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Chloroquine retinopathy: Is there a safe daily dose?

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SUMMARY Published case reports of chloroquine retinopathy rarely include details of daily dosage, but 30 reports where this information was available included 78 patients who developed impaired visual acuity and 13 had received daily doses of 250 mg or less. Eleven cases of ocular toxicity attributed to chloroquine were reported to the Committee on Safety of Medicines but only 2 developed impaired vision on 250 mg daily. A postal questionnaire among 41 rheumatology and 33 ophthalmology centres showed 2 patients who developed impaired vision as a result of treatment with chloroquine in a daily dose not exceeding 250 mg. Serious visual impairment related to chloroquine rarely occurs if the daily dose does not exceed 250 mg.

The beneficial effect of chloroquine in the treatment of rheumatoid arthritis was established by long-term controlled trials,[1 2] but reports of retinal toxicity resulted in the drug falling into disfavour.[3] The incidence of chloroquine retinopathy has varied from less than 1%[4 5] to 16%[6] in different series depending on the techniques used to establish the diagnosis.

Early studies suggested that the risk of chloroquine retinopathy is related to the total dose and total duration of treatment,[6–9] and this cumulative effect may be explained by its slow excretion[10] and preferential accumulation in the pigmented layers of the eye.[11] In animals the risk of chloroquine retinotoxicity is related to the daily dose,[12] and this correlates with the nonlinear rapid increase in chloroquine binding to melanin at increasing concentrations of the drug.[13] Mackenzie and Scherbel[14] suggested that the rate of administration governs the incidence of retinopathy, and there is a threshold level for the daily dose below which visual impairment does not occur irrespective of the cumulative drug consumption or the duration of treatment. In a recent retrospective study[15] on ophthalmic complications in 222 patients on long-term treatment with chloroquine a reduction in visual acuity was found in only 1 patient who had received 500–750 mg daily, and this suggested that the risk of serious visual impairment is negligible provided the daily dose does not exceed 250 mg. In the present study an attempt has been made to confirm or refute this observation, because it would have important implications on the necessity for regular ophthalmic supervision.

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This question cannot be resolved by a prospective study, since it would be unethical to continue treatment, in spite of possible abnormalities in retinal screening tests, until visual acuity became impaired. The alternative is to ascertain retrospectively those patients who developed visual impairment while on chloroquine with particular reference to the daily dose they had been receiving.

Materials and methods

All case reports of chloroquine retinopathy published in English were reviewed and the relationship between daily dose and ocular toxicity assessed from those reports in which the daily dose was stated and visual acuity was impaired.[6 8 9 15–41]

Adverse reactions to chloroquine reported to the Committee on Safety of Medicines (CSM) were reviewed with particular reference to the daily dose that had been used in those developing ocular complications.

A postal questionnaire was sent to 45 British rheumatology and 76 ophthalmology centres requesting information on the daily dose of chloroquine that had been used in any of their patients developing visual impairment while on treatment. The centres contacted were distributed throughout England and Scotland to take account of possible regional differences in susceptibility and criteria of ocular toxicity.

Results

There were 78 individual case reports among 30 publications on chloroquine retinopathy in which it

Table 1 *Review of published reports of chloroquine retinopathy with impaired vision*

