

Screening for antimalarial toxicity: current concepts

The 2002 *Compendium of Pharmaceuticals and Specialties* states: "When prolonged therapy with any antimalarial compound is contemplated, initial (baseline) and periodic (every 3 months) ophthalmologic examinations (including visual acuity, expert slit lamp, funduscopic, and visual field tests) should be done."¹ It is clear, however, that these recommendations are outdated, as the incidence of retinopathy in patients receiving appropriate dosages of antimalarials is very low. Indeed, several authors, particularly from the United Kingdom, have suggested that patients receiving appropriate dosages do not need to be screened.²⁻⁶ However, other authors feel that after a baseline examination, screening should be performed every 6 months,⁷ every 9 to 12 months,⁸ every 12 to 18 months,⁹ yearly¹⁰ or yearly after 3 years of treatment,¹¹ or that there should be no monitoring until after 5 years of treatment.¹² Anderson¹³ has proposed monitoring patients every 6 months after 6 years of treatment or a cumulative dose of 600 mg. A survey of all rheumatologists and ophthalmologists in Indiana showed that most (79% of ophthalmologists and 97% of rheumatologists) recommended examination every 6 months.¹⁴ The purpose of this editorial is to suggest current guidelines for screening patients receiving antimalarial therapy.

In 2000 the Canadian Consensus Conference on Hydroxychloroquine (in which I participated as the COS representative) published a workshop report.⁹ The workshop was attended by official representatives from ophthalmology, rheumatology, pediatric rheumatology, dermatology, family and internal medicine, the Canadian Pharmacists Association, patient advocate groups, Health Canada, the drug manufacturer and the Cochrane Collaboration. In the same year the American Academy of Ophthalmology (AAO) struck an expert panel on antimalarial toxicity, whose guidelines have now been published.¹⁵ I have personally

examined 156 patients with antimalarial maculopathy, associated with hydroxychloroquine alone in only six cases. These patients all had bilateral, irreversible field defects on Amsler grid testing and automated perimetry.

On the basis of these cases, the deliberations of the Canadian Consensus Conference on Hydroxychloroquine⁹ and the AAO guidelines,¹⁵ the following recommendations can be made regarding baseline examinations in all patients. All patients beginning hydroxychloroquine or chloroquine therapy should have a baseline examination within the first year in order to document any associated ocular conditions and to record the fundus appearance and visual field. A complete ophthalmologic examination, including determination of the visual acuity and a retinal examination, should be performed. Amsler grid testing or Humphrey 10-2 perimetry, or both, should be done. In my experience, a young, reliable patient is an excellent observer, and Amsler grid testing is adequate. The AAO suggests that colour vision testing be optional.¹⁵ Fundus photography and fluorescein angiography may be indicated in selected patients, particularly those with associated age-related macular degeneration. Multifocal electroretinography is an interesting new test that may be useful in diagnosing early retinopathy; however, the specificity and sensitivity of this test have yet to be determined.¹⁶⁻¹⁹

Should patients taking antimalarials be screened on a regular basis? Although the incidence of retinopathy is very low at dosages of less than 6.5 mg/kg of hydroxychloroquine or less than 3.0 mg/kg of chloroquine, 21 patients receiving 6.5 mg/kg or less of hydroxychloroquine who had definite retinopathy have been described^{10,20-26} (Dr. Howard Bernstein [retired]: personal communication, 1992). Only two cases occurred before 5 years of treatment.¹⁰ One of the two patients, who manifested retinopathy after 10 months of treatment, was probably receiving an overdose on an ideal body weight basis.²⁷ In addition, one case of a patient in whom retinopathy developed at a dosage of 6.75 mg/kg (Dr. Sanjay Sharma, Queen's University, Kingston, Ont.: personal communication, 1997) and two cases at dosages of 6.8 mg/kg and 6.9 mg/kg¹⁰ have been reported.

