IV. COMPARISON OF EFFECTS OF TWO ANTIMALARIAL AGENTS, HYDROXYCHLOROQUINE SULFATE AND CHLOROQUINE PHOSPHATE, IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SOME of the antimalarial agents that have a valuable anti-inflammatory action in patients having discoid or systemic lupus erythematosus have been found to have a similar effect in patients having rheumatoid arthritis.[34,35] However, these drugs have not been used widely for rheumatoid arthritis because of their undesirable side effects.

The first antimalarial agent used in the treatment of discoid lupus erythematosus was quinacrine hydrochloride*, an acridine derivative,[36] but the undesirable side effects of this drug often were serious and sometimes fatal; they included nausea, anorexia, vomiting, dermatitis, nervousness, insomnia, headache, blurring of vision, agranulocytosis, and aplastic anemia. Primaquine diphosphate**, an 8-aminoquinoline, also was found to have anti-inflammatory activity, but its side effects, as reported by Steck and his group,[37] prevented its widespread clinical use. They found methemoglobinemia and pallor in all, anorexia in 14, and leukopenia in 7 of 21 patients having rheumatoid arthritis who were given the drug for two weeks.

Chloroquine phosphate, a 4-aminoquinoline, has been reported to be effective in the treatment of both systemic lupus erythematosus and rheumatoid arthritis. Dubois and Martel[38] believe that chloroquine phosphate is as effective as quinacrine hydrochloride in the treatment of moderately active systemic lupus erythematosus. Freedman[39] reported the effect in 50 patients with rheumatoid arthritis who received 300 mg. of chloroquine sulfate daily for two years. Apparently 43 patients became entirely or nearly asymptomatic, although some continued to have elevated sedimentation rates, which indicated that disease activity persisted. Of the other seven patients, three continued to have slight joint inflammation and four failed to show satisfactory response to the drug. No significant toxic effects were noted in any of the 50 patients. Freedman believed that the results of his study warranted a larger investigation.

**Atabrine hydrochloride, Winthrop Laboratories.*

***Primaquine diphosphate, Parke, Davis & Co.*

In 1950 hydroxychloroquine sulfate, a new 4-aminoquinoline, was introduced as an antimalarial drug that potentially has a high degree of clinical safety and effectiveness. Reports [40-42] substantiate its efficacy in the management both of discoid and of systemic lupus erythematosus, and its relatively nontoxic influence. To date toxic reactions are reported as being few and not serious.[40,43]

It is the purpose of our report to describe the effects of hydroxychloroquine sulfate in patients with active rheumatoid arthritis, and to compare these effects with those in a similar group of patients who received chloroquine phosphate for 18 months.

Methods

Forty-five patients having active rheumatoid arthritis of varying severity of 15 months' to 26 years' duration received oral antimalarial therapy; results were evaluated after 18 months. Twenty-six patients were given hydroxychloroquine sulfate in doses of from 200 to 600 mg. daily. When improvement occurred the dose was reduced to one half of what they had been receiving. Ten of the 26 patients were hospitalized for treatment. Twenty-five patients received chloroquine phosphate. Initially the dosage was 0.5 gm. daily; when improvement occurred, usually within six to eight weeks, the dose was reduced to 0.25 gm. Eight of the 25 patients were hospitalized for treatment. Hospitalized patients in both groups received daily physiotherapy, and sodium salicylate, 1-gm. doses four times daily for the relief of pain.

Results

Clinical status after 18 months (Tables 1, 2). In the group of 26 patients who were receiving hydroxychloroquine sulfate, 15 patients were asymptomatic, 5 patients showed significant improvement, and 6 patients had unsatisfactory results (3 could not tolerate the medication, which had to be stopped after a few days, and 3 were considered 'drug failures' showing grade 4 improvement after from six to nine months of therapy).

The 25 patients who were receiving chloroquine phosphate could be classed nearly equally into three groups: Nine patients were asymptomatic, eight showed moderate improvement, and eight had unsatisfactory results (six could not tolerate the medication, which had to be stopped after a few days or weeks, and two were considered 'drug failures').

Improvement never was dramatic and usually began between the third day and the fourth week. The first sign of improvement usually was a decrease in joint pain, followed by a decrease in the gel reaction. Acute joint inflammation often persisted for 10 days or longer after therapy had been started; effusions disappeared slowly and at times incompletely. Muscular strength returned to normal in 11 and improved significantly in 4 of 18 patients who had muscular

Table 1.—*Comparison after 18 months of the effect of hydroxychloroquine sulfate and of chloroquine phosphate in patients with rheumatoid arthritis*

Drug	Number of patients	Grade* of disease	Class**				Duration of disease	Response† after 18 months			
			1	2	3	4		1	2	3	4
			No. of patients					No. of patients			
Hydroxychloroquine sulfate	7	1	0	2	3	2	16 mo. to 2 yr.	3	2	1	1
	10	2	0	5	5	0	19 mo. to 4 yr.	5	2	1	2
	5	3	0	1	3	1	3 yr. to 12 yr.	0	2	2	1
	4	4	0	1	2	1	3 yr. to 18 yr.	0	1	1	2
Total	26		0	9	13	4		8	7	5	6
Chloroquine phosphate	6	1	0	3	2	1	15 mo. to 3 yr.	2	1	1	2
	6	2	0	4	2	0	17 mo. to 8 yr.	1	1	3	1
	8	3	0	2	5	1	2 yr. to 15 yr.	1	1	3	3
	5	4	0	1	3	1	3 yr. to 26 yr.	0	2	1	2
Total	25		0	10	12	3		4	5	8	8

