Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial

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Abstract

Objectives—To compare the effects of hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis.

Methods—A six month randomised, multicentre, double blind trial with three parallel groups was performed. Ninety one outpatients with active rheumatoid arthritis were included. Monthly assessments of erythrocyte sedimentation rate, morning stiffness, number of swollen joints, a pain score, and global assessments were carried out. Radiographs of hands and wrists were taken before and after the trial.

Results—Sixty two patients completed the study. The 29 withdrawals caused no evident bias, and there was no difference in side effects among the three groups. All variables improved significantly with time. Patients treated with a combination of hydroxychloroquine and sulphasalazine responded better and faster than those treated with hydroxychloroquine alone, but there was no statistically significant difference between the combination treatment and single drug treatment with sulphasalazine or between treatment with hydroxychloroquine and sulphasalazine given alone.

Conclusion—The present results do not support a recommendation to use a combination of hydroxychloroquine and sulphasalazine in the treatment of rheumatoid arthritis.

(*Ann Rheum Dis* 1993; 52: 711–715)

and hydroxychloroquine was superior to treatment with a single drug. The two drugs were chosen because of their low incidence of serious side effects. In addition, we aimed to determine whether previous treatment with gold salts or penicillamine affected the outcome. Finally, the selection of patients for the study from the total population of patients with RA at the three participating rheumatological clinics was recorded.

Patients and methods

PATIENTS

During the inclusion period 776 patients with RA were registered in the three participating departments. Ninety one of these met the criteria for inclusion in the trial. They all had RA defined according to the American Rheumatism Association 1958 criteria.¹ The mean age was 61 years (range 18–82) and the male to female ratio was 35:56. The mean duration of RA was 6.3 years (range 0–37) and 71% belonged to Steinbrocker's functional class I and 29% to class II.² All the patients had active disease—that is, at least three swollen joints and at least two of the following three criteria: (a) a minimum of six tender joints; (b) duration of morning stiffness of 45 minutes or longer; or (c) an erythrocyte sedimentation rate (ESR) greater than 28 mm/h. Patients were excluded based on the criteria given in table 1.

The patients were randomised using a table of random numbers of three parallel groups and a double blind technique was used. The study was performed in accordance with the Helsinki declaration II and was approved by the local ethical committees.

Table 1 No of patients excluded according to the criteria used in this study

Lack of disease activity	408
Functional class III or IV (Steinbrocker ²)	117
Age <18 years	4
Pregnant or lactating women	4
Previous treatment with HC or SASP, or both	233
Treatment with disease modifying antirheumatic drugs within one month	328
Malignancies	1
Glucocorticosteroids within last six weeks	158
Refused participation	15
Allergic to the drugs in question, or eye disease which contraindicates HC	6

Each patient could be recorded with more than one exclusion criterion. The total number of excluded patients was 685. HC=Hydroxychloroquine; SASP=sulphasalazine.

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Accepted for publication 28 June 1993

A combination of two or more disease modifying antirheumatic drugs might have advantages compared with treatment with a single drug in the management of rheumatoid arthritis (RA). Little is known about the biological effects of disease modifying antirheumatic drugs, but possible differences in their actions might be used in combination treatment through either additive or synergistic effects. Potential advantages could be increased effect, a faster onset of the effect, or a greater response rate.

The purpose of this investigation was to study whether a combination of sulphasalazine

TREATMENT

The patients were allocated to six months of treatment with (a) hydroxychloroquine 250 mg/day and placebo (resembling enteric coated sulphasalazine 2 g/day), (b) sulphasalazine 2 g/day (enteric coated tablets) and placebo (resembling hydroxychloroquine 250 mg/day), or (c) hydroxychloroquine 250 mg/day and sulphasalazine 2 g/day (enteric coated tablets). The patients were allowed to continue current treatment with non-steroidal anti-inflammatory drugs, paracetamol, and dextro-propoxyphene during the study.

