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Mefloquine, sulfadoxine, and pyrimethamine in the treatment of symptomatic falciparum malaria: a double-blind trial for determining the most effective dose

T. HARINASUTA,[1] D. BUNNAG,[1] S. VANIJANOND,[1] P. CHAROENLARP,[1] P. SUNTHARASMAI,[1] S. CHITAMAS,[1] U. K. SHETH,[2] & W. H. WERNSDORFER[2]

A total of 89 adult male Thai patients who had acute, uncomplicated falciparum malaria were treated in a double-blind randomized trial with a single oral dose of two or three tablets, each consisting of 250 mg mefloquine, 500 mg sulfadoxine, and 25 mg pyrimethamine (MSP). The two-tablet regimen produced a cure rate (S response) of 93%, the three-tablet regimen a cure rate of 98%. The mean duration of parasitaemia for the two- and three-tablet groups was 50 and 29 hours, respectively, while the mean duration of fever was 43 and 40 hours, respectively. Differences between the groups were not statistically significant. Tolerance was good at both dose levels. The main side-effects were abdominal discomfort, nausea, vomiting, dizziness, and diarrhoea, but these were mild, transient, and required no specific treatment. The results of haematological and biochemical investigations and of urinalysis revealed no drug-related changes following administration of MSP. The electrocardiograms of some patients revealed sinus bradycardia or sinus arrythmia, but these conditions were transient, symptomless, and clinically not significant.

In Thailand, *Plasmodium falciparum* exhibits varying degrees of resistance to all commonly used antimalarial drugs, including chloroquine, amodiaquine, sulfadoxine-pyrimethamine, and quinine (*1*). At present, the only effective therapy for infections caused by highly multidrug-resistant *P. falciparum* is the combination of quinine and tetracycline given orally for 7 days (*2*); however, this regimen is associated with patient compliance problems. A single dose of 500–1000 mg mefloquine has been reported to produce nearly a 100%-cure rate (S-type response) for malaria caused by drug-resistant *P. falciparum* in Thailand (*3*) and Brazil (*4*).

Continued use of antimalarial drugs has caused strains of the parasite to emerge that exhibit multidrug resistance, and this has necessitated a search for newer drugs or drug combinations. Studies *in vitro* have already demonstrated the emergence of resistance to mefloquine (*5–7*), and clinical cases of malaria resistant to the drug have also been reported (*8*, *9*). There is evidence, however, that the development of resistance to mefloquine of *P. berghei* in continuous culture can be delayed by use of a combination of mefloquine, sulfadoxine, and pyrimethamine (MSP) (*10*, *11*). Phase I and dose-finding studies of MSP have been carried out in Zambia (*12*) and Belem, Brazil (J. M. de Souza, personal communication, 1985). Here we report the results of a trial to compare the clinical effectiveness of and tolerance towards one, two, or three tablets of MSP (each tablet consisting of 250 mg mefloquine, 500 mg sulfadoxine, and 25 mg pyrimethamine) given as a single oral dose to patients with falciparum malaria in Thailand, where the parasite is largely multidrug resistant.

MATERIALS AND METHODS

The study was carried out on adult male patients suffering from acute, uncomplicated falciparum malaria, who had been admitted during 1983–84 to

[1] Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand. Requests for reprints should be sent to Professor Harinasuta at this address.

[2] Research and Technical Intelligence, Malaria Action Programme, World Health Organization, Geneva, Switzerland.

the Hospital for Tropical Diseases, Bangkok, Thailand. The hospital is situated in a non-transmission area. The informed consent of patients was obtained before the trial began, and those with complications or other diseases were excluded. A total of 150 male adults took part.

Initially, each patient was given a complete clinical examination, covering history of illness, symptoms and signs, body weight, height, laboratory analysis of blood (haemoglobin levels, red blood cell counts, erythrocyte volume fraction (haematocrit), total and differential white blood cell counts, platelet count, reticulocyte count), and biochemical investigations (estimation of serum glucose, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, serum urea nitrogen and creatinine). The tests were carried out prior to drug administration on day zero of the study (D_0) and during the follow-up period on days 2, 4, 7, 14, and 28. Daily urinalysis was carried out in the first week after treatment and again on D_{14} and D_{28} of the study. Electrocardiograms were recorded and blood electrolytes (sodium, potassium, chloride, and calcium) were determined on a daily basis on D_0–D_7 and then on D_9, D_{11}, D_{14}, D_{28}, D_{35}, and D_{42}. On D_0 chest X-rays were performed, the level of glucose-6-phosphate dehydrogenase was determined, and the haemoglobin type categorized. Malaria parasite counts of asexual forms and of gametocytes were made every 12 hours during parasitaemia and subsequently daily throughout the observation period. Symptoms and signs were recorded once or twice daily during the first week and then at weekly intervals.