It is useful to classify patients as being at low risk or at higher risk (Table 1). Patients should understand that toxicity is unlikely, but not impossible, in the first 5

Correspondence to: Dr. Michael Easterbrook, 170 St. George St., Suite 826, Toronto ON M5R 2M8; fax (416) 926-0091

Can J Ophthalmol 2002;37:325-8

Table 1—Definition of risk for patients receiving antimalarials

Characteristic	Low risk	High risk
Dosage, mg/kg		
Hydroxychloroquine	< 6.5	≥ 6.5
Chloroquine	< 3.0	≥ 3.0
Duration of use, yr	< 5	≥ 5
Habitus	Lean	Higher fat level
Renal/liver disease	None	Present
Concomitant retinal disease	None	Present
Age, yr	< 60	≥ 60

years. The AAO suggests general, comprehensive eye examinations on a regular basis depending on the patient's age (Table 2). At each examination the cornea and retina should be examined. With hydroxychloroquine, deposition of antimalarial in the cornea is usually found (on dilated examination) in small patients, many of whom are receiving too high a dosage, whereas with chloroquine, deposition is most often seen in patients receiving appropriate dosages.²⁸ Although the AAO suggests that colour vision testing be optional,¹⁵ I find it very useful and do it routinely to detect early maculopathy. A patient who does not recognize all letters very quickly may have retinopathy, even with relative scotomas. I do Humphrey 10-2 visual field testing only if the vision is not 6/6, if the patient is symptomatic or if colour vision is disturbed in any way.

IDEAL BODY WEIGHT

In the past, rheumatologists often prescribed antimalarials on the basis of actual body weight rather than ideal body weight. In 1983 Mackenzie²⁹ suggested that the dosage be established according to *ideal body weight*, as chloroquine and hydroxy-

Table 2—Frequency of regular eye examinations recommended by the American Academy of Ophthalmology¹⁵

Age, yr	Frequency of examination
20–29	At least once during this period
30–39	At least twice during this period
40–64	Every 2 to 4 yr
≥ 65	Every 1 or 2 yr

Table 3—Suggested weekly dosages of hydroxychloroquine based on ideal body weight⁹

Ideal body weight, kg	Dosage
57–61	200 mg 1 day per week (e.g., Sunday) 400 mg/d all other days
53–56	200 mg 2 days per week (e.g., Saturday, Sunday) 400 mg/d all other days
49–52	200 mg 3 days per week (e.g., Monday, Wednesday, Friday) 400 mg/d all other days
44–48	400 mg 3 days per week (e.g., Monday, Wednesday, Friday) 200 mg/d all other days
40–43	400 mg 2 days per week (e.g., Saturday, Sunday) 200 mg/d all other days
36–39	400 mg 1 day per week (e.g., Sunday) 200 mg/d all other days
31–35	200 mg/d

chloroquine are poorly absorbed by fat and bone. It is my clinical impression, based on follow-up of many patients over many years, that patients in whom toxic effects develop are small or obese, or both, and are being treated on the basis of their actual, not their ideal, body weight. Ideal body weight has been defined as 50 kg plus 2.3 kg per inch (2.54 cm) over 5 feet (152.4 cm) for men and 45.5 kg plus 2.3 kg per inch over 5 feet for women.³⁰ Suggested dosages based on ideal body weight are given in Table 3.

In practice, this means that a patient who weighs less than 62 kg and is receiving 400 mg/d of hydroxychloroquine is at the very upper limit of the recommended dosage (6.5 mg/kg), as is a 62-kg patient taking five 250-mg tablets of chloroquine per week (recommended dosage 3.0 mg/kg per day). In one series of 67 patients with retinopathy who were taking chloroquine alone, only 5 patients (7.5%) were receiving less than the recommended dosage.³¹ Maculopathy developed in 27 patients (40.3%) taking 3.0 to 4.0 mg/kg per day. Ideal body weight was not used, so Mackenzie's original observation that the accepted dosage for chloroquine is 3.5 to 4.0 mg/kg of ideal body weight²⁹ is probably still accurate.

