Antimalarial Therapy and Early Retinal Changes in Patients with Rheumatoid Arthritis

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Brit. med. J., 1966, 1, 270-273

Patients with rheumatoid arthritis who are treated with large doses of the antimalarial drugs chloroquine and hydroxychloroquine (Plaquenil) may develop a severe disturbance of vision due to retinal damage. This retinopathy is irreversible, and may progress for long periods even though the treatment has stopped (Cambiaggi, 1957 ; Hobbs, Sorsby, and Freedman, 1959 ; Hobbs, Eadie, and Somerville, 1961). In this condition the electro-oculogram, an electrodiagnostic test, shows very abnormal results (Arden and Fojas, 1962), suggesting that the primary site of the lesion is the cells in the pigment-epithelium which produce the measured electrical potential. This hypothesis has since been proved in experimental chloroquine retinopathy induced in cats (Meier-Ruge, 1965). Furthermore, in patients who are taking antimalarials, but in whom the fundus and visual functions are normal, the electro-oculogram may be low (Arden, Friedmann, and Kolb, 1962).

During prolonged chloroquine treatment abnormalities may appear in the fundus while the patient's vision is still unaffected. The earliest change consists of slight pigmentary mottling of the macula and perimacular region (Henkind and Rothfield, 1963). At a later stage retinal and subretinal oedema, accompanied by definite pigmentary changes, give the picture of the macular "bull's-eye" (Henkind, Carr, and Siegel, 1964). In one case the appearance of a "bull's-eye" was followed by loss of visual field as a true retinopathy developed. However, if treatment is withdrawn at this stage the process may be arrested.

All these findings suggest that there is a stage of "pre-retinopathy" which might be recognized on careful examination before retinal neuronal activity is irreversibly impaired. It is of obvious interest to find out as much about the condition as possible, and for this purpose the survey was undertaken.

Methods

The patients in the survey were being treated for rheumatoid arthritis and allied collagenoses. They were drawn from hospitals in London and the provinces and were unselected except that they were willing to co-operate. Their ages ranged from 17 to 73. All of them received a thorough eye examination by an ophthalmologist attached to their local hospital. Electro-oculograms were performed within six weeks (before or after) of this examination. A specially developed portable electro-oculographic recorder was used. The technique employed was very similar to the one previously described (Arden, Barrada, and Kelsey, 1962), but bitemporal recording was employed.

The device was calibrated on normal healthy subjects prior to the survey. Copies of the ophthalmic findings and a full summary of the patients' medical histories were sent to a central register. The analysis of the data, by means of an

Elliot 803 computer, was straightforward. It was found impracticable to relate clinical pathological findings to the patient's disease, both because of variations in practice between different hospitals and because parallel clinical assessments were lacking. Most of the patients had corneal deposits of chloroquine. No analysis was made of these data. Electro-oculographic values were transformed by the programme into logarithmic values, to normalize the distribution, and also corrected for age (Arden and Barrada, 1962 ; Kolb, 1965). The antimalarials taken by the patients were chloroquine and hydroxychloroquine. Hydroxychloroquine doses were divided by the factor 1.25 to allow for what is held by some consultants to be a smaller therapeutic effect. In patients who had taken both drugs the total dosage was arrived at by adding this scaled dosage. Most of the patients had received other treatments, but no analysis could be made of the effects of these, because of their wide variety.

Results

Table I shows the major groups into which the 347 patients were divided, and the corresponding electro-oculographic values. The normal control electro-oculogram is 237 (S.E. 5.2), and a decrease from this value represents an abnormality. Two groups of patients served as additional controls—those who had never had antimalarial drugs but who were about to begin treatment, and those who had had the drugs in the past but whose courses had finished three months to three years prior to testing. Both groups had normal electro-oculograms.

TABLE I.—Analysis of Patient-groups

Type	No. of Patients	E.O.G.
Healthy controls	42	237
1. No antimalarials	30	230
2. Antimalarials stopped prior to testing ..	28	235
3. Patients without eye signs on antimalarials	192	216*
4. Patients with eye signs	29	200*
5. Patients excluded from analysis because of coincident disease	68	—
Total of patients	347	221

* Electro-oculogram significantly lower than preceding groups.

As always with control groups, the question arises whether they were comparable with the patients. So far as the electro-oculogram goes, we have corrected for age, and (see below) have been unable to find that the patients' rheumatic status had any influence on the electro-oculogram. The controls were taken from the same clinics as the other patients and had had rheumatic therapy other than antimalarials: they must be considered to be as closely comparable to the main patient group as possible.

