Chloroquine and Hydroxychloroquine Therapy in Rheumatoid Arthritis

By EDWARD SCULL

One hundred and ninety-six poorly controlled rheumatoid arthritics were divided into three groups: 80 received chloroquine, 80 hydroxychloroquine, and 36 placebo, for an average duration of 24, 18 and 5.2 months respectively. Fifty-seven per cent of patients were able to reduce or abolish their corticosteroid requirements while on the active drugs under study. It appeared from this study that chloroquine and hydroxychloroquine possessed definite antirheumatic effect. No serious side effects were observed.

Un serie de 196 patientes con mal stabilisate arthritis rheumatoide esseva devidite in tres gruppos: 80 recipeva chloroquina, 80 hydroxychloroquina, e 36 placebo durante, al media, 24, 18, e 5,2 menses, respectivemente. Cinquanta-septe pro cento del patientes esseva capace a reducer o abolir lor requirimentos de corticosteroide durante que illes recipeva le drogas active. Il pare ab iste studio que chloroquina e hydroxychloroquina possede definite virtutes antirheumatic. Nulle serie effectos lateral esseva notate.

FOLLOWING the accidental discovery in 1951 by Page[1] that quinacrine (Atabrine) produced an antirheumatic response in all but one of 18 patients with lupus erythematosus, several investigators have shown that antimalarial drugs are of potential value in the treatment of rheumatic and other inflammatory diseases. Encouraging results were obtained with both quinacrine and primaquine, but with such high incidence of toxicity that attention has been more recently turned toward the less toxic and better tolerated 4-aminoquinoline derivatives.[2-6]

It is well known that the successful management of rheumatoid arthritis is dependent upon the control of the systemic disease itself rather than the mere reduction of the inflammation in the affected joints. Although steroids assist in such control, the toxic effects frequently offset the benefits. Therefore, special attention was devoted to the degree, if any, by which the total daily dosage could be reduced during the course of antimalarial therapy.

This paper is a study of 196 patients who have classical or definite rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association. These 196 patients are divided into three groups: 80 patients received chloroquine;* 80 patients received hydroxychloroquine;* and 36 patients received a placebo tablet resembling hydroxychloroquine.

METHODS

Group I. Eighty rheumatoid arthritis patients (52 females, 28 males) whose progress under cortico-steroid medication and acetylsalicylic acid therapy was not satisfactory were given chloroquine (Aralen) as an adjunct. The age range was five to 75 years, and the

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*Chloroquine (Aralen) and hydroxychloroquine (Plaquenil) supplied by Winthrop Laboratories.

duration of the arthritic disease varied from three months to 30 years. Under the criteria of the American Rheumatism Association† the 80 patients were classified as follows: Stage I (early), 13 patients; Stage II (moderate), 24 patients; Stage III (severe), 26 patients; Stage IV (severe plus ankylosis), 17 patients. All had been on moderate dosage of corticosteroids as well as at least 40 gr. of acetylsalicylic acid daily for at least one month prior to the administration of chloroquine. A modified program of home physical therapy consisting of daily therapeutic exercises, heat to the affected joints, and modified physical activity was carried out.

Seventy-eight patients received a single daily dose of 250 mg. of chloroquine at bedtime. One child of five received 125 mg. daily and one adult female took 1,000 mg. daily through mistaken instructions. Chloroquine therapy for the group was maintained an average of 24.2 months, with one case so maintained for 48 months and 62 patients for nearly 36 months. Acetylsalicylic acid and corticosteroids were continued during chloroquine therapy except for repeated attempts to reduce or abolish steroid dosage when permitted by the clinical improvement of the patient. At the completion of this study the patients were evaluated as to grade of improvement and functional abilities (class) according to the criteria established by the American Rheumatism Association.

Group II. Eighty patients with rheumatoid arthritis of six months to 30 years duration (56 females, 24 males) ranging in age from 17 to 71 years constituted the second group under study. Under the criteria of the American Rheumatism Association, their disease was classified as follows: Stage I, 29; Stage II, 18; Stage III, 21; Stage IV, 12. Of these 80 patients, 59 had received corticosteroid therapy plus at least 40 gr. of acetylsalicylic acid for a minimum of one month prior to the study. The remaining 21 patients received acetylsalicylic acid only. All patients were on a modified home physical therapy program similar to those in Group I. The patients in this group received hydroxychloroquine (Plaquenil) in doses of 200 mg. at breakfast and again at bedtime for a period of two weeks to 29 months with the average duration being 17.7 months, 41 received hydroxychloroquine for 21 months or more.

