Immediate therapy was commenced with a standard acute angle closure glaucoma treatment regimen. IOPs were normalised by the next day and YAG laser peripheral iridotomies were performed. She made a full visual recovery to 6/6 in each eye. The venlafaxine was discontinued.

Discussion

Venlafaxine is a new class of SSRI, which is a potent inhibitor of serotonin and, to a lesser extent, of noradrenaline reuptake. It is widely used in the treatment of depression and has become widely accepted as a treatment for IBS by modulating central and peripheral sensory mechanisms and by reducing depression, which may be an aetiological factor.[1]

There has been a previous report of increase in pressure with chronic narrow angle glaucoma and venlafaxine.[2] We also note a report of nonsimultaneous bilateral acute angle closure glaucoma with venlafaxine treatment,[3] although the causative link is weak as the patient developed the closure many days after treatment began and there was intervening orbital trauma. In addition, the patient was commenced with other drugs, including chlorpromazine, which is known to cause angle closure by anticholinergic effects.[4]

Although SSRIs have been implicated in long-term IOP rise,[5] the very dramatic bilateral pressure rise so soon after treatment with venlafaxine is likely to implicate a mydriatic aetiology in this event. Animal studies have shown that SSRIs induce mydriasis by acting through central mechanisms.[6,7]

Acute angle closure glaucoma has been reported with older SSRIs such as paroxetine occurring 2 weeks[8] and 1 day[9] after commencing therapy. Although a serotoninergic mechanism for increase in pressure over the longer term has been postulated,[10] it was thought that cases of acute glaucoma were due to the weak anticholinergic effects of paroxetine.[11]

Venlafaxine does not have anticholinergic effects and as such may strengthen the premise of a seratoninergic aetiology for acute angle closure reported with older SSRIs.[8,9] Alternatively, the weak adrenergic effect of this medication may well be responsible.

While the exact mechanism of precipitation of acute angle closure remains unclear, awareness among ophthalmologists and physicians prescribing these drugs must be raised.

References

1 Tally NJ. SSRIs in IBS: sensing a dash of disappointment. *Clin Gastroenterol Hepatol* 2003; **1**(3): 155–159.
2 Aragona M, Inghilleri M. Increased ocular pressures in two patients with narrow angle glaucoma treated with venlafaxine. *Clin Neuropharmacol* 1998; **12**(2): 130–131.
3 Ng B, Sanbrook GM, Malouf AJ, Agarwal SA. Venlafaxine and bilateral acute angle closure glaucoma. *Med J Aust* 2002; **176**(5): 241.
4 Rennie IG. Clinically important ocular reactions to systemic drug therapy. *Drug Saf* 1993; **9**(3): 196–211.
5 Costagliola C, Parmeggiani F, Sebastiani A. SSRIs and intraocular pressure modifications: evidence, implications and possible mechanisms. *CNS drugs* 2004; **18**(8): 475–484.
6 Osborn NN. Serotonin and melatonin in the iris/cilliary processes and their involvement in intraocular pressure. *Acta Neurobiol Exp* 1994; **54**: 57–64.
7 Yu Y, Ramage AG, Koss MC. Pharmacological studies of 8-OH-DPAT induced pupillary dilatation in anaesthetised rats. *Eur J Pharmacol* 2004; **489**(3): 207–213.
8 Eke T, Bates AK, Carr S. Angle closure Glaucoma associated with paroxetine. *BMJ* 1997; **314**: 1387.
9 Kirwan JF, Subak-sharpe I, Teimory M. Bilateral acute angle closure glaucoma after administration of paroxetine. *Br J Ophthalmol*. 1997; **81**(3): 252.
10 Eke T, Carr S. Acute glaucoma, chronic glaucoma and serotoninergic drugs. *Br J Ophthalmol* 1998; **82**: 976.
11 Kirwan JF, Stephens JP. Acute glaucoma, chronic glaucoma and serotoninergic drugs. *Br J Ophthalmol* 1998; **82**: 976.

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Eye (2006) **20,** 128–129. doi:10.1038/sj.eye.6701815; published online 4 March 2005

Sir,

Abnormalities on the multifocal electroretingram may precede clinical signs of hydroxychloroquine retinotoxicity

Hydroxychloroquine is a widely used and effective antirheumatic drug since its production in 1940s, especially for systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Retinotoxicity as a side effect is well known despite concerted efforts by physicians and ophthalmologists in monitoring these patients.[1–6] The estimated risk of macular toxicity in patients on chronic hydroxychloroquine has been estimated to be less than 0.5%,[7] although Bernstein reports that incidence can be as high as 3–4% in

unmonitored patients.[8] Various recommendations have emerged in an attempt to reduce the risk of this irreversible complication. Most authors recommend 6 monthly to annual screening including symptomatology questioning, visual acuity, Amsler chart, and colour testing in addition to full ocular examination.[8–11] However, as our case clearly demonstrates, significant perimetric abnormalities can occur despite regular monitoring of these parameters. We report a case of asymptomatic hydroxychloroquine retinotoxicity diagnosed on multifocal electroretinogram (mfERG).