The main group of 192 patients were taking antimalarials, and had normal vision and normal fundi. Originally this group was much larger, but it was decided to exclude any person who had any local eye disease, or general disease other than rheumatoid arthritis. For example, myopes were excluded, since in myopia the electro-oculogram is reduced (Arden, Barrada, and Kelsey, 1962 ; Blach, Jay, and Kolb, 1966). So also were patients with diagnosed Sjögren's syndrome, those with any

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NOTE.—This survey was carried out in co-operation with the rheumatological and ophthalmological departments of Hackney Hospital, London ; the London Hospital ; the Worcester Royal Infirmary ; the Royal Berkshire Hospital, Reading ; the Canadian Red Cross Memorial Hospital, Taplow ; Sefton General Hospital, Liverpool ; the Royal National Hospital for Rheumatic Diseases, Bath ; and the Devonshire Royal Hospital, Buxton.

history (or signs) of previous eye disease or eye surgery, and those with any sign of arteriosclerotic retinal vessels (it has been suggested (ter Bals, 1964) that this is a precipitating cause of chloroquine retinopathy), diabetes, or evidence of other collagenoses—for example, skin lesions—or clinicopathological tests. In addition, the few patients whose records were in any way incomplete were disregarded. In a previous survey (Kolb, 1965) the exclusions were fewer and less rigorously applied. This may explain why in this survey, but not in the previous one, it has been found that patients who have never had antimalarials have normal electro-oculograms. It is known that patients with other collagenoses—for example, systemic lupus—have low electro-oculograms (Maguire and Kolb, 1964).

In the main group of patients—that is, those taking antimalarials and having no ophthalmological abnormality—the electro-oculogram is significantly lower than normal. In view of the types of control used, this decrease must be ascribed to the patients' medication. The last patient-group consists of those who had fundal abnormalities. These patients were subject to the same exclusions as the preceding group, and the eye signs consisted in pigmentation, "bull's-eyes," etc. Two further patients had such signs but were excluded because of myopia in one and arteriosclerotic changes in the fundus of another. In this group of patients with eye signs the electro-oculogram was still further depressed, and the difference between this group and the one without eye signs is significant. In view of the exclusions, it again seems that the development of eye signs and depression of the electro-oculogram must be ascribed to the patients' medication.

Analysis by Duration of Treatment

Table II shows the results obtained when the patients are divided into groups according to the duration of continuous treatment. Since the regimen employed differs from physician to physician, and alters during the course of treatment, the total dosage per year of treatment varies. Table II shows that in all groups the electro-oculogram is depressed, and a proportion of patients have fundal abnormalities. However, no very systematic change with length of treatment can be observed.

TABLE II.—Breakdown of Results by Duration of Continuous Therapy

Duration (Years)	Total No. of Patients	Average Dose (g./kg.)	No. of Patients with Eye Signs	E.O.G.
0-1	40	1.25	2	222
1-2	36	2.65	5	215
2-3	28	4.75	5	213
3-4	14	5.95	6	219
4-5	17	7.95	6	225
5+	13	10.3	5	210

Analysis by Dosage

When the patients are divided into groups according to the total dose (g./kg.) a slightly different pattern is observed (Table III). The electro-oculographic depression is apparent even in those who have taken less than 1 g./kg.—this corresponds to about six months' treatment with a commonly employed dosage.

TABLE III.—Breakdown of Results by Dosage

Total Dose (g./kg.)	No.	E.O.G.	No. with Eye Signs	Proportional Frequency
0	30	230	0	—
0-1	27	216	1	0.036
1-2	37	215	1	0.026
2-3	26	210	5	0.160
3-4	21	221	3	0.125
4-5	21	211	3	0.125
5-6	15	209	1	0.063
6-7	14	220	1	0.067
7-8	11	217	1	0.085
8+	20	201*	13	0.395

* E.O.G. significantly lower than average of patients on drugs.

An increase in dosage up to 7 g./kg. has little further effect on the electro-oculogram. However, in the highest-dosage group (more than 8 g./kg.) the average electro-oculogram is significantly lower (t-test) than the rest. Thus total dosage rather than length of treatment may be the decisive factor in causing a decrease in the electro-oculogram.

