of chloroquine therapy in Table II.

TABLE I.
Results of selected specialised tests of macular function (mean ± SD)

Test	Variable	Eye tested	Result
VEPs	Latency of P100 (ms)	Right	97,6 ± 5,8
		Left	98,5 ± 6,2
	Amplitude of P100 (μV)	Right	5,6 ± 2,3
		Left	5,2 ± 2,2
Critical flicker fusion	Frequency (Hz)	Right	26,5 ± 3,5
		Left	27,2 ± 3,8
Cambridge contrast sensitivity	Contrast score	Right	208,6 ± 113,2
		Left	206,2 ± 105,0
Macular dazzle	Score (s)	Right	44,8 ± 36,5
		Left	45,5 ± 34,6

TABLE II.
Partial correlation coefficients between the cumulative dose of chloroquine and scores on various tests of visual function.*

Test	Variable	r†	P
VEPs	Mean latency of P100	–0,092	0,47
	Maximum latency of P100	–0,106	0,40
	Mean amplitude of P100	0,004	0,97
	Minimum amplitude of P100	–0,017	0,89
Critical flicker fusion	Mean frequency	–0,123	0,34
	Minimum frequency	–0,176	0,17
Cambridge contrast sensitivity	Mean contrast score	–0,044	0,73
	Minimum contrast score	–0,106	0,41
Macular dazzle	Mean score	–0,035	0,78
	Maximum score	–0,04	0,69

* The mean scores derived from scores for the right and left eyes tested separately and the worst score (maximum or minimum as appropriate) for either eye were considered.
† Partial correlation between the cumulative dose of chloroquine and test score after correcting for age.

Patients with relatively poor performance in the VEP, critical flicker fusion and macular dazzle tests were identified using a criterion of 2 or more standard deviations above or below the group mean score for both eyes, as appropriate. Owing to high variability in the contrast sensitivity scores, an arbitrary cut-off of 100 or less points bilaterally was used. These findings appear in Table III. Within patients, relatively poor scores were isolated and, furthermore, there was no association between these scores and the cumulative dose of chloroquine.

Discussion

This study showed that retinal pigmentary changes plus visual field defects were not associated with chloroquine toxicity, a finding which is not surprising in view of the relatively low doses involved.[2]

After commencement of this study it became apparent that red stimuli, and not white as we used, are optimal in the Humphrey automated perimeter.[4] However, it is unlikely that field defects were missed, since the Amsler grids appear to have a higher sensitivity than kinetic and static field testing.[4]

The Amsler grids were bilaterally abnormal in 2 patients with normal ophthalmological findings and unexceptional results on the other tests of visual functioning. Findings on computerised perimetry in these

TABLE III.
Findings in patients with relatively poor scores bilaterally on certain tests*

Patient No.	VEPs	CFFT	MD	CCS	AG	HAP	IT	FR	CDC
3	–	+	–	–	–	–	–	–	102
4	–	–	–	+	–	–	–	–	84
23	–	–	–	–	+	–	–	–	156
35	–	–	–	–	+	–	–	–	90
38	–	–	–	–	–	–	+	+	90
40	–	–	–	–	–	–	–	+	126
41	+	–	–	–	–	–	–	–	150
47	–	–	+	–	–	–	–	–	72
59	–	–	+	+	–	–	+	–	140

*Poor scores (+) on VEPs, critical flicker fusion threshold (CFFT), macular dazzle (MD) and Cambridge contrast sensitivity (CCS) are indicated; + also indicates bilateral Amsler grid (AG) abnormalities, and abnormalities on Humphrey automated perimetry (HAP) and Ishihara tests for colour blindness (IT), and fundoscopic findings suggestive of retinal chloroquine toxicity (FR). The cumulative dose of chloroquine (CDC) (in grams) is given for each patient with relatively poor test scores. The group mean cumulative chloroquine dose was 136 g.

cases were normal. The sensitivity of the Amsler grid has been established, and its use in patients on long-term chloroquine therapy is strongly advocated because it is also inexpensive and can be self-administered by the patient.[5] However, false-negative findings in the presence of suggestive macular pigmentary changes and central field defects have been reported.[6]

The 2 patients with retinal pigmentary changes suggestive of chloroquine toxicity had no signs of visual disturbance apart from red-green colour blindness in 1 case. However, it was recommended by the ophthalmologist that chloroquine should be withdrawn as a safety precaution.

The other specialised tests of visual functioning did not correlate significantly with the duration of chloroquine therapy, and retinal findings in the 2 cases in which these suggested chloroquine toxicity were unexceptional. The few patients with relatively poor test scores tended to have isolated positive findings for one test only and no ophthalmic and/or visual field abnormalities compatible with chloroquine toxicity. One patient with markedly prolonged macular dazzle times also had poor contrast sensitivity scores and a colour vision deficit. However, the visual field, visual acuity and findings on ophthalmic examination were normal. The role of these tests in the routine assessment of patients using chloroquine is questionable without further evidence.

Apart from the various visual field tests, other specialised tests of visual function have not found a place in the routine evaluation of patients for possible chloroquine toxicity. Contrast sensitivity has been reported as being superior to VEPs and to the electro-oculogram in the detection of macular dysfunction.[7] These positive findings occurred in patients with normal clinical results and were not assessed relative to visual fields. False-positive results were also noted. In some cases contrast sensitivity was markedly reduced in patients with normal visual fields and normal ophthalmic findings.

The critical flicker fusion threshold has been advocated as a potential predictor of retinal toxicity.[8] Our patients with relatively low thresholds had normal visual fields and ophthalmological findings. This also applied to patients with unusually prolonged macular dazzle times. It has been reported that dazzle times are often longer in patients taking chloroquine than in controls; however, in patients with early chloroquine retinopathy they were no longer than in patients without retinopathy.[4]

Findings of reduced macular function in specialised tests of vision, in the absence of positive visual field and clinical results, do not at present seem to warrant discontinuation of chloroquine therapy. Even early, small, relative scotomas are not necessarily regarded as absolute indications for its cessation.[4]

The results of this study are compatible with the opinion that doses of chloroquine currently advocated for patients with connective tissue disease pose a minimal risk of retinal toxicity. A baseline ocular examination followed by annual examinations is regarded as sufficient to detect reversible retinal disease before visual loss.[2] The inexpensive and easily self-administered Amsler grid could be offered to patients as an additional precaution. This test has been modified to improve its reliability and sensitivity,[9] and its self-administration every 2 weeks has been strongly advocated.[4] Another group considers screening for retinal toxicity unnecessary when hydroxychloroquine is prescribed according to body mass after a circumscribed baseline ophthalmic examination.[10]

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