Case report

A 50-year-old lady of small stature (height 1.50 m, body weight 52.4 kg) with seronegative rheumatoid arthritis was treated with hydroxychloroquine since 1992. She was screened regularly by an ophthalmologist annually since 1993 with no retinotoxicity detected clinically. A reliable automated perimetry (Humphrey 24-2) performed in 1999 was normal.

She had no ocular symptoms throughout her 11 years therapy. She had no blurring of vision, metamorphopsia, or visual field abnormalities. On examination, there were no corneal verticillata and dilated fundi examination were normal. Red amsler chart (no. 4), Ishihara pseudoisochromatic chart, and Farnsworth D15 colour testing were all normal. Repeated automated perimetry revealed bilateral symmetrical superior and inferior concentric ring scotomata within central 10° (Figure 1). Intraocular pressures were 12 mmHg and optic discs were healthy.

Further colour assessment with standard pseudoisochromatic plates (part 2) (SPP2) showed early blue-yellow and red-green deficiencies, which were duplicated on the Hardy-Rand-Rittler (HRR) pseudoisochromatic plates. Fundal fluorescein angiogram (FFA) was normal. Optical coherence tomography (OCT) of the maculae showed normal foveal and parafoveal thickness.

Ganzfeld full-field electroretinography (ERG) showed an unrecordable scotopic dim flash response, while the photopic transient response showed reduced amplitudes of a- and particularly b-waves, with delayed b-wave implicit time (Table 1). The multifocal ERG (mfERG) showed retention of foveal responses from both eyes, but a parafoveal ring of diminished and delayed P1 responses, classic of a bull's eye pattern of macular dysfunction. There was also widespread rod and cone dysfunction (Figure 2) consistent with hydroxychloroquine retinotoxicity.

mfERG was performed to ISCEV standards and recorded using the Veris II program designed by Sutter and co-workers.[12] A 103-hexagon stimulus array that covered an estimated $36^\circ \times 50^\circ$ field on a 17-in cathode-ray tube (CRT) monitor (multiscan Sony 17 SE) was used. Maximum and minimum luminances were 100 and 2 cd/m^2, respectively; contrast was 96%. Signal amplification was 100 000 and filter setting was bandpass 10–300 Hz.Recording was performed with full pupillary dilation by one drop of phenylephrine hydrochloride 2.5% and cyclopentolate hydrochloride 1%. Topical anaesthesia (two drops of proparacaine hydrochloride 0.5%) was administered prior to insertion of a Burian-Allen bipolar contact lens electrode. A silver–silver chloride ground electrode was attached to the left ear lobe. Only one eye was recorded at a time, and the other eye was occluded for the duration of the test. Refractive errors were optically corrected to achieve the best visual acuity in each case, and black cross extending about 25° was placed in the centre of the screen as a point of

Table 1 ISCEV standard full-field photopic ERG findings

	OD	*OS*	*Normal mean (limit)*
a-Amplitude	18.4	25.0	44.4 (27.1) μV
b-Amplitude	30.8	26.6	141.8 (85.6) μV
b-Implicit	38	35	30.0 (34.0) ms

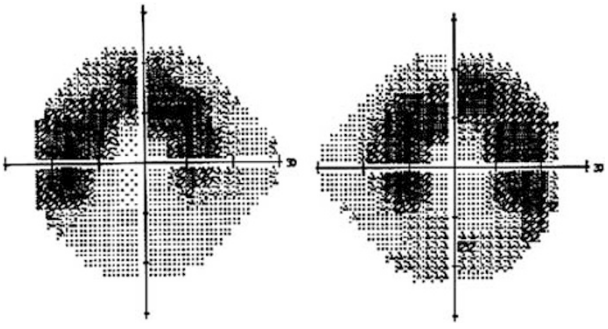

Figure 1 Bilateral symmetrical superior and inferior concentric ring scotomata within central 10°.