More revealing is the comparison between electro-oculographic value in the subgroups and the incidence of eye signs. It is apparent that in the highest-dosage group the incidence of eye signs is greater, and significantly greater, than in any of the others. This feature also does not show in Table II, where the patients are divided according to length of treatment. When patients are divided according to total dosage there is a highly significant correlation ($r = -0.74$) between the incidence of eye signs and the depression of the electro-oculogram. This suggests that the same mechanism is responsible for both phenomena. It would be impracticable to analyse the patients with eye signs into further subgroups, for the numbers involved are too few. However, if the electro-oculographic abnormality and the fundal abnormality have a common cause, it is possible to analyse the results of electro-oculographic tests on the large group of patients with normal fundi and extrapolate the result to the disturbance caused by antimalarials in general. This has been done by determining if there is any regression of electro-oculogram on dosage in selected subgroups.

The analysis was undertaken to discover if (1) any particular antimalarial was preferable, (2) if the daily dosage employed was important, and (3) if there was a synergy between drug and disease which together caused the visual disturbance. The result of the analysis has been almost entirely negative. Not only has no correlation been found between dose and electro-oculogram in any subgroup, but the average electro-oculogram in all subgroups are nearly identical. It was found that chloroquine and hydroxychloroquine affect the electro-oculogram identically. Within the limits employed, dose-rate makes no difference, and the electro-oculograms of patients who have had intermittent or continuous therapy are similar. Patients in remission gave the same values as those actively deteriorating; and in those who obtained relief from the drug the results were the same as in those in whom it was ineffectual. It was, however, found that men had slightly higher electro-oculograms than women, as has been previously shown (Kolb, 1965). Since no variable was found to affect the electro-oculogram, slight differences between the control patients and the rest (Table II) could not have caused the observed electro-oculographic depressions: it seems to be proved that antimalarial therapy caused these decreases.

Details of Patients with Eye Signs

Tables IV, V, and VI show the details of patients with eye signs, and give comparisons with the other patients. Those patients with fundal abnormalities have been divided into two groups, depending upon whether or not they were taking the drug when the electro-oculogram was measured. The latter group either had finished a course, had complained of visual symptoms, or had had the drug withdrawn as a result of the ophthalmologist's examination. The former group, taking the drug, either had not seen an ophthalmologist or had been allowed to continue. Consequently, this group shows less severe signs than those who had stopped treatment. In other respects the two groups are very similar. The average age is the same as in the total patient group, and the sex ratio is similar (Table V). The average duration of illness is as expected (Table VI). The total amount of drug ingested varies greatly, but the average is nearly twice that of the drug taken by the patient-population as a whole—a highly significant difference (Table VI). The dose-rate is not significantly different from normal.

The most common eye sign reported is pigmentation—in fact in only 2 of the 16 cases still on medication was any other sign reported. The reports made it clear that the pigmentation was not always bilateral or confined to the central retina. The next most common eye sign was the "bull's-eye." Again this was not always bilateral. In only two cases were alterations of vessels noted, in association with obvious retinopathies with field loss. In only one case was visual acuity severely decreased. The electro-oculogram was depressed in both groups of patients (Table VI). The absolute value is lower in those still taking the drug, but the percentage depression is greatest in the second group, for their average electro-oculogram should be compared with the higher normal value. In both groups the additional depression associated with the development of eye signs is highly significant.

In view of the minimal funduscopy findings, especially in the patients still taking antimalarials, it might be argued that the ophthalmologist's report of pigmentation was often mistaken.

This is most unlikely to be the case, since patients who had never taken antimalarials were not found to have an abnormal fundus. In addition, this group of patients had a high average intake of antimalarials, and the electro-oculogram was very low. This could not have occurred in a random sample.

Additional Results

The electro-oculograms of patients without eye signs and not taking antimalarials (Table I, group 2) were regressed against the length of time the drug had been discontinued. No significant correlation was found. Finally, the statistical analysis of the results has been confined to *average* electro-oculographic values. These, it has been shown, are reliable, but it should be emphasized that individual results are subject to considerable scatter. The accompanying Chart shows individual electro-oculographic results plotted against total dosage. Electro-oculograms are plotted as logarithmic fractions of the mean. It

