Hydroxychloroquine sulphate in the treatment of rheumatoid arthritis: a double blind comparison of two dose regimens

K PAVELKA JR, K PAVELKA SEN, Z PELÍŠKOVÁ, J VÁCHA, AND K TRNAVSKÝ

From the Research Institute of Rheumatic Diseases, Prague, Czechoslovakia

SUMMARY A controlled, double blind, parallel group, long term study of hydroxychloroquine sulphate in the treatment of rheumatoid arthritis, comparing daily doses of 200 mg and 400 mg, is described. The trial involved 54 patients with moderate disease activity who had not previously received antimalarial drugs. Forty three patients completed the one year treatment. The groups receiving different doses were homogeneous and did not differ in any of the 25 monitored indicators. Both dose regimens were effective, and a significant reduction of disease activity was observed after one year's treatment. Of the nine laboratory and 11 clinical indices of efficacy monitored, no statistically significant differences were reported, but in the group of patients treated with the 400 mg daily dose the number of side effects was three times greater. As there have been no reports of retinopathy with hydroxychloroquine at daily doses of 200 mg the effectiveness of this dose is of practical importance.

Hydroxychloroquine sulphate has been used for the treatment of rheumatoid arthritis for more than 30 years. Clinical experience with this drug has been presented in at least 250 publications, thus permitting evaluation of its position in the treatment of rheumatoid arthritis.

Hydroxychloroquine is one of the so-called disease modifying drugs (formerly called basic drugs, long term effect drugs, second line antirheumatic drugs) because its ability to suppress rheumatoid arthritis activity has been repeatedly proved in double blind studies against placebo. A decrease of disease activity of at least 30% has been described in up to 63% of patients.¹

Most studies indicate that hydroxychloroquine is slightly less effective than gold or penicillamine, while its tolerance is substantially better than that of the other two drugs.² There are reports of combined treatment with hydroxychloroquine and low doses of cytostatic drugs,³ and combinations with gold,⁴ but the combination of hydroxychloroquine and penicillamine did not produce good results.⁵ The most undesirable complication of hydroxychloroquine treatment is possible damage to the retina. It

has been proved beyond any doubt that the incidence of retinopathy during hydroxychloroquine treatment is much lower than with chloroquine in equipotent doses.^{6,7} The development of retinopathy depends on the dose, especially the daily dose rather than the cumulative dose.⁸ As the initial stages of retinopathy are fully reversible the risk of severe retinopathy at a daily dose of 400 mg is very low. No retinopathy has been described with daily doses of 200 mg hydroxychloroquine. As the role of the cumulative dose in the incidence of retinopathy has not yet been fully explained it was necessary to verify the clinical efficacy of hydroxychloroquine in lower doses (200 mg daily), thus allowing long term administration of the drug.

The purpose of this study was to compare the efficacy of daily doses of 200 mg and 400 mg of hydroxychloroquine in patients with rheumatoid arthritis.

Patients and methods

We carried out a controlled, double blind, parallel group, long term clinical study.

PATIENT SELECTION

We included patients with either definite or classical

Accepted for publication 30 January 1989.
Correspondence to Professor K Trnavský, Research Institute of Rheumatic Diseases, Na slupi 4, 128 50 Praha 2, Czechoslovakia.

rheumatoid arthritis according to the American Rheumatism Association criteria,⁹ with moderate disease activity. No basic (disease modifying) treatment had been administered for at least three months, and the daily maintenance dose of corticosteroids did not exceed the equivalent of 10 mg prednisone. Excluded were patients older than 75 years, children, pregnant women, patients with severe disfunction of parenchymal organs, and patients taking antimalarial drugs before the onset of the study. Fifty four patients entered the study, of whom 11 did not complete the one year treatment. Thus results for 43 patients (36 women, seven men), with a mean age of 51.3 years and average duration of disease of 5.9 years, were evaluated statistically.

DOSAGE

We used hydroxychloroquine sulphate tablets (Winthrop) and placebo tablets which were of identical appearance, colour, weight, and packing. Each patient was given one tablet of the active substance in the morning, and in the evening took another tablet from a second bottle so that one randomly selected group of patients was taking a second active dose of 200 mg hydroxychloroquine while the other group was receiving placebo. Twenty two patients received the 200 mg daily dose of hydroxychloroquine and 21 patients the 400 mg dose.

CLINICAL AND LABORATORY INVESTIGATION

Each patient underwent a clinical, laboratory, and x ray examination before treatment. Clinical monitoring was carried out always by the same physician once a month. Duration of the trial was 12 months. Laboratory and x ray examinations were carried out after 12 months' treatment, ophthalmological examination after six and 12 months.