Adapted in part from A.R.A. classification.[18]

**Grade of disease: 1—joint swelling; 2—early cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class: 1—no symptoms with full activity; 2—minor symptoms with full activity; 3—moderate-to-severe symptoms with restricted activity; 4—moderate-to-severe symptoms at rest.*

†*Response: 1—asymptomatic, normal sedimentation rate and serum polysaccharide-protein ratio; 2—asymptomatic, abnormal sedimentation rate and serum polysaccharide-protein ratio; 3—significant improvement with minor joint manifestations; 4—minor improvement with significant joint manifestations.*

Table 2.—*Summary of results after 18 months of treatment with hydroxychloroquine sulfate or with chloroquine phosphate in patients with rheumatoid arthritis*

Grade of disease (See Table 1.)	Results* in 26 patients treated with hydroxychloroquine sulfate	Results** in 25 patients treated with chloroquine phosphate
1	**7 patients:** Of 6 patients able to tolerate drug, 5 were asymptomatic, 1 had minor symptoms. Drug was stopped in 1 patient because of gastrointestinal distress.	**6 patients:** Of 4 patients able to tolerate drug, 3 were asymptomatic, 1 had minor symptoms. Drug was stopped in 2 patients: 1 because of skin reaction, 1 because of gastrointestinal distress.
2	**10 patients:** Of 9 patients able to tolerate drug, 7 were asymptomatic, 1 had significant improvement, 1 had minor or grade 4 improvement. Dose was reduced in 1 patient and drug was stopped in 1 patient because of gastrointestinal distress.	**6 patients:** Of 5 patients able to tolerate drug, all were asymptomatic sometime during 18 months, but 3 developed additional joint manifestations after six months. Dose was reduced in 2 patients: 1 because of gastrointestinal distress, 1 because of tinnitus. Drug was stopped in 1 patient because of gastrointestinal distress.
3	**5 patients:** Of 4 patients able to tolerate drug, 2 were asymptomatic and 2 had significant improvement. Dose was reduced in 1 patient because of gastrointestinal distress. Drug was stopped in 1 patient because of maculopapular rash with local exfoliation.	**8 patients:** Of 6 patients able to tolerate drug, 2 were asymptomatic, 3 had significant improvement, 1 had minor or grade 4 improvement. Dose was reduced in 5 patients: 3 because of mild gastrointestinal distress, 2 because of nervousness. Drug was stopped in 2 patients: 1 because of dermatitis, 1 because of gastrointestinal distress.
4	**4 patients:** Of 4 patients able to tolerate drug, 1 patient was asymptomatic, 1 had significant improvement, 2 patients had minor or grade 4 improvement. Dose was reduced in 1 patient because of nervousness and slight mental confusion which subsided after first week of therapy.	**5 patients:** Of 4 patients able to tolerate drug, 2 were asymptomatic, 1 had significant and 1 had minor or grade 4 improvement. Dose was reduced in 1 patient because of gastrointestinal distress. Drug was stopped in 1 patient because of itching of the skin.

**Of 6 patients classified as showing grade 4 improvement, 3 were unable to tolerate the drug and 3 showed unsatisfactory improvement under medication.*

***Of 8 patients classified as showing grade 4 improvement, 6 were unable to tolerate the drug, and 2 showed unsatisfactory improvement under medication.*

weakness with or without atrophy. An increase in sense of well-being occurred in one patient; however, depressed psychomotor activity usually remained unaltered. Increased sedimentation rates and serum polysaccharide-protein ratios were noted in all patients; they returned to normal in 8 of 26 patients receiving hydroxychloroquine sulfate, and in 4 of 25 patients receiving chloroquine phosphate. No patient had abnormal changes in the blood count.

Side effects (Table 3). Headache or blurring of vision, which disappeared spontaneously after a few weeks, occurred in five patients and gastrointestinal symptoms in four of the 26 patients receiving hydroxychloroquine sulfate; medication was stopped in two of the latter four patients because of the severity and persistence of symptoms. One patient developed a maculopapular rash with mild exfoliation over the hands and feet; the drug was stopped. Increased nervousness and lightheadedness associated with mild temporary mental confusion during the first week of therapy were noted in one patient. These symptoms subsided spontaneously during the second week of therapy.