Drug administration

Each patient was assigned to one of three groups by a randomized double-blind process. Tablets of MSP together with identical placebo tablets were administered as a single oral dose as follows:

—patients in group 1 received one MSP tablet plus two placebo tablets;
—those in group 2 received two MSP tablets plus one placebo tablet; and
—those in group 3 received three MSP tablets.

Clinical staff were not informed about the total amount of active drug given to patients until the end of the trial.

Tablets were taken as a single oral dose, with a glass of water, under supervision. If necessary, patients received other drugs, such as analgesics (e.g., paracetamol), tranquillizers (e.g., diazepam), intravenous fluids, or vitamin supplements. Patients received no other antimalarial drug during the trial, unless they experienced a relapse due to infection with *P. vivax* and developed fever, whereupon 150–300 mg of chloroquine base was given as a palliative; however, this did not affect the cure rate of falciparum malaria. Those who experienced recrudescence of *P. falciparum* were excluded from the trial and given appropriate treatment.

RESULTS

Each of the three groups originally comprised 50 patients. However, a number of RI responses occurred among the first 30 patients to complete the trial, and, a monitor therefore decoded the trial without revealing the code to the clinical investigators. It was found that patients in group 1, who had received the one-tablet MSP regimen plus two placebos, exhibited a 37%-RI response. A fresh randomization was therefore carried out, and the study continued as a double-blind randomized trial for comparison of the two- and three-tablet schedules.

A total of 94 patients took part in the reorganized trial, 46 in the two-tablet group and 48 in the three-tablet group; 89 patients completed the 42 days' follow-up period—44 in the two-tablet group and 45 in the three-tablet group. Five patients dropped out of the study at various times for personal reasons not related to the drug administration.

Characteristics of patients

Age and weight. There was no significant difference in the mean ages and body weights of patients in the two groups. For the two-tablet group the mean age on D_0 was 26.15 ± 8.93 years and the mean body weight 53.18 ± 6.38 kg (range, 42–72 kg); and for the three-tablet group 26.08 ± 9.36 years and 53.45 ± 6.39 kg (range, 43–71 kg), respectively.

Body temperature. On D_0, 45 patients in the two-tablet group had fever. After administration of the drug the mean duration of fever was 43.29 ± 26.7 hours. The rate of clearance of pyrexia (number of patients) was 33% in 24 hours and 82% in 48 hours; however, for one patient the fever persisted until D_5. In the three-tablet group, 43 patients had fever on D_0, and its mean duration was 40.87 ± 23.8 hours. The rate of clearance of pyrexia was 28% in 24 hours and 77% in 48 hours. No patient had fever from D_4 onwards. Differences in body temperatures between the two groups were not significant.

Clinical findings

The blood pressures, as well as respiratory and central nervous systems of all patients were normal

throughout the trial. In some cases, pulse rates were higher during fever but decreased when the body temperature returned to normal.

On D_0, splenomegaly was observed in 41% of patients in the two-tablet group and in 62% of those in the three-tablet group (mean enlargements were graded as Hackett 0.6 and 0.88, respectively, in the two groups). In contrast, on D_{42} splenomegaly occurred only in 11% of patients in the two-tablet group and in 9% of the three-tablet group.

Hepatomegaly was recorded in 64% of those in the two-tablet group on D_0 and in 67% of the three-tablet group. However, by D_{42} hepatic enlargement had cleared from all patients in the two-tablet group, although it persisted in 4% of those in the three-tablet group.

Haematology parameters

A general increase in haemoglobin level, haematocrit, and red blood cell count occurred in all patients during the study. On D_0 the mean haemoglobin level was 7.63 ± 1.34 mmol/l and the mean haematocrit level 37.70 ± 6.23 in both groups. By D_{42} the mean haemoglobin and haematocrit levels were 8.03 ± 0.81 mmol/l and 40.05 ± 3.71, respectively, in the two-tablet group and 8.25 ± 0.81 mmol/l and 41.08 ± 3.77, respectively, in the three-tablet group.