INVESTIGATIONS

Before onset, and once a month throughout the trial, disease activity was assessed by the same observer in each centre. Assessments consisted of a recording of the ESR, the duration of morning stiffness, number of swollen joints (0–40), a pain score (none=0, mild=1, moderate=2, severe=3, very severe=4), and the global assessments of the patients and doctors (better=1, unchanged=0, worse=-1 with respect to the previous visit). Side effects were noted. Radiological examinations were performed blindly at the time of randomisation and six months later by the same radiologist. The following joints were evaluated for definite RA change (that is, juxta-articular erosions with a diameter of at least one millimetre, or marked narrowing of the joint space combined with subluxation): the metacarpophalangeal and proximal interphalangeal joints; interphalangeal joint of the thumb, wrist (evaluated as one joint); metatarsophalangeal joints; and the interphalangeal joint of the first toe and the tarsus (evaluated as one joint). The number of joints with definite RA changes was counted and the two

sets of images was compared for marked progression of the number or size of lesions. This method has been used previously and has been described in detail elsewhere.³ Routine laboratory tests were performed once a month and an ophthalmological examination was carried out every third month. Previous treatment with gold salts or penicillamine, or both, was recorded.

SAMPLE SIZE AND STATISTICAL METHODS

We wanted to be reasonably sure of finding significant differences in the trial if there was a difference of at least 25% between two treatments. For this reason we set $2\alpha=5\%$ and the power to 80%. The standard deviation was estimated to be 30%. Considering also the possibility of a dropout rate of up to 30% we estimated that each group should comprise 30–35 patients at randomisation.

The statistical evaluation of the results was carried out using a non-parametric model corresponding to one and two way ANOVA.³ The factors were treatment and time (repeated measures). In addition, parametric analyses were performed; only p values <0.05 were regarded as statistically significant.

The primary analyses were based only on those patients who completed the stipulated trial time and supplied the required data. To delimit the potential for bias due to various reasons for withdrawal (table 3) we performed additional analyses in which missing data were input. These outside analyses were based on those completing a shorter trial time and used interpolation, extrapolation (carrying last value forwards), and regression models. These analyses all yielded principally the same conclusion with respect to the comparison between treatments.

Table 2 Median (25/75 centiles) (at baseline) values during six months of treatment with hydroxychloroquine (HC), sulphasalazine (SASP), or a combination of the two (HC+SASP)

Drug treatment	Month						
	0	1	2	3	4	5	6
ESR (mm/h)							
HC (n=23)	48 (30/80)	42 (21/73)	44 (17/76)	37 (17/84)	37 (17/76)	31 (10/63)	33 (10/60)
SASP (n=17)	48 (34/84)	39 (16/62)	27 (14/59)	27 (9/49)	28 (10/36)	25 (7/32)	16 (9/43)
HC+SASP (n=22)	53 (32/67)	41 (17/52)	24 (9/51)	19 (7/32)*	18 (6/32)*	16 (7/25)	16 (9/33)
Morning stiffness (minutes)							
HC (n=23)	60 (30/120)	60 (30/113)	60 (16/120)	60 (6/90)	30 (6/60)	15 (1/60)	15 (1/80)
SASP (n=17)	60 (30/120)	45 (26/90)	30 (26/68)	30 (0/41)	15 (4/60)	15 (0/38)	15 (4/38)
HC+SASP (n=22)	60 (60/120)	60 (30/60)	30 (0/60)	18 (0/60)	18 (0/60)	5 (0/30)	5 (0/30)
Number of swollen joints (0–40)							
HC (n=23)	9 (5/13)	8 (6/11)	8 (6/12)	7 (4/11)	6 (4/11)	5 (3/7)	5 (2/7)
SASP (n=17)	8 (5/13)	8 (7/12)	6 (4/8)	5 (4/8)	5 (2/8)	3 (2/6)	4 (1/6)
HC+SASP (n=22)	10 (6/12)	8 (5/10)	7 (3/8)	5 (2/7)	3 (1/6)*	4 (2/6)	2 (1/3)*
Joint pain (0–4)							
HC (n=23)	2 (2/3)	2 (2/2)	2 (2/2)	2 (1/2)	2 (1/2)	1 (1/2)	1 (1/2)
SASP (n=17)	2 (2/3)	2 (2/2)	2 (1/2)	1 (1/2)	2 (1/2)	2 (1/2)	2 (1/2)
HC+SASP (n=22)	2 (2/3)	2 (2/2)	1 (1/2)	1 (1/2)*	1 (1/2)	1 (0/2)	1 (1/2)
Patients' global assessments (accumulated values of -1, 0, +1)†							
HC (n=23)	0 (-1/1)	0 (-1/1)	0 (-1/1)	0 (-1/1)	0 (-1/2)	1 (0/3)	1 (0/3)
SASP (n=17)	0 (0/1)	1 (1/2)	2 (1/2)	2 (1/2)	2 (1/3)	2 (2/3)	2 (1/3)
HC+SASP (n=22)	1 (0/1)*	1 (0/2)*	2 (1/3)*	2 (1/3)*	2 (1/3)*	3 (2/4)*	3 (2/4)*
Doctors' global assessments (accumulated values of -1, 0, +1)†							
HC (n=23)	0 (-1/1)	0 (-1/1)	0 (0/1)	1 (0/2)	1 (0/3)	1 (0/3)	1 (0/3)
SASP (n=17)	0 (0/1)	1 (0/1)	2 (1/2)	2 (1/3)	2 (1/3)	2 (1/3)	2 (1/3)
HC+SASP (n=22)	1 (0/1)*	1 (0/2)*	2 (1/3)*	2 (1/3)*	3 (2/3)*	3 (2/3)*	3 (1/4)