Authors	*Diagnosis*	*Age*	*Sex*	*Daily dose (mg)*	*Total duration (years)*	*Visual Acuity*		*Field loss*	*Macular changes*
						R	*L*		
Cambiaggi[16]	SLE	37	F	500	2	20/40	20/30	Constricted to 10°	Pigmented
Hobbs *et al.*[17]									
No. 1	DLE	68	F	100–600	3½	6/9	6/6	Paracentral	Pigmented
No. 2	RA	60	F	200–300*	3	6/9	6/9	Paracentral	Atrophic
No. 3	Arthritis	66	F	400	3	6/18	6/12	Peripheral	Oedema
Wells[18]	DLE	26	F	200*	2	6/18	6/9	Central	Diffuse pigmentation
Hobbs *et al.*[19]	DLE	43	F	400–600	3	6/9	6/12	Peripheral	Oedema
Richards and Zeller[20]	RA	42	F	500	2½	20/40	20/40	Peripheral	Oedema
Ellsworth and Wilson[21]									
No. 1	SLE	22	F	1000	3¼	20/30	20/30	Paracentral	Pigmentation
No. 2	RA	34	F	200–300	2	20/30	20/30	Paracentral	Pigmentation
Price[22]									
No. 1	RA	45	F	750	1	6/18	6/12	Paracentral	Pigmented
No. 2	SLE	40	F	600	1½	6/9	6/9	Peripheral	Pigmented
No. 3	SLE	34	F	750	5	6/9	6/36	—	Degeneration
No. 4	DLE	66	F	400	5	6/18	6/18	Peripheral	Optic atrophy
No. 5	Arthritis	75	F	400	'Years'	6/60	6/12	—	Optic atrophy
No. 6	Arthritis	31	F	250–500	'Years'	6/18	6/24	Paracentral	Pigmented
George & Mitchell 1962 (23)	SLE	37	F	200–600	3	6/6	6/9	Contracted	Pigmented
Ormrod[24]									
No. 1	SLE	28	M	300–500	4	6/9	6/9	Ring	Pigmented
No. 2	Skin disease	53	M	200–400	7	6/12	6/12	Ring	Pigmented
Penner and Somers[25]	DLE	42	F	500–1000	3	20/30	20/30	Paracentral	Pigmented
Mayer[26]	RA	30	F	250	3¼	20/30	20/30	Ring	Pigmented
Reed and Campbell[27]	RA	55	F	250	1	20/120	20/120	Central	Normal
Smith[28]									
No. 1	Scleroderma	52	M	400*	½	20/200	20/50	Central	Bull's eyes
No. 2	RA	45	F	250	2	20/40	20/40	Pericentral	Bull's eyes
No. 3	RA	48	F	500	2½	20/400	20/400	—	Degeneration
Jansson[29]									
No. 1	DLE	60	M	200–400	5	6/9	6/9	Pericentral	Pigmented
No. 2	RA	53	F	250–500	2½	6/60	6/60	Pericentral	Pigmented
Algvere *et al.*[30]									
No. 1	RA	55	M	500	3½	6/9	6/6	Pericentral	Bull's eye
No. 2	SLE	40	M	400–600	3	6/60	6/18	Pericentral	Pigmented
Okun *et al.*[31]									
No. 1	DLE	50	F	250–500	8½	20/30	20/25	Pericentral	Granular
No. 2	DLE	39	F	250–500	5½	20/200	20/50	Pericentral	Bull's eye
No. 3	DLE	49	M	500–750*	5½	20/30	20/20	Pericentral	Bull's eye
No. 4	DLE	40	F	250–500*	1	20/30	20/25	Ring	Pigmented
No. 5	Asthma	53	M	250–375*	4	20/40	20/50	Pericentral	Pigmented
No. 6	DLE	54	F	500	6½	7/400	11/400	Central	Pigmented
No. 7	DLE	52	F	250–750*	3½	20/50	20/500	Peripheral	Diffuse pigment
No. 8	DLE	39	F	500	3	15/200	4/200	Small islands of vision	Diffuse pigment
Elliot and Mills[32]									
No. 1	RA	61	F	250–500*	6	1/200	10/200	Central	Degeneration
No. 2	RA	47	F	500	2½	20/25	5/400	Pericentral	Pigmentation
Crews[33]									
No. 1	RA	68	F	400–800	¾	6/6	6/36	Central	Pigmented
No. 2	SLE	72	F	500	1½	6/9	6/9	Peripheral	Diffuse pigment and optic atrophy
Henkind *et al.*[34]									
No. 1	SLE	36	F	500	6	20/40	20/40	Central	Granular
No. 2	SLE	40	F	500	7	20/50	20/20	Nil	Pigmented
No. 3	DLE	27	M	500	3½	20/20	20/35	Central	Pigmented
Lewis[35]	RA	64	F	250–500	7	20/40	20/40	Peripheral	Atrophic discs
Lloyd Hiltz[36]									
No. 1	SLE	36	F	450	6	6/18	C/F	Bitemporal hemianopia	Diffuse pigment
No. 2	RA	34	F	250–500	4	6/18	6/18	Paracentral	Bull's eyes
No. 3	RA	58	F	250–750	6	5/12	5/12	Ring	Bull's eyes
Kearns and Hollenhorst[37]									
No. 1	RA	48	F	500	5	20/30	20/30	Pericentral	Pigmented
No. 2	SLE	56	F	500	6	20/40	20/40	Ring	Pigmented
No. 3	SLE	54	F	500	—	20/30	8/200	Ring	Bull's eye
Burns[38]									
No. 1	Epilepsy	14	F	250–750	2¼	20/30	20/60	Pericentral	Bull's eye
No. 2	DLE	51	F	750	2	20/60	20/20	Pericentral	Bull's eye

