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A double-blind comparative clinical trial of mefloquine and chloroquine in symptomatic falciparum malaria

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A total of 99 male Zambian patients with symptomatic falciparum malaria were treated in a double-blind randomized manner with either mefloquine (1000 mg given in one day) or chloroquine (1500 mg given over 3 days). An S-type response was seen in all the chloroquine patients and 98% of the mefloquine group; one patient in the latter group (2%) showed an RI-type response, but the parasites obtained during the recrudescence were sensitive to both chloroquine and mefloquine in the in vitro *microtest, and the patient responded satisfactorily to oral chloroquine. The rate of clearance of parasitaemia was marginally faster in the chloroquine-treated group. The rate of clearance of fever was similar in the two groups. Both drugs were well tolerated and side-effects such as nausea, vomiting, dizziness, loose stools, and pruritus were mild and transient. Pruritus was more common after chloroquine administration and dizziness more common in the mefloquine group. There were no drug-induced alterations in the haematological and biochemical profiles.*

Mefloquine is a new antimalarial drug, which was developed by the Walter Reed Army Institute of Research in Washington, DC. It is a quinoline methanol derivative and is chemically related to quinine.

Mefloquine has been found to be effective against all types of human and animal malaria, including chloroquine-resistant falciparum malaria (*1–6*).[a] Observations have been made on the tolerance and bioavailability of mefloquine and chloroquine in nine adult Zambians at the Tropical Disease Research Centre (TDRC), Ndola, Zambia, and both drugs were well tolerated and showed good absorption (*7*, J. M. K. Ekue et al., unpublished observations, 1980). The side-effects and clinical effectiveness of mefloquine and chloroquine have also been compared at the TDRC in a randomized, double-blind trial in adult male patients with oligosymptomatic falciparum malaria; both drugs were found to be effective and well tolerated when given in doses of 1 g of mefloquine (one-day treatment) or 1.5 g of chloroquine (administered over three days) (J. M. K. Ekue et al., unpublished observations, 1982).

The present trial compared the tolerance and clinical and parasitological response to mefloquine and chloroquine of adult males with symptomatic falciparum malaria, in an area where *Plasmodium falciparum* is highly susceptible to chloroquine.

PATIENTS, MATERIALS, AND METHODS

All the patients in the study were males over 12 years of age who attended the outpatients' department of Ndola Central Hospital with symptomatic falciparum malaria. Informed consent for inclusion in the trial was obtained from the patients and their relatives.

A total of 100 patients were admitted to the study, and stayed in the hospital throughout the trial period (28–42 days). The wards were mosquito-proof, and so transmission of malaria was not possible. Two weeks after the administration of the trial drugs, some patients, who would not otherwise have been available for regular follow-up, were allowed to attend to their work outside the hospital between 09h 00 and 16h 00.

Mefloquine was administered in tablets of 250 mg base. Chloroquine tablets were identical in appearance, but contained 150 mg base. Each patient received, in a randomized double-blind manner, either:

(*a*) oral mefloquine, 750 mg, and one placebo tablet, followed 2–6 hours later by 250 mg of mefloquine and one placebo, and a further 2 placebo tablets daily on the next 2 days; or

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[a] *Mefloquine hydrochloride (WR 14290.HCl); clinical brochure.* Washington, DC, Walter Reed Army Institute of Research, 1978 (unpublished document).

(*b*) oral chloroquine, 600 mg, followed 2–6 hours later by 300 mg of chloroquine, and a further 300 mg daily for the next 2 days.

The patients received other drugs, such as analgesics, sedatives, and anthelmintics as necessary. One patient was found to be schizophrenic and was given thioridazine each day during the study period.

Each patient provided a detailed history and was given a full clinical examination according to a standard protocol. Clinical measurements and laboratory investigations were also carried out. The patients were examined prior to the administration of the trial drug on day 0. They were examined daily from day 0 to day 7, then once a week until day 28 and, when possible, on days 35 and 42. Haematological studies were repeated on days 2, 4, 7, 14, 28, and in some cases, on days 35 and 42. Biochemical studies were repeated on days 1, 4, 7, 14, 28, and if possible, on days 35 and 42. Urinalysis was performed daily for the first week, and then on days 14, 28, and, if necessary, day 42. Blood smears were prepared and examined for malarial parasites (asexual forms and gametocytes) daily until day 7 and weekly thereafter until day 42; in many cases, blood smears were examined daily from day 20 to day 28. *In vitro* drug susceptibility tests for *P. falciparum* were carried out on day 0 and repeated as necessary. Plasma samples were collected and tested for drug level on day 7, and additionally if there was recrudescence or a serious adverse reaction or vomiting. The Dill-Glazko urine test for chloroquine, a qualitative test for glucose-6-phosphate dehydrogenase (G6PD), determination of haemoglobin genotype, and measurement of body weight and height were carried out on day 0; patients were reweighed on days 7, 28, and 42. Body temperature was recorded twice a day (morning and evening). Stool samples were examined for blood and helminths. Clinical features such as symptoms, pulse rate, and respiration were recorded daily. Blood pressure was recorded on days 0–7, and weekly thereafter.