p (Time)<0.01 for all six variables.

*p (Treatment)<0.05 (combination treatment superior to hydroxychloroquine).

†-1=Worse, 0=unchanged, +1=better, in relation to the previous visit.

Results

Thirty one patients were treated with hydroxychloroquine and placebo, 29 with sulphasalazine and placebo, and 31 with hydroxychloroquine and sulphasalazine. Sixty two patients completed the six months of treatment (23 hydroxychloroquine, 17 sulphasalazine, and 22 hydroxychloroquine and sulphasalazine). At inclusion there was no statistically significant difference between the three groups.

There was no significant difference between hydroxychloroquine and sulphasalazine treatment. Neither was there any significant difference between combination and single drug treatment with sulphasalazine. The combination treatment, but not the single drug treatment with sulphasalazine, was, however, significantly better than single drug treatment with hydroxychloroquine (ESR months 3 and 4, number of swollen joints months 4 and 6, joint pain month 3, patients' global assessments months 1–6, and doctors' global assessments months 1–5) (table 2; figs 1–3).

Radiographs of the hands and wrists showed a slight progression of the lesions specific to RA in all groups after six months of treatment ($p < 0.01$), but there was no statistically significant difference among the three groups. The patients receiving hydroxychloroquine showed a median increase in erosions in 0.6 joints, and the patients receiving sulphasalazine or combination treatment in 0.4 joints. Most of the patients showed no changes in lesions specific to RA during the trial and no patients showed a decrease in the number of lesions.

Of the 29 patients who withdrew from the trial (table 3), the main reasons were gastrointestinal side effects (four patients receiving sulphasalazine, six receiving hydroxychloroquine, and three receiving combination treatment) and hypersensitivity (three receiving sulphasalazine, one receiving hydroxychloroquine, and two receiving combination treatment). There was no significant difference between the three treatment groups and no serious side effects were recorded. No

Figure 1 Effect of drug treatment on median erythrocyte sedimentation rate (ESR).

Figure 2 Effect of drug treatment on median length of morning stiffness.

ophthalmological side effects to hydroxychloroquine treatment were seen.

Thirty nine patients had previously been treated with gold salts and 36 patients with penicillamine. The disease was of longer duration in these patients (mean of 12 years compared with one year), but no statistically significant difference in response to any of the drug regimens was noted in these patients.

Seven hundred and seventy six patients with RA were initially registered but 685 were excluded (table 1). The main reasons were lack of disease activity (408 patients), either due to inactive disease or ongoing treatment with disease modifying drugs (328 patients) or glucocorticosteroids (158 patients). Each patient could be registered with more than one exclusion criterion.

Figure 3 Effect of drug treatment on median number of swollen joints.