About one half (13) of the 25 patients who received chloroquine phosphate noted headache or blurring of vision, symptoms that usually were transient and subsided spontaneously in from two to four weeks. Varying degrees of gastrointestinal distress (anorexia or nausea) were noted in eight patients. These symptoms were partially alleviated by medication taken with meals; occasionally they subsided spontaneously or by reduction in dosage, but in three patients they were so severe that administration of the chloroquine phosphate had to be stopped and hydroxychloroquine sulfate then was substituted. In two patients dermatitis developed within two weeks after chloroquine phosphate therapy was started and medication had to be discontinued. In one patient the maculopapular rash disappeared within 36 hours after medication was stopped, but in the other patient exfoliative dermatitis developed. Another patient noted generalized itching of the skin, which disappeared when administration of chloroquine phosphate was stopped. An increase in nervousness and aggravation of pre-existing insomnia occurred in one patient, and tinnitus and lightheadedness in another, but these symptoms subsided when the dose was reduced.

Contraindications

The antimalarial agents appear to cause very few serious side actions in rheumatoid arthritis and consequently there are few contraindications to their use in this disease. Because of high concentrations of the drugs found in the liver, it is our opinion that these drugs should not be used or, if used, used with caution in the presence of hepatic disease. They should not be administered again if a skin reaction occurs. Severe gastrointestinal symptoms, nervousness, or persistent tinnitus are other possible contraindications. Leukopenia did not occur in this study but it should be kept in mind and watched for during therapy.

Table 3.—*Side effects in patients having rheumatoid arthritis treated with hydroxychloroquine sulfate or with chloroquine phosphate*

Side effect	Number of times noted in 26 patients receiving hydroxychloroquine sulfate	Hydroxychloroquine sulfate			Number of times noted in 25 patients receiving chloroquine phosphate	Chloroquine phosphate		
		Maintained	Reduced	Stopped		Maintained	Reduced	Stopped
Not clinically significant								
Blurring of vision (transient)	2	2	0	0	5	5	0	0
Headache (transient)	3	3	0	0	8	8	0	0
Lightheadedness (transient)	1	1	0	0	1	1	0	0
Mental confusion (transient)	1	1	0	0	0	—	—	—
Nervousness	1	0	1	0	2	0	2	0
Tinnitus	0	—	—	—	1	0	1	0
Clinically significant								
Anorexia*	2	0	1	1	4	0	2	2
Dermatitis	1	0	0	1 (Maculopapular with local exfoliation)	2	0	0	2 (1 maculopapular, 1 exfoliative)
Itching	0	—	—	—	1	0	0	1
Nausea*	2	0	1	1	4	0	3	1
Leukopenia	0	—	—	—	0	—	—	—

**These studies were carried out with uncoated tablets. Recently both drugs have been coated with approximately 2 mg. of pharmaceutical-grade shellac,[44] which has reduced appreciably the incidence of gastrointestinal side effects; however, further study will be necessary pertaining to intestinal absorption.*

Comment

Hydroxychloroquine sulfate, one of the new 4-aminoquinoline antimalarial agents, has a significant but limited anti-inflammatory effect on active rheumatoid arthritis. It has an advantage over chloroquine phosphate: it causes less gastrointestinal disturbance and can be administered in larger doses during the initial period of therapy, which appears to be necessary occasionally. However, we do not believe that hydroxychloroquine sulfate administered in comparable dosage results in greater anti-inflammatory response than that from chloroquine phosphate in the treatment of rheumatoid arthritis. In our series, 15 of 26 patients receiving hydroxychloroquine sulfate became asymptomatic, as compared to 9 of 25 patients receiving chloroquine phosphate. The therapeutic effect was limited with either drug, and patients with mild disease improved more quickly and more completely than those with severe, deep-seated disease.

Skin reactions occurred after using either drug, but it usually was possible to continue treatment after the lesions had disappeared, by substituting the other antimalarial agent for the drug that had precipitated the reaction.

The mechanism by which an antimalarial agent suppresses inflammation in rheumatoid arthritis has not yet been established. High concentrations of the drug have been found in the liver, spleen, lungs, and skin.[11] The high concentrations found in the skin are believed to be responsible for the effectiveness of the drug in the treatment of discoid lupus erythematosus. According to Haydu[45] the effectiveness of chloroquine phosphate in the treatment of rheumatoid arthritis is related to its influence on the activity of adenosinetriphosphate (ATP). He believes that the tissue requirements of ATP are increased in this disease and that chloroquine phosphate is effective because of its inhibition of adenosinetriphosphatase (ATPase) activity.

It is concluded from our study that hydroxychloroquine sulfate is moderately effective in suppressing inflammation of rheumatoid arthritis but has no apparent effect on psychomotor activity. It has a high degree of clinical safety and can be used in combination with other therapeutic agents in patients with severe disease. It is considered to be the preferred antimalarial drug for treatment of disorders of connective tissue, because of the low incidence of gastrointestinal distress as compared to that with chloroquine phosphate. The incidence of significant toxicity reactions occurring from the use of either antimalarial agent in the long-term treatment of rheumatoid arthritis has been less than was anticipated, and no instance of leukopenia has been observed in any of the patients of this study, and in well over 250 patients who are not included in this study but who are receiving one of these drugs at the present time. Recently both antimalarial drugs have been coated with pharmaceutical-grade shellac,[44] resulting in further decrease of gastrointestinal disturbance. Preliminary studies suggest that intestinal absorption with the coated tablets is comparable to that with the uncoated tablets.