RESULTS

A total of 99 male patients, aged between 13 and 51 years, were included in the study. Of these, 50 patients received mefloquine and 49 received chloroquine. (One patient who received chloroquine was omitted from the study because of misdiagnosis.) Altogether, 98 patients completed 28 days of observation, with additional observations until day 42 for 16 patients in the mefloquine group and 15 patients in the chloroquine group. One patient in the mefloquine group was observed for 26 days only.

The mean body weight of patients in the mefloquine group was 55.6 kg (range, 37–72 kg) on day 0 and 56.6 kg (range, 42–74 kg) on day 28; there was a mean weight gain of 1 kg. The mean body weight of subjects in the chloroquine group was 54.9 kg (range, 31–65 kg) on day 28, with a mean gain of 3.7 kg. There were wide individual variations in weight gain. The difference between the two groups was not statistically significant.

Clinical findings

The blood pressure and respiratory system were not significantly affected by the administration of either mefloquine or chloroquine. There was a reversible mild sinus bradycardia (pulse, 50–52 per minute) in 18% of the patients who received mefloquine and in 16.3% of those who received chloroquine. The bradycardia was observed 4–7 days after drug administration; it was asymptomatic, required no specific therapy, and lasted for 3–4 days.

Splenomegaly was observed on day 0 in 15 patients who received mefloquine and 21 who received chloroquine. A significant reduction in the number of enlarged spleens and in the individual size occurred in both groups during the 28-day study period. There was no significant difference between the two groups. Mild hepatomegaly was observed in 15 patients who received mefloquine (mean enlargement, 0.32 cm below the costal margin) and three patients who received chloroquine (mean enlargement, 0.33 cm below the costal margin). No liver enlargement was seen after day 14.

Laboratory investigations

There were no significant changes in haemoglobin, haematocrit, red and white blood cell counts, differential white blood cell counts, or reticulocytes after the administration of the trial drugs. The values before and after treatment were generally within normal limits. Eosinophil counts were up to 30% of the total white blood cell count in some cases. One patient who received chloroquine had anaemia with low haemoglobin, erythrocyte volume fraction, and red blood cell levels before drug administration. These values persisted in spite of treatment for the duration of the study; the reasons for this remained unclear. The erythrocyte sedimentation rate was measured in some cases in the early part of the study, but no drug-induced changes were observed in either group.

Serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and serum creatinine levels were within normal limits in both the mefloquine and chloroquine groups before and after the administration of the trial drugs.

Altogether 34–36% of the patients in both groups had a helminth infection on day 0.

In both groups of patients, traces of albumin and urobilinogen were observed in the urine in a number of cases for the first 3–4 days. Some cases had an increased number of leukocytes and red blood cells in their urine on a few occasions, but the levels reverted to normal spontaneously. These changes were not significant in either the mefloquine or the chloroquine group.

The plasma levels of chloroquine and mefloquine will be reported later.

Parasitological response

Table 1 shows the details of parasite counts and rates of clearance of parasitaemia.

Mefloquine. All 50 patients who received mefloquine had *P. falciparum* asexual forms in blood smears on day 0. Parasitaemia was observed after drug administration in 49 cases on day 1 and all patients were negative by day 7 (Table 1). One patient was again positive on day 19; this was thought to be due to recrudescence.

Gametocytes of *P. falciparum* were present in 2 patients on day 0, in 12 patients on days 2 and 3, and in 2–4 patients until day 14, after which all subjects were negative till day 42.

There was one mixed infection, with a concomitant presence of asexual forms of *P. malariae*.

Chloroquine. All 49 cases who received chloroquine had *P. falciparum* asexual parasitaemia on day 0 (Table 1). All cases became negative by day 4, and remained so, except for one case who became positive again on day 30. As this patient was exposed to transmission during the study, this was considered to be a reinfection.

Gametocytes of *P. falciparum* were present in 3 subjects on day 0 and day 1, 5 subjects on days 2 and 3, 6 subjects on day 4, 3 subjects on day 6, 7 subjects on day 7, and 2 on day 14. All patients were negative after day 14.

Comparative response. Table 1 shows the comparative parasitological responses to mefloquine and chloroquine. The mefloquine group showed a virtual 100% clearance of parasitaemia on day 5 and the chloroquine group on day 4; by day 3 mefloquine had produced 74.0% clearance and chloroquine 94.0% clearance of parasitaemia. One patient who took mefloquine showed an RI-type recrudescence on day 19. No cases of recrudescence were observed in the chloroquine group.