Group III. The third group consisted of 36 patients (26 females, 10 males) who received placebo medication resembling hydroxychloroquine in appearance. The age range was from 22 to 55 years and duration of the disease process from nine months to 15 years. By stage they were classified as: Stage I, 18; Stage II, 8; Stage III, 8; Stage IV, 2. Thirty patients had been receiving corticosteroid medication plus acetylsalicylic acid, 40 gr. or more daily, while six received only high doses of salicylates. All patients were observed

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†I. Stage of disease according to American Rheumatism Association criteria:
- Stage I: Early (no destructive changes radiologically).
- Stage II: Moderate (slight cartilage or bone destruction without joint deformity).
- Stage III: Severe (cartilage and bone destruction with joint deformity).
- Stage IV: Terminal (bony or fibrous ankylosis).

II. Grades of response according to American Rheumatism Association criteria:
- Grade I: Complete remission.
- Grade II: Major improvement.
- Grade III: Minor improvement.
- Grade IV: No improvement or regression.

III. Classification of functional impairment according to American Rheumatism Association criteria:
- Class I: Ability to carry out all usual duties without handicaps.
- Class II: Ability adequate for normal activities despite discomfort or limited joint motion.
- Class III: Ability to perform only few or none of the duties of usual occupation or self care.
- Class IV: Largely or wholly incapacitated, able to perform little or no self care.

Table 1.—*Grade and Class Before and After Chloroquine Therapy*

	Grade*	I	II	III	IV
Initial	Number	0	4	62	14
	Percentage	0	5	77.5	17.5
Final	Number	7	38	28	7
	Percentage	9	47	35	9
	Class*	I	II	III	IV
Initial	Number	2	40	30	8
	Percentage	2.5	50	37.5	10
Final	Number	27	39	12	2
	Percentage	33.5	49	15	2.5

*American Rheumatism Association classification.

a minimum of one month prior to the addition of placebo to their already established therapeutic program. The placebo was administered for a minimum duration of four months and a maximum duration of six months with average duration being 5.2 months.

Results

As can be seen from table 1, the effect of chloroquine upon the group as a whole was quite favorable. Of the 80 patients, 76 (95 per cent) had shown either Grade III or IV response to corticosteroid and aspirin therapy prior to the addition of chloroquine to their therapeutic regimen, while distribution by grade after chloroquine therapy shows only 35 (44 per cent) in these poor response categories. Forty-five patients (56 per cent) fell within Grades I and II upon conclusion of the study.

Similarly, comparison of patient distribution by functional abilities before and after chloroquine therapy shows the number in Classes I and II raised from an initial 42 (52.5 per cent) to a final 66 (82.5 per cent). The degree of improvement in 71 individual cases varied from imperceptible to dramatic. In the other nine cases the disease process worsened during chloroquine therapy. No correlations between degree of improvement and physical, hematologic, or historical factors were observed, making it impossible to predict the response of a given patient to the drug.

Of this group of 80 patients, 44 (55 per cent) were able to reduce or abolish their steroid intake. Of these, 11 (14 per cent) were able to forgo steroids entirely. Reduction in total daily dosage ranged from 20 to 100 per cent with a mean of 72 per cent for the 44 cases. Twenty-seven patients (34 per cent) were maintained on the same steroid dosage as before chloroquine therapy. Of these, 14 remained in the same grade and class, three improved as to grade alone, four improved as to class alone, and six improved in both grade and class. In the remaining nine (11 per cent) patients, it was necessary to increase steroid dosage while on chloroquine therapy to maintain the initial grade and class.