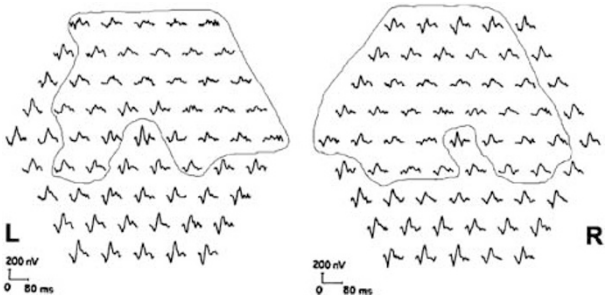

Figure 2 Trace analysis of mfERG showing areas of reduced amplitudes and latencies in a bull's-eye pattern.

fixation during the test. Recording was conducted in eight segments of 54 s each, making up a total recording time of 7.2 min per eye.

The amount of noise contaminating the recordings was reduced by careful explanation of the test to subjects in order to increase the level of cooperation, observation of the real-time wave-forms captured on screen during recording and discarding segments that contained considerable artefacts generated by saccadic eye movements, and the use of the artefact rejection technique.In our study, we examined only the first-order kernel of the mfERG, the the largest component of the standard flicker. Analysis of amplitudes and implicit times of the N (corneal negative) and P (corneal positive) waves were performed by comparing waves in each zone with those from corresponding zones in age-matched normal subjects.

Hydroxychloroquine was discontinued immediately. She was monitored for retinotoxicity progression at 3-monthly intervals with automated perimetry and electrophysiological testing. At 6 months after diagnosis, there has been no progression of the visual field defect or worsening of vision.

Discussion

To date, the most significant risk factor for retinotoxicity accepted widely by ophthalmologists has been the dose per body weight per day, rather than cumulative dosage. Although there have been no randomized controlled studies, from various large observational case series, it is accepted that the risk of retinotoxicity is low at dosages of <6.5 mg/kg/day.[9–11,13] Other systemic risk factors include impaired renal and/or liver function and pre-existing macular disease. However, in the absence of any medical problems, the duration of use and the stature of the patient (namely small *vs* obese) are of significance as well.

Our patient showed significant depression of rod and cone function demonstrated on full-field ERG. This implies that there was widespread effect on photoreceptor function (both rods and cones) extending well beyond the macula. As this disease has a slow insidious progression, we feel that the onset of retinotoxicity occurred well before clinically visible changes were seen, and antecedent to documentation of ring-scotomata on perimtetry. We feel that this represents a preclinical stage of retinotoxicity that occurs prior to the onset of symptoms. This demonstrates that a patient on appropriate dosing and no systemic risk factors can develop retinotoxicity way before the 'safety limit' of 10 years in contrast to recommendations by Bernstein[8] and Mackenzie.[14] Bienfang and Mavrikakis also reported retinotoxicity occurring as early as 6 years in patients with no systemic risk factors.[2,5]

Over 11 years, our patient had consumed a total dose of 3039 g of hydroxychloroquine. The computed approximate daily dose was 3.91 mg/kg, which was well within current accepted recommendations. Despite this 'low' and appropriate dosing coupled with regular screening with Ishihara colour testing, automated perimetry, Amsler monitoring, and thorough eye examination including dilated fundi examinations, retinotoxicity still occurred. There is thus a need to re-evaluate our current screening strategies with a view to identify early, subclinical macular toxicity.

It is well known that by the time symptoms appear, clinical macular retinotoxicity is irreversible. Visual acuity, colour acuity, field defects, and clinical bull's-eye maculopathy is permanent once it occurs and may continue to deteriorate for several years after even upon cessation of therapy.[15] These parameters currently form the basis of most recommended screening strategies.[9,10,13] However, even in the presence of high-risk factors, the recommendations generally suggest clinical follow-up with visual field assessment. Marmor *et al*[13] reserved mfERG only as an optional tool during follow-up *after* macular toxicity has occurred. Recent studies have reported cases that, like our patient, had significant mfERG abnormalities despite being asymptomatic with normal or minimal clinical findings.[16–18] Typically, the mfERG will demonstrate a paracentral ring depression of signals around the fovea as was seen in our patient.[19] Moschos *et al*[19] reported that early cessation of hydroxychloroquine in patients resulted in improvement of mfERG patterns and reversible of toxicity over a period of 6 months. This suggests that early toxicity detectable only on mfERG is possibly reversible. There is thus a need to identify this subclinical stage of macular toxicity to prevent irreversible retinal changes.

We recognize that electrophysiological assessment is time-consuming and testing is not practical in all patients on hydroxychloroquine. To maximize limited resources and improve yield, we propose that electrophysiological testing with mfERG could be considered in the following patients:

1. Symptoms with no changes on routine screening tests.
2. Early changes on screening tests, for example, early visual field alterations.
3. High-risk characteristics, namely, impaired liver and renal function, obese or small build, or patients on high-dose treatment.
4. In the absence of risk factors, symptoms or signs, baseline mfERG testing can be considered after about 5 years of treatment.