INDICES OF TREATMENT EFFICACY

Pain at rest and on movement was assessed on a visual analogue scale in millimetres. Duration of morning stiffness, fatigue, consumption of analgesics, grip strength, erythrocyte sedimentation rate, and Lansbury's joint and systemic indices were evaluated as percentages according to Lansbury's tables.¹⁰ The Ritchie articular index was scored accordingly, and, finally, there were also two functional tests—namely, walking 20 metres and rising from a chair six times, both measured in seconds.

LABORATORY EXAMINATION

We selected several immunological indices and other laboratory indices, where the mutual correlation and correlation with clinical x ray criteria could

contribute to the study of second line antirheumatic drugs. We monitored the rheumatoid factor titre by the latex fixation test, immunoglobulins were determined in g/l, E rosettes (T lymphocytes) in percentage, sulphhydryl groups in $\mu\text{mol/l}$, and erythrocyte sedimentation rate in mm/h.

Plasma concentrations of hydroxychloroquine were determined during the last month of treatment before administration of the morning dose and twice more at one hourly intervals using high pressure liquid chromatography.

X RAY EXAMINATION

The upper and lower extremities were x rayed before and after one year's treatment in a standard manner, the progression of the disease being assessed by the methods of Sharp *et al*¹¹ and Amos *et al*.¹²

RECORDING OF DATA

All findings were entered on a record form and processed on a medium sized computer.

Results

The two groups (receiving 200 mg or 400 mg hydroxychloroquine) showed no statistically significant differences in terms of age, sex, duration of the disease, its stage of progression (Steinbrocker), or the actual non-steroidal antirheumatic drug used at the time of the study. These variables were tested by a χ^2 test at a 95% level of significance. Twenty further variables (nine laboratory and 11 clinical indices of activity and efficacy of treatment) were entered into the computer. For 19 of the variables there was no significant difference between the groups. The E rosette count before treatment, however, was significantly higher (58.5%) in the group treated with doses of 400 mg than in the second group (49.2%) at a 95% level of significance. Student's *t* test and the Wilcoxon two sample test were applied.

To evaluate the effect of treatment with a daily dose of 200 mg hydroxychloroquine the values for the clinical indices before and after one year's treatment were compared. The rheumatoid disease activity was significantly reduced, and this was manifested by a significant reduction in pain at rest and on movement, the systemic Lansbury and Ritchie articular indices ($p=0.01$), a decrease in fatigue, and an improved grip strength ($p=0.05$). The remaining indices were not significantly changed by the treatment, though a tendency towards improvement was noted (Table 1).

When the results of one year's treatment with daily doses of 400 mg hydroxychloroquine were assessed in the same way there was a decrease in

Table 1 Clinical indices: comparison of the changes before and after treatment with 200 mg and 400 mg hydroxychloroquine (mean values of the entire groups)

Criterion	200 mg		400 mg		Significance of difference between 200 mg and 400 mg
	Before treatment	After treatment	Before treatment	After treatment	
Pain at rest*	31.23	16.36	25.38	12.71	NS
Pain on movement*	56.36	30.18	58.00	27.48	NS
Morning stiffness†	6.09	3.72	7.67	2.62	NS
Fatigue†	9.73	4.14§	10.14	4.05	NS
Consumption of analgesics†	3.14	2.18	3.67	1.09§	NS
Grip strength†	18.81	14.09§	19.38	14.33§	NS
Articular index†	12.82	10.55	15.48	8.29	NS
Systemic Lansbury index†	61.64	41.31	67.86	39.00	NS
Ritchie index‡	14.86	6.95	13.57	6.33	NS
Rising from a chair six times (s)	18.23	16.41	22.57	19.45	NS
20 m walk (s)	20.23	18.09	21.86	18.90	

*On a 100 mm visual analogue scale.

†In percentage according to Lansbury tables.¹⁰

‡In points according to Ritchie score.

§Significant at a level of $p=0.05$.||Significant at a level of $p=0.01$.

pain at rest and on movement, in fatigue, and in the articular and systemic Lansbury and Ritchie indices ($p=0.01$), a reduced consumption of analgesics ($p=0.05$), and improved grip strength ($p=0.05$). The improvements in functional tests and morning stiffness were not statistically significant.

Although there were more improvements with the 400 mg/day dose, there were no statistically significant differences in improvement from baseline between the two treatments (Table 1).

There were significant changes in selected laboratory indices, especially immunological ones, after one year's treatment with 200 mg hydroxychloroquine: plasma IgG concentrations decreased

($p=0.01$), sedimentation rate decreased ($p=0.05$) and IgM concentrations increased substantially ($p=0.01$). Other laboratory variables were not influenced by the treatment to any significant degree.