Side effects: Severe gastrointestinal upsets requiring drug withdrawal occurred in six patients. However, these patients had been easily and frequently provoked to similar symptoms by other medications prior to the institution

of the antimalarial drug, suggesting the effect was not drug specific. Aside from these, 16 patients (20 per cent) exhibited side effects consisting of significant (10 pounds plus) weight loss (6 cases), rash (three cases), depigmentation of hair (four cases), and one case each of nausea, vertigo and worsening of psoriasis. The "seasickness" described by Bagnall[5] was notably absent, perhaps because all patients took the medication at bedtime. There were no cases of corneal deposits as described by Zeller and Deering.[7]

In all six cases of weight loss (which varied from 10 to 20 pounds) chloroquine was discontinued, although five of the six cases had shown definite improvement while receiving the drug. All returned to their previous body weights within four months after cessation of chloroquine therapy. Two of the patients with rashes were notoriously sensitive to various medications. The four cases of depigmentation of hair occurred in females (with very light complexion and blond hair). Normal hair color returned within four months after cessation of chloroquine therapy in all four cases. It may be noteworthy that the single case of worsened psoriasis was in contrast to two other cases of rheumatoid arthritis with psoriasis in which there was no evidence of psoriatic flare-up during the treatment period. No evidence of depression of white blood counts or other hematologic disorders were observed.

One female patient took 1,000 mg. of chloroquine daily by mistaken instructions (250 milligrams q.i.d.) and serves as an indicator of the result of massive overdose of this medication. This patient had been on a regimen of 250 mg. of chloroquine daily for 12 months and had shown improvement from Grade III to Grade II when the medication was discontinued. During the following seven-month period there was gradual increase in stiffness and pain, and the drug was reinstituted at the incorrect 1,000 mg. daily dosage for five months. By the fourth month the patient gradually noted development of nausea, blurred vision, vertigo, very severe depigmentation of her hair, eyebrows and eyelashes, and a 20-pound weight loss. Despite the above complaints she stated, however, that she generally felt well and that her arthritis and functional capacities were considerably improved. No changes occurred in her hemogram and liver function studies; serum electrolytes and renal function studies were all within normal limits. Within two weeks after stopping chloroquine her rheumatoid arthritis became worse objectively and subjectively. Return of pigmentation of her hair started within two weeks and weight was regained to her previous amount at the end of four months.

With regard to Group II, it can be seen in table 2 that the number of patients initially falling into Grades III and IV was 48 (60 per cent). At the completion of this study only 17 patients (21 per cent) were in either Grade III or IV and 63 patients (79 per cent) were classified as Grade I or II.

The functional classification of this group showed a similar improvement with 73 patients (91 per cent) being in Class I or II in contrast to the initial evaluation of 60 patients (75 per cent) in Classes I or II. It should be noted that the significant change was the increase of Class I from eight patients (10 per cent) to 47 patients (59 per cent).

Of the 59 patients in Group II who were on corticosteroid medication at the beginning of this study, 35 (59 per cent) were able to reduce or abolish their

Table 2.—*Grade and Class Before and After Hydroxychloroquine Therapy*

	Grade*	I	II	III	IV
Initial	Number	0	32	38	10
	Percentage	0	40	47.5	12.5
Final	Number	15	48	14	3
	Percentage	18.75	60	17.5	3.75
	Class*	I	II	III	IV
Initial	Number	8	52	20	0
	Percentage	10	65	25	0
Final	Number	47	26	6	1
	Percentage	58.75	32.5	7.5	1.25

*American Rheumatism Association classification.

corticosteroid requirements with the average reduction being 67.4 per cent of the initial steroid dosage. The average reduction for the 59 patients as a group was 40 per cent. Ten patients (17 per cent of the 59 patients) were able to abolish their corticosteroid needs. However, there were eight patients (10 per cent) who, because of increased severity of their disease process, had to increase their corticosteroid medication to maintain their initial grade and/or class. Two of these eight patients had acute exacerbations while on hydroxychloroquine therapy. One case had a generalized flare-up following an automobile accident in which she received multiple contusions. The other patient exacerbated following severe menorrhagia causing her to develop a profound anemia.

In this second group of 80 patients, seven (8.75 per cent) developed significant side effects necessitating cessation of hydroxychloroquine therapy. Two patients developed generalized maculopapular rashes and in one of these a high spiking fever of eight days duration occurred. (No other cause for this could be found, hence hydroxychloroquine was incriminated.) Of the remaining five, two had severe gastrointestinal upsets, two had vertigo ("seasickness") and one woman experienced a 10-pound weight loss. In no case was depression of the white blood count or other hematologic abnormalities observed.

Twenty-six of the 36 patients in Group III (72 per cent) were in Grade II and 10 patients (28 per cent) were in Grade III at the initiation of this study. (See table 3.) At the completion of the observation period, 23 patients (64 per cent) were in either Grades I or II and 13 patients (36 per cent) were in either Grades III or IV.