In conclusion, together with advancements in the mfERG, ophthalmologists should consider modifying current clinical practices to detect early subclinical macular toxicity in patients on hydroxychloroquine. Larger studies are required to evaluate its sensitivity and to institute recommendations for its routine use. However till then, the use of electrophysiological testing should only be an adjunct to standard annual screening tests including Snellen visual acuity, red-on-black Amsler test,[20] colour tests with HRR, and/or SPP2 plates[21,22] which are more sensitive and automated visual field testing (white target) at least of the central 10°.[22]

References

1 Falcone PM, Paolini L, Lou PL. Hydroxychloroquine toxicity despite normal dose therapy. *Ann Ophthalmol* 1993; **25**: 385–388.
2 Mavrikakis M, Papazoglou S, Sfikakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in long term hydroxychloroquine treatment. *Ann Rheum Dis* 1996; **55**: 187–189.
3 Weiner A, Sandberg MA, Gaudio AR, Kini MM, Berson EL. Hydroxychloroquine retinopathy. *Am J Ophthalmol* 1991; **112**: 528–534.
4 Thorne JE, Maguire AM. Retinopathy after long term, standard doses of hydroxychloroquine. *Br J Ophthalmol* 1999; **83**: 1201–1202.
5 Bienfang D, Coblyn JS, Liang MH, Corzillus M. Hydroxychloroquine retinopathy despite regular ophthalmology evaluation: a consecutive series. *J Rheumatol* 2000; **27**: 2703–2706.
6 Warner AE. Early hydroxychloroquine macular toxicity. *Arthritis Rheum* 2001; **44**: 1959–1961.
7 Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum* 1997; **40**: 1482–1486.
8 Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term anti-malarial therapy. *Am J Med* 1983; **75**: 25–34.
9 Easterbrook M. Editorial: Current concepts in monitoring patients on antimalarials. *Aust NZ J Ophthalmol* 1998; **26**: 101–103.
10 Fielder A, Graham E, Tullo A. Royal college of ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. *Eye* 1998; **12**: 907–909.
11 Mavrikakis I, Sfikakis PP, Mavrikakis E, Rougas K, Nikolaou A, Kostopoutos C *et al*. The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. *Ophthalmology* 2003; **110**: 1321–1326.
12 Penrose PJ, Tzekov RT, Sutter EE, Fu AD, Allen Jr AW, Fung WE *et al*. Multifocal electroretinography evaluation for early detection of retinal dysfunction in patients taking hydroxychloroquine. *Retina* 2003; **23**: 503–512.
13 Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the AAO. *Ophthalmology* 2002; **109**: 1377–1382.
14 Mackenzie AH. Dose refinement in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; **75**: 40–47.
15 Easterbrook M. Long-term course of anti-malarial maculopathy after cessation of treatment. *Can J Ophthalmol* 1992; **27**: 237–239.
16 Tzekov RT, Serrato A, Marmor MF. ERG findings in patients using hydroxychloroquine. *Doc Ophthalmol* 2004; **108**: 87–97.
17 Maturi RK, Yu M, Weleber RG. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users. *Arch Ophthalmol* 2004; **122**: 973–981.
18 Kellner U, Kraus H, Forester MH. Multifocal ERG in chloroquine retinopathy: regional variance of retinal dysfunction. *Graefes Arch Clin Exp Ophthalmol* 2000; **238**: 94–97.
19 Moschos MN, Moschos MM, Apostolopoulous M, Mallias JA, Bouros C, Theodossiadis GP. Assessing hydroxychloroquine toxicity by the multifocal ERG. *Doc Ophthalmol* 2004; **108**: 47–53.
20 Easterbrook M. The sensitivity of amsler grid testing in early chloroquine retinopathy. *Trans Ophthalmol Soc UK* 1985; **104**: 204–207.
21 Vu LBL, Easterbrook M, Hovis JK. Detection of color vision defects in chloroquine retinopathy. *Ophthalmology* 1999; **106**: 1799–1804.
22 Easterbrook M. Detection and prevention of maculoapthy associated with antimalarial agents. *Int Ophthalmol Clin* 1999; **39**: 49–57.

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Eye (2006) **20,** 129–132. doi:10.1038/sj.eye.6701818; published online 25 February 2005

Sir,

Structural and functional recovery in juvenile open angle glaucoma after trabeculectomy

Glaucomatous damage was traditionally regarded as an irreversible condition. We report a case of juvenile open-angle glaucoma which had substantial structural and functional improvement after trabeculectomy.

Case report

A 20-year-old Chinese lady was diagnosed to have ocular hypertension 3 years ago. At presentation, her intraocular pressure (IOP) was 30 mmHg on the right eye