After one year's treatment with 400 mg hydroxychloroquine the IgG concentration decreased significantly ($p=0.01$), while other laboratory indices remained unchanged (Table 2).

Comparison of the effect of treatment on the above mentioned laboratory and immunological indices did not show any statistically significant differences between the treatments (Table 2). (For the sake of simplicity only the mean values have

Table 2 Laboratory indices: comparison of the changes before and after treatment with 200 mg and 400 mg hydroxychloroquine (mean values)

Criterion	200 mg		400 mg		Significance of difference between 200 mg and 400 mg
	Before treatment	After treatment	Before treatment	After treatment	
Latex fixation test titre	2305	2750	7870	3009	NS
IgA (g/l)	3.60	3.30	3.15	2.75	NS
IgG (g/l)	17.46	13.08‡	16.84	13.12‡	NS
IgM (g/l)	1.46	2.37‡	1.97	2.58	NS
E rosettes (%)	49.21	50.38	58.53	54.32	NS
Sulphydryl groups ($\mu\text{mol/l}$)	409.5	391.8	382.0	317.7	NS
Circulating immune complexes (PEG* E $\times$ 1000)	82.41	83.41	85.35	92.75	NS
CRP* (mg/l)	21.3	12.4	15.1	15.0	NS
ESR* (mm/1st h)	43.91	28.91†	42.33	36.25	NS

*PEG=polyethylene glycol; CRP=C reactive protein; ESR=erythrocyte sedimentation rate.

†Significant at a level of $p=0.05$.‡Significant at a level of $p=0.01$.

been presented. The non-significance of some parameters—for example, latex—is due to the large standard deviation and the wide range of the results.)

After one year's treatment with 200 mg hydroxychloroquine 11 patients were highly satisfied, eight

Fig. 1 Evaluation of treatment by the patient.

Fig. 2 Evaluation of treatment by the physician.

Table 3 Reason for treatment discontinuation. Values are shown as No (%)

Daily dose (mg)	Adverse side effects			Lack of effect	Non-compliance	Total
	Skin	Gastrointestinal	Ocular			
200	2 (9)	—	1 (5)*	2 (9)	—	5 (23)
400	3 (14)	3 (14)	1 (5)*	—	1 (5)	8 (38)

*Impaired vision after 12 months' hydroxychloroquine treatment; the trial was not discontinued, but further administration of the drug was contraindicated.

satisfied, and three dissatisfied with the treatment (Fig. 1). After treatment with 400 mg hydroxychloroquine 13 patients were highly satisfied, six satisfied, and two dissatisfied (Fig. 1). The differences in the patients' evaluations were not statistically significant. The physician's assessment of the treatment was tested by the same method (χ^2 test), and again there were no statistically significant differences between the two groups (Fig. 2). During the last month of treatment we determined plasma hydroxychloroquine concentrations in 18 patients before administration of the daily dose and one and two hours afterwards. Before the dose was given the plasma hydroxychloroquine concentration (steady state) in patients with a daily dose of 200 mg hydroxychloroquine was $0.46 \mu\text{mol/l}$ on average and in patients with 400 mg hydroxychloroquine it was $0.93 \mu\text{mol/l}$. Although the average concentration after 400 mg was double the value of the group receiving 200 mg, the differences in nine samples from each group were not statistically significant. Similarly, the differences between the groups in plasma hydroxychloroquine concentrations one and two hours after the administration of the drug were non-significant. This lack of significance is attributed to the small number of observations, and we believe that if more observations were made the plasma hydroxychloroquine concentration would be shown to be dose dependent. It was not possible to prove with either dose regimen, however, that clinical success of the treatment was dependent on the plasma hydroxychloroquine concentration. The low level of reliability in the determination of plasma chloroquine concentrations and the large variability of results were reported recently by Frisk-Holmberg.¹³

Tolerance of hydroxychloroquine was generally good (Table 3). Cutaneous side effects occurred most frequently, but they did not appear to be dose dependent. Gastrointestinal disorders occurred after the higher doses (400 mg daily). An ophthalmological examination after one year showed temporarily impaired vision and electroretinogram changes in two patients, one in each group.

Discussion

Long term studies with disease modifying drugs in rheumatoid arthritis are rather complicated owing to a relatively high drop out rate due to side effects, spontaneous fluctuations of activity during a long term study, and low sensitivity of some clinical and laboratory tests. In our study we used a large number of clinical, laboratory, x ray, and pharmacokinetic indices to avoid some of these problems.