In his series of patients receiving an overdose of hydroxychloroquine, Anderson¹³ reported that the

most common reason for a patient's inadvertently receiving greater than 6.5 mg/kg was insidious weight loss without appropriate dosage adjustment. In recent years rheumatologists have been using ideal rather than actual body weight in view of apparent overdosing in some obese patients. This change of practice may explain the decreasing incidence of maculopathy in patients receiving hydroxychloroquine.

PRACTITIONERS' PERSPECTIVE

Are these recommendations realistic? What do the prescribers of these drugs, the dermatologists and rheumatologists, think? In a survey of 325 UK dermatologists (response rate 70%), 30 respondents reported that they had encountered ocular side effects of antimalarials, which were mild in most cases.³² However, of a random sample of 300 US rheumatologists listed in the directory of the American College of Rheumatology, 75% stated that they would continue to screen for hydroxychloroquine retinopathy because they were unwilling to accept any risk of visual loss among their patients, 74% would continue to screen because of legal liability, and 56% felt that their patients would insist on being screened regardless of their physician's opinion.³³ A total of 44% stated that they would continue to screen regularly even if the College published guidelines discouraging routine screening.

A recent survey of all ophthalmologists in Texas showed that 77% follow patients receiving hydroxychloroquine therapy every 6 months.³⁴ A total of 122 respondents (42%) had diagnosed hydroxychloroquine toxicity in at least one patient; of the 122, 37 (30%) had had a patient with permanent visual loss from hydroxychloroquine.

CONCLUSION

At least in North America, surveys of dermatologists, ophthalmologists and rheumatologists suggest that some screening of patients taking antimalarials is indicated, as cases of definite retinopathy have been reported in patients receiving less than the recommended dosage. It appears reasonable to perform a baseline examination, including determination of visual acuity, Amsler grid or Humphrey 10-2 white testing or both, and colour vision testing within the first year of therapy. If patients are at low risk (Table 1), an examination after 5 years of therapy seems reasonable. Despite guidelines and recommendations

agreed to by expert panels, the ophthalmologist, rheumatologist or patient may elect to screen more frequently. Screening is recommended more often (every 6 months or yearly), however, for any patient at high risk (Table 1). ◀

Michael Easterbrook, MD, FRCSC, FACS
Department of Ophthalmology
University of Toronto
Toronto, Ont.

REFERENCES

1. *Compendium of pharmaceuticals and specialties*. 37th ed. Ottawa: Canadian Pharmacists Association; 2002. p. 1306.
2. Royal College of Ophthalmologists. *Ocular toxicity and hydroxychloroquine: guidelines for screening*. London: The College; 1998.
3. Grierson DJ. Hydroxychloroquine and visual screening in a rheumatology outpatient clinic. *Ann Rheum Dis* 1997; 56:188–90.
4. Silman A, Shipley M. Ophthalmologic monitoring for hydroxychloroquine toxicity: a scientific review of available data. *Br J Rheumatol* 1997;36:599–601.
5. Blyth C, Lane C. Hydroxychloroquine retinopathy: Is intensive screening necessary? *BMJ* 1998;316:716–7.
6. 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;40:1482–6.
7. Rynes RI. Ophthalmic considerations in using antimalarials in the United States. *Lupus* 1996;5(suppl 1):S73–4.
8. Ruiz RS, Saatci OA. Chloroquine and hydroxychloroquine retinopathy: how to follow affected patients. *Ann Ophthalmol* 1991;23:290–1.
9. Canadian Consensus Conference on Hydroxychloroquine. Canadian Rheumatology Association. *J Rheumatol* 2000; 27:2919–21.
10. Browning DI. Hydroxychloroquine and chloroquine retinopathy: screening for drug toxicity. *Am J Ophthalmol* 2002;133:649–56.
11. Spalton DJ. Retinopathy and antimalarial drugs — the British experience. *Lupus* 1996;5(suppl 1):S70–2.
12. Block JA. Hydroxychloroquine and retinal safety. *Lancet* 1998;351:771.
13. Anderson LG. Retinal toxicity is a late complication of hydroxychloroquine treatment: proposal for modifications of monitoring guidelines [lecture]. American College of Rheumatology meeting; 1998 Nov 8–12; San Diego.
14. Mazzuca SA, Yung R, Brandt KD, Lee RD, Katz BP. Current practices in monitoring ocular toxicity related to hydroxychloroquine (Plaquenil) toxicity. *J Rheumatol* 1994;21:59–63.
15. Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American