TABLE IV.—Summary of Data on Patients with Eye Signs

Case No.	Age	Sex	Drug	Time Off Drug (Months)	Dose (g./kg.)	Dosage Duration (Months)	Illness Duration (Months)	Eye Signs* (Summary of Fundoscopy Report)	Fields	Corrected Acuity		E.O.G.
										R.	L.	
2	52	M	C	—	3.75	18	61	Peripheral and macular pigmentation	Full	6/5	6/5	186
16	32	F	C	—	7.15	60	246	Bull's-eyes	"	6/18	6/16	155
19	51	F	H	—	6.75	40	61	Pigmentation	"	6/5	6/5	235
29	63	M	H	—	12.95	57	120	"	"	6/5	6/5	205
30	39	F	H	—	2.35	22	24	Faint granular pigmentation	"	6/5	6/9	204
37	45	M	C	—	2.09	28	120	Pigmentation	"	6/5	6/5	170
39	37	F	H	—	17.85	77	120	Diffuse pigmentation	R. upper temporal constriction	6/6	6/6	144
40	37	M	H	—	14.10	48	48	Slight pigmentation	Full	6/5	6/5	218
41	34	M	C	—	13.35	60	166	Pigmentation	"	6/5	6/5	258
105	53	F	C	—	4.20	41	96	Granular pigmentation	"	6/5	6/5	160
284	72	F	C	—	16.05	18	60	"	"	6/12	6/12	200
293	64	M	C	—	17.65	55	132	Pigmentation left eye	"	6/6	6/6	179
331	50	M	C	—	2.19	22	24	Abnormal macular appearance	"	6/4	6/5	195
51	48	F	H	—	0.50	6	72	Progressive central and peripheral pigmentation and loss of foveal reflex	"	6/5	6/5	195
253	79	F	C	—	3.72	36	48	Macular degeneration	Peripheral constriction	6/12	6/12	192
305	54	M	H	—	2.85	24	48	? Early macular changes	Full	6/6	6/4	230
34	49	F	H	4	2.90	28	130	Faint pigmentation	"	6/6	6/6	193
64	45	F	C	60	10.60	28	144	Disciform degeneration, arteries attenuated	Bilateral central scotomata	6/60	6/60	194
84	70	M	C	6	4.25	39	60	Bull's-eyes	—	6/12	6/9	282
85	50	M	C	4	4.35	51	96	Bull's-eye R.	Full	6/6	6/6	177
141	58	F	C	9	16.05	48	96	Bull's-eyes	—	6/18	6/18	194
145	59	F	C	6	14.65	66	384	"	Full	6/4	6/6	253
159	59	F	C	2	8.55	57	132	Granular pigmentation R. fundus	"	6/5	6/4	231
162	61	F	C	15	5.20	48	60	Progressive granular change R. eye	Paracentral scotoma	6/6	6/6	221
168	45	F	C	12	3.05	31	96	Abnormal maculae	Full	6/4	6/4	180
296	63	F	C	4	12.10	100	156	Progressive pigmentation	"	6/9	6/6	161
328	53	M	C	3	9.60	98	120	Vessels attenuated, bull's-eyes	Central scotoma	6/5	6/5	128
7	54	M	C	6	1.35	7	18	Diffuse pigmentation? due to chloroquine?	Full	6/5	6/5	302
14	53	F	C	2	12.25	72	92	Macular degeneration	R. central scotoma	6/12	6/6	197

C = Chloroquine. H = Hydroxychloroquine

* Bilateral macular pigmentation unless otherwise noted.

TABLE V.—Summary of Age, Sex Ratio, and Drug Employed

	Age	Men	Women	Chloroquine	Hydroxy-chloroquine
Patients with eye signs	52.6	12	17	21	8
Patients without eye signs	51.0	138	63	152*	38*

* In two cases both drugs were employed in equivalent doses.

TABLE VI.—Summary of Dosage, Length of Treatment, Length of Illness, and E.O.G.

	No.	Dosage (g./kg)	Duration of Therapy (Months)	Rate of Ingestion (g./month)	Illness Duration (Months)	E.O.G.
Patients with eye signs	16	7.87	38.3	11.94	91	195 ±
Patients without eye signs	13	8.07	39.1	12.02	104	209 ±
	192	4.46	25.7	10.32	98	216 ±
	28					235 ±

Probability (P) of these being due to chance (t test):
* P < 0.01. † P < 0.01. ‡ 0.05 < P < 0.10.

Scattergram of all E.O.G.s of 192 patients without eye signs and on drugs.

can be seen that many individual patients had electro-oculograms well above the average normal: the average retinopathy result is above the lower limit of normal; and about 10% of the results are below the lower limit of normal even though no abnormality was detected in the fundus. The significance of these results is discussed below.

Discussion

The incidence of minor retinal abnormalities in this survey (29 out of 211 patients) is high, but is in agreement with the results of most previous surveys (Nylander, 1963; Henkind *et al.*, 1964; Lloyd and Hiltz, 1965; Butler, 1965). As a result of this survey it is possible to give some answers relating to the management of patients who are taking chloroquine. It appears from our analysis that the ocular complications observed are related to the drugs, and have no relation to rheumatoid arthritis or senescence. Within the range of dosage employed by the clinicians the determining factor appears to be the total dosage ingested.