Body temperature

Of the patients who received mefloquine, 46 had fever on day 0. After drug administration, the average duration of fever was 2 days, lasting 12–72 hours in individual patients (Table 2). In the chloroquine group, 45 patients had fever on day 0. There was a 97.8% clearance of pyrexia by day 3. Fever persisted in one patient until day 5, after which all patients were free of fever.

Side-effects

The main subjective side-effects observed between day 0 and day 4 that may be attributed to the trial drug were nausea, vomiting, mild diarrhoea, dizziness,

Table 1. Clearance of parasitaemia (*P. falciparum* asexual forms) and mean parasite counts in patients given mefloquine or chloroquine

Day of treatment	Mefloquine			Chloroquine		
	No. positive	%	Mean parasite count (per mm^3)	No. positive	%	Mean parasite count (per mm^3)
0	50	100	15 659	49	100	18 394
1	49	98	16 292	45	91.8	10 352
2	35	70	1 585	32	65.0	550
3	13	26	340	3	6	4
4	5	10	16	0	0	0
5	1	2	1	0	0	0
6	1	2	1	0	0	0
7	0	0	0	0	0	0

Table 2. Clearance of fever in malaria patients given mefloquine or chloroquine

Day of treatment	Mefloquine		Chloroquine	
	No. of patients with fever	%	No.of patients with fever	%
0	46[a]	100	45[b]	100
1	14	30.4	6	13.0
2	10	22.0	3	6.6
3	2	4	1	2.2
4	0	0	1	2.2
5	0	0	1	2.2
6	0	0	0	0

[a] Mean body temperature, 38.64 ± 1.39 °C.
[b] Mean body temperature, 38.61 ± 6.62 °C.

abdominal pain, and pruritus. These results are summarized in Table 3. Dizziness was more frequent in patients who received mefloquine (22%). In some patients, it was moderate to severe and one subject fell as a result of dizziness after the administration of mefloquine. He subsequently developed a marked tenderness over one rib, although an X-ray examination did not reveal any fracture; he recovered in about two weeks.

The incidence of loose stools or mild diarrhoea (4–5 stools per day) was 16% in the mefloquine group and 10% in the chloroquine group. None of the patients required any specific treatment.

Table 3. The incidence of side-effects after administration of mefloquine or chloroquine

Side-effect	After mefloquine (%)	After chloroquine (%)
Nausea	0	10.2
Vomiting	12.0	8.2
Diarrhoea (more than 3 stools per day)	16.0	10.2
Dizziness	22.0	6.1
Itching and rash	2.0	45.0
Myoglobinuria	2.0	2.0
Sinus bradycardia	18.0	16.3
Abdominal pain	16.0	24.5
Convulsions	0	2.0
Behavioural disturbance	2.0	0

Mild sinus bradycardia with a pulse rate of 50–52 per minute was observed in 18% of patients receiving mefloquine and 16% of those receiving chloroquine. The bradycardia appeared 4–7 days after drug administration and lasted for a few days. The pulse rate reverted to normal without any specific treatment.

Itching, alone or accompanied by a rash, was seen in a large number of subjects (45%) who received chloroquine. The itching started within 12 hours of drug administration and subsided after 3–4 days. A few cases needed antihistaminic drugs for relief. In some cases, there was a history of similar experience after receiving an antimalarial drug. Only one patient developed itching after receiving mefloquine.

One patient given chloroquine had convulsions and momentary loss of consciousness on the morning of day 1 (16 hours after receiving the drug). The convulsions lasted about two minutes, and he recovered by the next day. There was no neurological deficit and no history of epilepsy.

One patient receiving mefloquine complained on day 9 of a headache and was uncooperative, but conscious. No abnormal neurological signs were found; blood pressure and pulse rate were normal. He was given 10 mg of diazepam intramuscularly and antacids orally. He recovered the next day and remained well during the 42 days of observation. There was no history of behavioural disturbances.

One patient in each group developed transient suspected myoglobinuria within 24 hours of drug administration. The patient who received mefloquine complained of abdominal pain on day 1; there was oliguria on days 1 and 3 and anuria on day 2. Urine samples on day 3 showed the presence of myoglobin. His fluid intake was increased and he recovered completely without any specific treatment. One patient who received chloroquine developed pruritus, headache, chills, arthralgia, and dark urine on day 1. The urine was found to contain myoglobin. He had a history of "itching" after taking antimalarial drugs. A Coomb's test was negative and there was no G6PD deficiency. He recovered by day 6 without any specific treatment.