Table 1—*continued*

Authors	*Diagnosis*	*Age*	*Sex*	*Daily dose (mg)*	*Total duration (years)*	*Visual acuity*		*Field loss*	*Macular changes*
						R	*L*		
Crews[39]									
No. 1	RA	55	F	500	3	6/18	6/18	Annular	Diffuse pigment
No. 2	RA	66	F	400	4d	6/9	6/9	Nil	Pre-retinopathy
No. 3	RA	80	F	400	1½	6/9	6/9	Nil	Pre-retinopathy
Carlberg[40]									
No. 1	DLE	48	M	600	3	6/18	6/18	Pericentral	Bull's eye
No. 2	RA	50	F	250	5	6/12	6/12	Pericentral	Bull's eye
Nylander[6]									
No. 1	DLE	38	F	250–750*	5	6/12	5/9	Central	Oedema
No. 2	SLE	46	F	250–500	6	5/9	6/6	Central	Pigmented
No. 3	RA	53	F	250	9	6/9	6/18	Central	Oedema
No. 4	DLE	63	M	250*	10½	6/9	5/9	Central	Degeneration
No. 5	DLE	61	M	200*	7	6/9	6/9	Tube	Pigment
No. 6	SLE	41	F	375	8½	6/9	6/9	Peripheral	Atrophic
No. 7	RA	43	F	250	4	5/12	5/12	Central	Bull's eye
No. 8	SLE	55	F	250	5	6/6	5/12	Paracentral	Pigmented
No. 9	SLE	30	F	250–500	5½	6/9	6/9	Central	Pigmented
No. 10	RA	51	F	250–500	4	6/9	6/6	Ring	Pigmented
No. 11	RA	44	F	250	5	6/9	6/9	Central	Degeneration
Vorpio and Karjalainen[18]									
No. 1	SLE	36	F	200	8	6/12	6/6	Pericentral	Bull's eye
No. 2	DLE	50	F	250	5	5/9	6/12	Pericentral	Granular
Carr *et al.*[9]									
No. 1	SLE	41	F	500	8	20/20	20/40	Pericentral	Pigmented
No. 2	SLE	40	F	500	6	20/40	20/40	Central	Bull's eyes
Brinkley *et al.*[41]									
No. 1	SLE	47	F	420	3	6/9	6/9	Constricted	Bull's eyes
No. 2	SLE	63	F	405	4	6/9	6/9	Constricted	Bull's eyes
No. 3	SLE	59	F	500*	2	6/60	6/30	Pericentral	Mottling
No. 4	SLE	54	F	500*	1½	6/9	6/9	Constricted	Mottling
No. 5	SLE	62	F	500*	6½	6/7·5	6/9	Constricted	Normal
Marks and Power[15]	RA	50	F	500–750	4½	6/18	1/60	Paracentral	Bull's eyes

*Other antimalarial therapy

was possible to examine the relationship between the daily dose and visual impairment (Table 1). Chloroquine retinopathy associated with visual impairment was reported in only 13 cases where the daily dose did not exceed 250 mg, and in 3 of these the patients had also received other antimalarials. The remaining case reports all referred to patients who had received more than 250 mg daily: 47 received up to 500 mg daily, 15 up to 750 mg daily, and 3 more than 750 mg daily.

There were 11 reports of chloroquine retinopathy to the CSM (Table 2). Five of these (cases 1, 2, 6, 8, 9) were stated to have visual impairment, but 2 (cases 8, 9) developed eye symptoms after only a few days of treatment, and these were unlikely to be the result of a retinopathy. One patient (case 6) had been taking chloroquine intermittently for 2 years for malaria chemoprophylaxis and developed sudden deterioration in vision, but it is unclear whether this was the result of a retinopathy. There were 2 patients (cases 1, 2) who developed an unquestionable chloroquine retinopathy associated with visual impairment, and both had received daily doses of 250 mg or less.

A postal questionnaire was sent to 45 rheumatology centres and replies were received from 41. Twenty-three centres had no cases of ocular toxicity, but 11 of these commented that chloro-

Table 2 *Chloroquine retinopathy reports to Committee on Safety of Medicines*

Case	*Diagnosis*	*Age*	*Sex*	*Daily dose (mg)*	*Total duration (years)*	*Ophthalmic findings*
1	—	53	F	200	8	6/36 6/24 Retinal degeneration
2	—	40	F	250	5	Retinopathy. Partial blindness
3	—	45	F	250	4	Maculat retinopathy
4	—	61	F	400	2½	Retinopathy
5	Malaria	50	M	'Several'	10	'Typical' retinopathy
6	Malaria	45	M	500 Weekly	2	Sudden deterioration in vision
7	RA	—	—	—	9	6/6 6/6 Macular degeneration
8	—	43	F	500–750	4 days	Acute eye symptoms
9	RA	63	F	750	2 days	Blurred vision
10	—	64	M	250	1½	Granular macula. Later tobacco amblyopia
11	—	55	M	1000	6 weeks	Nonprogressive retinopathy