Of the warning signs that retinal damage may occur the most promising would seem to be the detection of fundal pigmentation. It is obviously of no use waiting till visual disturbances occur. The striking appearance of the "bull's-eye" was in three of six instances associated with depressed visual acuity. Though the "bull's-eye" may clear up when the drug is withdrawn (Crews, 1964), it may also progress (Henkind *et al.*, 1964) to a retinopathy with field loss; it would therefore not be wise to wait for the development of a "bull's-eye" before taking patients off their antimalarial therapy.

The individual variation of the electro-oculogram is so great that a single test cannot be used to decide whether a patient should continue taking antimalarial drugs or not. Progressive decline in the electro-oculogram during medication might be more reliable; no statistical information is, however, available. Since antimalarial drugs cause a rapid decrease in the electro-oculogram in the absence of other evidence of retinal damage, any additional decrease occurring just before a retinopathy developed would be hard to detect with certainty.

Though the presence of fundal pigmentation seems the most promising way of detecting antimalaria-induced damage, it is necessary to inquire how a positive diagnosis can be made, and what is the exact relation between pigmentation and the onset of the retinal damage. In this survey the diagnosis was made on subjective grounds alone, but the aid of fundus photography would be desirable. Some normal fundi may have been termed pigmented by the ophthalmologist—Case 7 (Table IV) may be such an instance. However, the incidence of false-positive diagnoses must be low. No patient who had not taken antimalarial drugs was so diagnosed, and the pigmented group has significantly different electro-oculograms and drug intakes from the rest of the patients.

About 10% of the patients who were said to have normal fundi had electro-oculograms below the lower limit of normal. If the effect of antimalarials was merely to depress the average electro-oculogram slightly, such a large proportion of abnormal electro-oculograms would not have been found. In addition, some of the patients who had low electro-oculograms were re-examined (at a later date), and fundal abnormalities were then detected. These facts make it likely that the ophthalmologists were rather conservative in their diagnoses, and passed as normal fundi those which were truly abnormally pigmented. This would also be expected if the incidence of false-positive diagnoses was low. The electro-oculogram may therefore be of use in doubtful cases.

This survey was not designed to find out how long after the development of fundal pigmentation a true retinopathy developed, but it is obvious from the results that some time must elapse; otherwise the incidence of florid retinopathy would be much higher than it was. Table IV, column 5, illustrates this point. If, very soon after the eye signs appeared, vision was lost to an extent where the patient complained, the drug would at once be withdrawn. The proportional incidence column would then be cumulative: no patient who developed an eye sign would go on taking the drug and enter the next dosage group. Less than half would complete a course of 500–600 g. This obviously does not describe the true situation.

It seems, therefore, that the development of pigmentation in the fundus of a patient who is taking antimalarial drugs need not be an absolute and automatic bar to continuing treatment. However, these signs (and florid retinopathies) can occur very soon after treatment has started. It does seem certain that doses of 8 g./kg. or more carry a high risk of producing retinal damage/fundal abnormalities. It is of some importance that no less than 10% of our patients had received such doses.

Summary

A survey has been made of patients with rheumatoid arthritis who were treated with antimalarial drugs. The overall incidence of retinal changes attributable to this therapy is 13%, and in the group who had taken more than 8 g./kg., 40%. Doses of this size were given to one patient in seven. No specific rheumatic factor could be demonstrated.

The most common retinal change was an alteration in pigmentation. No specific regimen of dosage was preferable. The high incidence of retinal change found is related to the minor nature of the eye signs noted, but it is felt that these are indications for stopping treatment, since the appearance of the more dramatic lesions, "bull's-eyes," is associated with irrecoverable loss of vision.

The patients for this survey were provided by Professor J. H. Kellgren and Dr. A. J. Popert (Manchester), Dr. H. L. F. Curry (London Hospital), Dr. L. Fuld (Liverpool), Professor E. G. L. Bywaters and Dr. M. Ward (Hammersmith and Taplow), Dr. I. Meanock (Reading), Dr. A. Friedman (Hackney), and Dr. G. D. Kersley (Bath). We thank them for their help, which made the work possible, and for assistance in preparing the paper. We are also greatly indebted to the numerous ophthalmologists associated with the hospitals concerned for their valuable co-operation.

This work was financed by a grant from the Bayer Products Company Ltd., and we would like to express our thanks to them for this, and for the assistance given by Dr. L. Goldmann, their Medical Director.

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