DISCUSSION

The aim of the present trial was to compare the safety, efficacy, and side-effects of mefloquine (1000 mg given orally in one day) with those of chloroquine (1500 mg given orally over 3 days) in the treatment of malaria in adult male patients. The study examined the cure rate, response of *P. falciparum* to the trial drug, speed of clearance of fever and parasitaemia, side-effects, and the results of haematological

and biochemical investigations.

The cure rate (S-response) was 98% for mefloquine and 100% for chloroquine. There was one case of an RI response in the mefloquine group (2%). However, the *in vitro* microtest showed that the parasites were sensitive to both chloroquine and mefloquine; the patient responded satisfactorily to oral chloroquine. There were no RII or RIII responses with either drug (*8*).

The rate of clearance of parasitaemia was marginally faster with chloroquine than with mefloquine (Table 1). In the chloroquine group, 94% of patients were clear on day 3 and 100% on day 4; in the mefloquine group, 98% of patients were negative on day 5 and 100% on day 7. Neither chloroquine nor mefloquine had any effects on gametocytes.

The rate of clearance of fever was not significantly different between the two groups. Chloroquine produced a clearance rate of 98% on day 3. One patient continued to have fever for two more days, so that a 100% clearance was not seen until day 6. In the mefloquine group, 96% of subjects were clear of fever by day 3 and 100% by day 4.

A similar incidence of side-effects was seen in the mefloquine and chloroquine groups. The common side-effects were nausea, vomiting, diarrhoea, dizziness, abdominal pain, and pruritus. There was a higher incidence of dizziness after the administration of mefloquine and a higher incidence of pruritus with chloroquine. The incidence of symptomless sinus bradycardia was similar in both treatment groups. In both groups, traces of albumin and urobilinogen were observed in urine samples for the first 3–4 days. This was probably due to haemolysis, which usually occurs with clinical malaria.

Two cases of suspected myoglobinuria were observed. In view of the fact that the two patients received different drugs in a double-blind manner and were acutely ill, it is probable that the changes seen in the urine were related to infection and toxaemia rather than to a particular drug.

One patient who took chloroquine had an epileptic fit and one who took mefloquine showed behavioural disturbance, which may have been drug-induced.

Neither mefloquine nor chloroquine produced any adverse effects on the haemopoietic system, liver, or kidney functions, as shown by various laboratory tests. No drug interactions were observed in either group.

Mefloquine, given as an oral dose of 1000 mg was well tolerated, effective, and safe. Clinically, there were no significant differences in safety, effectiveness, and incidence of side-effects between mefloquine and chloroquine in the treatment of falciparum malaria. However, in one patient who received mefloquine, an RI response was observed, although the organisms cultured from this case were sensitive to both mefloquine and chloroquine.

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RÉSUMÉ

ESSAI CLINIQUE COMPARÉ EN DOUBLE INSU DE LA MÉFLOQUINE ET DE LA CHLOROQUINE POUR LE TRAITEMENT DU PALUDISME SYMPTOMATIQUE À *PLASMODIUM FALCIPARUM*

Dans le cadre d'un essai clinique aléatoire mené en double insu en Zambie, des malades atteints de paludisme à *P. falciparum* ont été traités les uns par la méfloquine (1000 mg en une journée, par voie orale) et les autres par la chloroquine (1500 mg en trois jours, par voie orale). Les patients étaient des hommes adultes, dont 50 ont reçu de la méfloquine et 49 de la chloroquine.

Les taux de guérison obtenus ont été de 98% avec la méfloquine et de 100% avec la chloroquine. Il y a eu dans le groupe traité à la méfloquine un cas de réponse de type R-1 (2%); toutefois, le microtest *in vitro* pratiqué lors de la recrudescence a montré que les parasites étaient sensibles à la fois à la chloroquine et à la méfloquine; le patient a répondu de façon satisfaisante au traitement oral par la chloroquine. La disparition de la parasitémie a été un peu plus rapide avec la chloroquine qu'avec la méfloquine; il n'y a pas eu de différence dans la disparition de la fièvre.

Les effets secondaires ont été en règle générale mineurs et passagers. Il s'agissiat principalement de nausées, vomissements, douleurs abdominales, diarrhée, étourdissements et prurit. L'incidence des étourdissements a été plus élevée dans le groupe traité à la méfloquine (22%) tandis que le prurit était beaucoup plus fréquent avec la chloroquine. On a observé chez 18% des patients recevant de la méfloquine et 16% de ceux qui ont reçu de la chloroquine une bradycardie sinusale bénigne (50 à 52 pulsations/minute) qui n'a pas nécessité de traitement spécifique.

Aucune modification imputable aux médicaments n'a été enregistrée dans les profils hématologiques et biochimiques.

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