Table 3 *Chloroquine retinopathy: Cases from rheumatology questionnaire*

Case	*Diagnosis*	*Age*	*Sex*	*Daily dose (mg)*	*Total duration (years)*	*Visual Acuity*		*Field loss*	*Macular changes*	
						R	*L*		*R*	*L*
1	—	—	—	500	4	6/18	6/18	—	++	+
2	—	34	F	'12 Tablets'	4	6/60	6/60	Central	+	+
3	RA	57	M	250	1½	6/24	6/6	—	+++	+
4	RA	53	F	100–600	10	6/12	6/9	Ring	+	+
5	RA	72	F	250	2 weeks	—	—	—	++	++
6	RA	59	F	250	½	6/9	C/F	L central	+	++
7	RA	51	M	250	4½	6/12	C/F	Paracentral	++	++
8	SLE	33	F	500	5	6/12	6/60	—	+++	+++
9	—	38	F	400	5	6/24	6/12	Paracentral	+++	+++

+Macular mottling. ++Bull's eye macula. +++Bull's eye and diffuse pigmentation.

Table 4 *Chloroquine retinopathy: cases from ophthamology questionnaire*

Case	*Diagnosis*	*Age*	*Sex*	*Daily dose (mg)*	*Total duration (years)*	*Visual Acuity*		*Field loss*	*Macular changes*	
						R	*L*		*R*	*L*
1	RA	38	F	750	2	6/12	6/24	Paracentral	++	++
2	Cramps	69	F	250	7	3/60	6/18	central	++	++
3	SLE	69	M	500	15	6/60	6/60	—	++	++

++Bull's eye macula.

quine was rarely used. Eighteen centres had seen patients with ocular toxicity, and these included 17 cases of retinopathy without visual impairment and 13 cases of retinopathy with impaired vision. Adequate information on the daily dose was available in only 9 of these 13 cases (Table 3). Four patients had been receiving a daily dose of 250 mg, but in 2 (cases 3 and 6) the diagnosis of chloroquine retinopathy was doubtful because the ocular abnormalities were unilateral. One patient (case 5) developed bull's eye maculae after only 2 weeks of treatment and the retinal changes were probably coincidental to chloroquine therapy. Only 1 patient (case 7) appears to have developed a genuine chloroquine retinopathy on a dose of 250 mg daily, but this patient had received chloroquine phosphate for 4 years until 1967, and in 1973 when seen by an optician was reported to have 6/6 vision in both eyes. The chloroquine was resumed the following year, and routine ophthalmic assessment after 6 months showed 6/9 vision in both eyes. Although the chloroquine was there upon discontinued, his vision deteriorated over the next 4 years to 6/12 and counting fingers.

A postal questionnaire was sent to 76 ophthalmology centres, and replies were received from 33. Twenty-six centres had no cases of ocular toxicity. Seven centres reported a total of 4 cases of retinopathy without visual impairment and 8 cases with impaired vision. Adequate information on the daily dose was available in only 3 of these 8 cases (Table 4). One patient (case 2) had taken chloroquine phosphate 250 mg daily for 7 years for nocturnal cramps and developed typical features of chloroquine retinopathy associated with loss of vision. Another patient (case 3) who became blind was stated to have received chloroquine phosphate 100 mg twice daily, but tablets of chloroquine containing 100 mg in chloroquine phosphate have never been available in the United Kingdom, and she was probably receiving 250 mg twice daily.

Discussion

The major hazard associated with the use of chloroquine is retinopathy, which may be irreversible[17 22 24] or may progress after treatment is discontinued.[21 31] Many rheumatologists are reluctant to use antimalarials, and the *British National Formulary* 1976–8 condemns their use and states that chloroquine 'is now regarded as obsolete.'

The retinopathy may be reversible if diagnosed in the early stages,[33 42 43] but there is disagreement about which methods should be used to establish the diagnosis. The earliest retinal change is abnormal pigmentation around the macula, referred to as stippling or mottling, but there is a wide variation in normal macular appearance, and similar changes may occur in the aging eye[44] and have also been found in rheumatoid patients who have never received chloroquine.[4 45] In the well-established chloroquine retinopathy there are concentric rings

of hyperpigmentation and depigmentation around the macula producing a bull's eye appearance, but this configuration is not pathognomonic of chloroquine toxicity[46] and was probably a chance finding in one of the patients reported in this study (Table 3, case 5).