We proved that both doses of hydroxychloroquine—200 mg and 400 mg—are effective after one year's treatment, reducing both clinical and laboratory signs of activity. The improvement was reflected in most of the indicators used and statistically did not differ significantly between the two groups. The incidence of side effects was higher after the 400 mg dose. As it is known that clinically significant retinopathy has not been found after a daily dose of 200 mg hydroxychloroquine the effectiveness of this dose is of practical importance. After the daily dose of 200 mg hydroxychloroquine 19/22 (86%) of patients were satisfied with their treatment after one year, as were 19/21 (90%) in the group treated with 400 mg. These results correspond with some reported results,¹⁴ but in most studies the therapeutic response has been evaluated as good in only 60% of patients receiving continuous treatment.¹

The pharmacokinetic data confirmed that the higher plasma hydroxychloroquine concentrations after daily doses of 400 mg were not followed by a better clinical response, and that plasma concentrations did not correlate with Lansbury's index of systemic activity, which in our study was found to be the most sensitive indicator of therapeutic effect.

The relatively good therapeutic effect of antimalarial drugs, their low toxicity, acceptable price, and easy oral administration have led to a certain renaissance of their use in the treatment of rheumatoid arthritis. The recommended lowering of the daily dose to 200 mg will probably be accompanied by a decrease in the incidence of side effects.¹⁵

The good therapeutic response and reduced therapeutic risk will permit antimalarial drugs to be given for prolonged periods and may provide a more profound and lasting suppression of the rheumatoid process.

Hydroxychloroquine may be considered as the basic drug of choice among disease modifying drugs for patients in the initial stage of rheumatoid arthritis and with a medium degree of activity and progression of the disease.¹⁶

References

- 1 Bell C Y N. Hydroxychloroquine sulphate in rheumatoid arthritis: long term response rate and predictive parameters. *Am J Med* 1983; 75: 46–51.
- 2 Husain Z, Runge L A. Treatment complications of rheumatoid arthritis with gold, hydroxychloroquine, D-penicillamine and levamisole. *J Rheumatol* 1980; 7: 825–30.
- 3 McCarty D J, Carrera G F. Intractable rheumatoid arthritis: treatment with combined cyclophosphamide, azathioprine and hydroxychloroquine. *JAMA* 1982; 248: 1718–23.
- 4 Severs K, Hurri L. Combined therapy of rheumatoid arthritis with gold and chloroquine. Evaluation of therapeutic effect. *Acta Rheumatologica Scandinavica* 1983; 9: 48–55.
- 5 Bunch T W, O'Duffy J D, Tompkins R B, O'Fallon W M. Controlled trial of hydroxychloroquine and D-penicillamine singly and in combination in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1984; 27: 267–76.
- 6 Bernstein H N. Ophthalmologic considerations and testing in patients receiving long term antimalarial therapy. *Am J Med* 1983; 75: 25–34.
- 7 Finbloom D S, Silver K, Newsome D A, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; 12: 692–4.
- 8 McKenzie A H. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75: 40–5.
- 9 Ropes M W, Bennett G A, Cobb S, Jacox R, Jessar R A. Revision of diagnostic criteria for rheumatoid arthritis. *Arthritis Rheum* 1959; 2: 16–20.
- 10 Lansbury J. Quantitation of activity of rheumatoid arthritis. Method for summation of systemic indices of rheumatoid activity. *Am J Med Sci* 1956; 232: 232–300.
- 11 Sharp J T, Lidskey M D, Collins L C, et al. Methods of scoring the progression of radiological changes in rheumatoid arthritis. *Arthritis Rheum* 1971; 14: 706–20.
- 12 Amos R S, Constable T J, Crockson R A, Crockson A P, McConkey B. Rheumatoid arthritis: relation of serum C reactive protein and erythrocyte sedimentation rates to radiographic changes. *Br Med J* 1977; i: 195–7.
- 13 Frisk-Holmberg M. Variation in chloroquine pharmacokinetics due to assay sensitivity and duration of sampling. *Eur J Clin Pharmacol* 1987; 31: 743–8.
- 14 Rynes R I. Antimalarial treatment of rheumatoid arthritis: 1986 status. *J Rheumatol* 1985; 12: 657–9.
- 15 Day R O, Sambrook P, Champion G D, Graham G G. Antimalarials in rheumatic diseases. *Aust N Z J Med* 1982; 12: 645–9.
- 16 Runge L A. Risk/benefit analysis of hydroxychloroquine sulfate treatment in rheumatoid arthritis. *Am J Med* 1983; 75: 52–6.