Discussion

In a randomised double blind study of combination treatment with sodium aurothiomalate and penicillamine McKenna *et al*⁶ found that significant clinical and biochemical improvements were seen within four weeks of combination treatment, whereas treatment with a single drug showed an effect after eight weeks; otherwise the efficacy appeared to be similar among the three groups. Scott *et al*⁶ found in a randomised double blind study a small advantage of combination treatment with sodium aurothiomalate and hydroxychloroquine compared with treatment with sodium aurothiomalate alone after one year of treatment. They tested 13 clinical laboratory, and radiological variables and favoured the combination treatment by 20–25%, though only the C reactive protein and an overall disease activity index differed significantly. An analysis of the transitory interaction between the two groups was not performed. Two randomised studies of a combination of anti-malarial drugs and penicillamine showed no beneficial effects of the combination treatment.^{7 8} Surprisingly, in one of the studies⁷ the group receiving combination treatment did not fare as well as the group receiving penicillamine alone. Williams *et al*⁶ have compared auranofin, methotrexate, and the combination of the two in a double blind randomised trial. Except for fewer withdrawals because of a lack of response, the combination treatment did not show any advantage over treatment with a single drug.

In addition to these five randomised studies a number of open studies and case reports have been published. Most of these indicated that combination treatment was effective and potentially advantageous compared with treatment with a single disease modifying anti-rheumatic drug.^{10–14}

The significant differences in this study between a combination treatment with hydroxychloroquine and sulphasalazine and treatment with a single drug (hydroxychloroquine) (table 2) may indicate a better and faster effect with the combination treatment. There was, however, no significant difference between combination treatment and treatment with sulphasalazine alone, so it is a question of whether the combination treatment with its higher cost and potential risk of more side effects is of any clinical importance. Most studies have shown more side effects with combination treatment.^{5 7 9–11} In this study

there were no indications of an increased risk by combining hydroxychloroquine and sulphasalazine (table 3).

It is possible that an increase in the dose of hydroxychloroquine could have improved the effect of this treatment as well as that of combination treatment, but we chose a relatively small dose (250 mg/day) to avoid ophthalmological side effects, which may be a risk, particularly in long term treatment. Lower doses of hydroxychloroquine were used in some studies.^{6–8} For hydroxychloroquine and sulphasalazine we chose fixed, not weight related, doses to make it possible to carry out a double blind trial.

Most studies have shown more side effects if combination treatment was used.^{6 8 10–12} There was no indication of an increased risk by combining hydroxychloroquine and sulphasalazine in the present study.

Previous treatment with gold salts or penicillamine did not affect the response to treatment nor withdrawal profiles. At randomisation these patients had had RA for a much longer time than patients without treatment with these drugs (mean 12 years *v* 1 year). Previous studies have shown that the effect of disease modifying antirheumatic drugs is negatively correlated with the duration of RA,¹⁵ possibly owing to more irreversible changes in patients with longstanding RA. In this study this was counteracted by the exclusion of patients in functional groups III and IV.

There are several possibilities for bias in controlled trials. Firstly, we had a substantial attrition of patients before randomisation because only patients referred to the participating departments could be enrolled and of these many did not fulfil the inclusion criteria (table 1). This may exclude less complicated cases and perhaps patients who are better responders. Secondly, about 30% of the patients randomised did not complete all six months of treatment. The former is a bias only as far as the definition of our target population is concerned, whereas the latter is a real potential for bias in comparisons between treatments. Accordingly, we conducted several additional statistical analyses. Although the possibility of bias remains—primarily because the reasons for withdrawal may differ even though numbers were comparable—we found no evidence of this.

The previously randomised studies of combination treatments differ in design and analysis, which makes direct comparisons difficult. Paulus¹⁶ and Boers and Ramsden¹⁷ concluded that the evidence presently available does not support the general use of combination treatment. More well designed, controlled clinical trials are needed to determine which, if any, combinations of drugs are most beneficial. More studies are being carried out,^{18–20} and hopefully more knowledge about the mechanisms and biological effects of disease modifying antirheumatic drugs might be helpful in selecting combination treatments where an additive or even synergistic effect is seen.

Table 3 Reasons for withdrawal from the trial. Values are number of patients

	Drug treatment*		
	SASP	HC	HC/SASP
Gastrointestinal symptoms	4	6	3
Hypersensitivity	3	1	2
Adenocarcinoma coli	1	0	0
Non-compliance	4	1	1
Missing data	0	1	2
Total	12	9	8

*HC=Hydroxychloroquine, SASP=sulphasalazine, and HC/SASP=hydroxychloroquine and sulphasalazine in combination.

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