The unreliability of fundus examination may explain the multiplicity of other techniques which have been advocated in the diagnosis of chloroquine retinopathy. Visual field examination characteristically shows a pericentral scotoma to a red target,[47] but there is a 6% incidence of red scotomata in the normal population,[48] and accurate testing of visual acuity requires a co-operative patient. Tests of colour vision may be used as a screening test for macular damage,[43] but some patients have normal colour vision in the presence of macular mottling and scotomata,[6 8] and colour discrimination may be abnormal in rheumatoid patients who have never received chloroquine.[49] There have been enthusiastic claims for the value of electroretinography[50] and electro-oculography,[51 52] but both tests may be normal even if macular pigmentation is grossly disturbed.[31 34 53] Serial recordings of the electro-oculogram in the normal eye have shown variation with time,[54] and in patients on chloroquine the individual variation is too great for the test to be of diagnostic value.[55] Other tests that have been tried include fluorescein angiography,[37] the macular dazzle or photostress test,[9 56] and dark adaptometry,[57] but abnormalities in these tests may be age-related and are not specific for chloroquine retinotoxicity.[46 49 58] The reliability of ophthalmic assessment might be improved by performing a battery of tests,[6] but this would be time consuming and is impracticable for monitoring most patients. There is therefore no completely reliable means of diagnosing chloroquine retinopathy before serious visual impairment has occurred.

The review of published case reports on chloroquine retinopathy (Table 1) has confirmed that the major risk of visual impairment relates to those patients receiving a daily dose above 250 mg. There were only 13 reported cases of patients developing a permanent reduction in visual acuity on a daily dose of 250 mg, and 3 of these had previously received other antimalarials. Mayer[26] reported the case of a 30-year-old woman with rheumatoid arthritis who developed impaired vision on 250 mg daily but commented that she had received a total dose of 782 g over 3¼ years, which means she was probably receiving 500 mg daily. The case described by Reed and Campbell[27] is not typical of chloroquine retinopathy because the patient developed a central scotoma and became blind but had a normal macula and fundus. The only patients who developed unquestionable chloroquine retinopathy with impaired vision on a daily dose not exceeding 250 mg and had not received other antimalarials are 4 cases described by Nylander,[6] 2 by Voipio and Karjalainen,[8] and one each by Smith[28] and Carlberg.[40]

The cases of chloroquine retinopathy reported to the CSM were unsuitable for retrospective analysis because the details of their ophthalmic examination were usually inadequate. The visual acuity was recorded in only 2 patients, one of whom developed a chloroquine retinopathy associated with impaired vision on a daily dose of 200 mg. Three other patients treated with chloroquine 250 mg daily developed a retinopathy, but in 2 there was no comment on whether vision was impaired, though the third was stated to have developed partial blindness. There is therefore evidence from 2 cases reported to the CSM (Table 2, cases 1, 2) that chloroquine may cause visual impairment even if the daily dose does not exceed 250 mg.

The results of the postal questionnaire completed by rheumatologists at 41 centres in Great Britain showed that serious retinal problems rarely occurred as a result of chloroquine therapy and visual impairment was reported in only 13 cases. Six patients had unequivocal evidence that their visual impairment was the result of a chloroquine retinopathy, but 5 of these had been receiving daily doses of chloroquine phosphate above 250 mg. In 3 other cases the visual impairment was probably coincidental to chloroquine therapy. There was therefore only 1 patient (Table 3, case 7) on chloroquine 250 mg daily who developed impaired vision as a result of treatment.

The postal questionnaire was completed by ophthalmologists at 33 centres. Eight patients treated with chloroquine developed impaired vision, but details were available in only 3, and only 1 of these (Table 4, case 2) had been receiving chloroquine 250 mg daily. There was therefore little evidence from ophthalmic sources that chloroquine use in Great Britain is causing visual problems.

The purpose of this study was to establish whether there is a safe daily dose of chloroquine which does not lead to impaired vision. From a review of cases from 3 different sources, namely, published case reports, reports to the CSM, and from personal communication with British rheumatologists and ophthalmologists, the risk of visual impairment associated with chloroquine therapy appears to be very small provided the daily dose does not exceed 250 mg. But occasional cases may occur at this dose level, so that ophthalmic supervision should still be undertaken.

I thank the members of the Heberden Society and Othalmological Society of the United Kingdom for their replies to the questionnaire on chloroquine retinopathy.

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