The overall functional classifications remained unchanged with 31 patients (86 per cent) being in Class I or II and 5 patients (14 per cent) being in Class III or IV both at the beginning and end of the study. Of the 30 patients who were on corticosteroid medication, 6 (20 per cent) were able to reduce, but not abolish, their corticosteroid requirements for an average of 33.3 per cent. Three patients (8.3 per cent) during this observation period, while receiving corticosteroid medication, had definite worsening of their disease process.

Table 3.—*Grade and Class Before and After Placebo Therapy*

	Grade*	I	II	III	IV
Initial	Number	0	26	10	0
	Percentage	0	72.2	27.75	0
Final	Number	2	21	12	1
	Percentage	5.5	58.3	33.1	2.7
	Class*	I	II	III	IV
Initial	Number	7	24	3	2
	Percentage	19.4	66.6	8.3	5.8
Final	Number	11	20	4	1
	Percentage	30.6	55.5	11.1	2.7

*American Rheumatism Association classification.

Within this group of 36 patients, two developed rashes (not observed by the author) and two developed gastrointestinal distress. In no cases were any hematologic changes observed.

Discussion

By analyzing the clinical response of 196 patients with classical or definite rheumatoid arthritis (meeting the criteria of the American Rheumatism Association), 160 of whom received an antimalarial and 36 a placebo, it appeared that chloroquine and hydroxychloroquine possessed definite antirheumatic effect in rheumatoid arthritis. A highly significant change of both grade and class from the initial evaluation to the final evaluation occurred in patients receiving the supplementary active agents ($P = > .001$).

Comparison of Group I (chloroquine) with Group II (hydroxychloroquine) cannot be made because the two groups of 80 patients are not exactly comparable due to the highly variable nature of rheumatoid arthritis. The patients themselves, however, served as their own controls in that all were observed for one or more months and graded as to their therapeutic response prior to the institution of the antimalarial compounds. Those patients receiving corticosteroid medication were almost exclusively on prednisone with the dosage varying from 4 mg. up to 12.5 mg. daily and the average daily prednisone requirement for all three groups at large being approximately 7.5 mg. All patients, with the exception of three who were sensitive to acetylsalicylic acid, received a daily dosage varying betwen 40 to 80 gr. With few exceptions the patients did not alter their daily acetylsalicylic acid intake according to the minor fluctuations of their basic disease process.

It is noteworthy that 57 per cent of those patients receiving corticosteroid medication in both Groups I and II were able to either reduce or abolish their corticosteroid therapy and of these 11 (14 per cent) and 10 patients (17 per cent) in Groups I and II respectively were able to completely forgo their steroid needs. The average reduction of corticosteroids in both groups was surprisingly similar (72 per cent and 67 per cent) as compared with 33.3 per cent in the placebo group. In both groups a similar percentage (11 per cent for Group I and 10 per cent for Group II) had definite exacerbation or relapses of

their rheumatoid arthritis. This corresponds to the 8.3 per cent of the placebo treated group that had worsening of their disease process during the observation period.

Evaluation of the functional capacities of the patients comprising these study groups was more difficult to determine because of the problems involved in obtaining comprehensive objective measurements and the subjective interpretation by both the patients and the observer. Most patients of the groups receiving chloroquine and hydroxychloroquine, although not necessarily having a rated improvement in their functional classification, nevertheless stated that they noted moderate to marked dimunition of morning pain and stiffness in particular, and definite increase in their ability to do ordinary activities, such as dressing, house cleaning and other household chores, as well as employment requirements.

Fifteen of the 17 patients in whom the antimalarial drugs had to be stopped because of adverse side effects, noted a definite increase in their morning stiffness and soreness on cessation of the drug. This increase, however, was not necessarily of such severity as to reduce their broad functional classification.

It is of interest to note that the placebo treated group had an incidence of 11.1 per cent side effects in contrast to the 9 per cent of the hydroxychloroquine treated group and the 20 per cent (or more) of the chloroquine treated Group.

SUMMARY

In a comparative study involving 196 patients with rheumatoid arthritis, both chloroquine and hydroxychloroquine, in contrast to a placebo, were shown to bring about clinical improvement in a significant percentage of cases. These drugs allowed the reduction or withdrawal of corticosteroid therapy in considerable number. Although side effects were observed, these were not serious in that all readily reversed when the drugs were withdrawn.

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