- Academy of Ophthalmology. *Ophthalmology* 2002;109:1377–82.
16. Maturi RK, Folk JC, Nichols B, Oetting TT, Kardon RH. Hydroxychloroquine retinopathy. *Arch Ophthalmol* 1999; 117:1262–3.
 17. Kellner U, Kraus H, Foerster MH. Multifocal ERG in chloroquine retinopathy: regional variance of retinal dysfunction. *Graefes Arch Clin Exp Ophthalmol* 2000;238: 94–7.
 18. Penrose P, Tzechove R, Fu A, Menz MD, Menz MK, Wang M, et al. Multifocal ERG for early detection of retinal dysfunction in patients taking hydroxychloroquine [poster]. Association for Research in Vision and Ophthalmology meeting; 2002 May 5–10; Fort Lauderdale (FL).
 19. Bhargava A, Coupland SG, Kertes PJ, Leonard BC. Multifocal electroretinography in chloroquine maculopathy. Canadian Ophthalmological Society meeting; 2002 June 13–16; Hull (QC).
 20. Mavrikakis M, Papazoglou S, Sfrikakis PP, Vaiopoulos G, Rougas K. Retinal toxicity in long term hydroxychloroquine treatment. *Ann Rheum Dis* 1996;55:187–9.
 21. Falcone PM, Paolini L, Lou PL. Hydroxychloroquine toxicity despite normal dose therapy. *Ann Ophthalmol* 1993; 25:385–8.
 22. Weiner A, Sandberg MA, Gaudio AR, Kini MM, Berson EL. Hydroxychloroquine retinopathy. *Am J Ophthalmol* 1991;112:528–34.
 23. Raines MF, Bhargava SK, Rosen ES. The blood–retinal barrier in chloroquine retinopathy. *Invest Ophthalmol Vis Sci* 1989;30:1726–31.
 24. Wang C, Fortin PR, Li Y, Panaritis T, Gans M, Esdaile JM. Discontinuation of antimalarial drugs in systemic lupus erythematosus. *J Rheumatol* 1999;26:808–15.
 25. Bienfang D, Coblyn JS, Liang MH, Corzilius M. Hydroxychloroquine retinopathy despite regular ophthalmological evaluation: a consecutive series. *J Rheumatol* 2000;27: 2703–6.
 26. Thorne JE, Maguire AM. Retinopathy after long-term standard doses of hydroxychloroquine [letter]. *Br J Ophthalmol* 1999;83:1201–2.
 27. Alarcon GS. How frequently and how soon should we screen our patients for the presence of antimalarial retinopathy? *Arthritis Rheum* 2002;46:561.
 28. Easterbrook M. Is corneal deposition of antimalarial any indication of retinal toxicity? *Can J Ophthalmol* 1990;25: 249–51.
 29. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75(1A):40–5.
 30. *Pharmacopoeia 2000*. Loma Linda (CA): Tarascon Publishing; 2000. p. 4.
 31. Easterbrook M. Dose relationships in patients with early chloroquine retinopathy. *J Rheumatol* 1987;14:472–5.
 32. Cox NH, Paterson WD. Ocular toxicity of antimalarials in dermatology: a survey of current practice. *Br J Dermatol* 1994;131:878–82.
 33. Fraenkel L, Felson DT. Rheumatologists' attitudes toward routine screening for hydroxychloroquine retinopathy. *J Rheumatol* 2001;28:1218–21.
 34. Blomquist PB, Chundru RK. Screening for hydroxychloroquine toxicity by Texas ophthalmologists. *J Rheumatol* 2002;29:1665–70.