A deficiency in glucose-6-phosphate dehydrogenase was exhibited by 11 patients (nine in the two-tablet group and two in the three-tablet group). All of these patients tolerated MSP well, with no evidence of haemolysis.

In both groups, the number of reticulocytes and platelets as well as the white blood cell and differential white blood cell counts were similar before treatment. No drug-related changes were observed in these parameters. A number of patients exhibited elevated eosinophil counts, and this was probably related to a high level of helminthic infection (60% positive).

Biochemical parameters

No significant drug-related changes occurred in any of the biochemical parameters determined.

On D_0 five patients in the two-tablet group and four in the three-tablet group had raised serum aspartate aminotransferase levels. These returned to normal during the study, except for one patient in the two-tablet group, whose level of serum alanine aminotransferase was also high. For this patient, the levels of both these transaminases remained elevated until D_{42} of the trial. On D_0 one patient each in the two- and three-tablet groups had raised serum bilirubin values, but these returned to normal after one week of treatment.

None of the patients in either group exhibited any significant drug-dependent changes in their urine.

Parasitaemia

Two-tablet group. On D_0 all 46 patients in this group exhibited parasitaemia associated with asexual forms of *P. falciparum*, but all were cleared by D_5 (Table 1) (rate of clearance: 2% on D_1, 26% on D_2, 84% on D_3, and 97% on D_4; mean clearance time: 59.6 ± 15.3 hours). The cure rate (S response) was 93%; recrudescence (RI type) was observed in three patients on D_{20}, D_{23}, and D_{24}. One patient vomited 25 hours after drug administration. Gametocytes were detected in 19 patients on D_0, in 20 on D_4, but in none on D_{28}. Six patients relapsed on D_{30} to D_{41} because of infection with *P. vivax*.

Three-tablet group. On D_0 all 48 patients in the three-tablet group had parasitaemia with asexual forms of *P. falciparum* and all were cleared by D_6 (Table 1). The rate of clearance of parasitaemia was 0% on D_1, 25% on D_2, 81% on D_3, and 95.8% on D_4, while the mean clearance time was 58.9 ± 20.5 hours. The cure rate (S response) was 98%. One patient, who had vomited 5 minutes after taking the drug, underwent recrudescence (RI type) on D_{13}, and, if this case had been excluded, the cure rate would have been 100%. Gametocytes were detected in 12 patients on D_0, in 19 on D_4, and persisted in one patient until D_{42}. On D_{37} there was one case of relapse caused by *P. vivax*.

Table 1. Number of patients with parasitaemia caused by *Plasmodium falciparum* asexual forms and mean parasite count in patients given two or three tablets of MSP[a]

	Two-tablet group		Three-tablet group	
Day of trial	No. with parasitaemia	Mean parasite count (per mm^3)	No with parasitaemia	Mean parasite count (per mm^3)
0	46 (100)[b]	26 316	48 (100)	28 907
1	45 (97.8)	25 624	48 (100)	23 689
2	34 (73.9)	254	36 (75)	108
3	7 (15.2)	16	9 (18.7)	8
4	1 (2.2)	1	2 (4.2)	4
5	0	0	2 (4.2)	1
6	0	0	0	0
7	0	0	0	0

[a] MSP = 250 mg mefloquine, 500 mg sulfadoxine, and 25 mg pyrimethamine.

[b] Figures in parentheses are percentages.

Table 2. Side-effects caused by MSP observed during the first 4 days after administration of the drug[a]

Symptom	No. of patients	
	Two-tablet group	Three-tablet group
Nausea	5 (10.8)[b]	5 (10.4)
Vomiting	10 (21.7)	11 (22.9)
Diarrhoea	3 (6.5)	6 (12.5)
Dizziness	3 (6.5)	5 (10.4)
Abdominal pain	1 (2.1)	3 (6.2)
Tinnitus	5 (10.8)	5 (10.4)
Partial loss of hearing	2 (4.3)	0

[a] MSP = 250 mg mefloquine, 500 mg sulfadoxine, and 25 mg pyrimethamine.
[b] Figures in parentheses are percentages.

Side-effects

The main subjective side-effects that could be attributed to MSP were nausea, vomiting, diarrhoea, dizziness, and tinnitus (Table 2). The electrocardiograms of patients in the two-tablet group exhibited the following anomalies: 52% had sinus bradycardia; 26% had a prolonged Q–T_c interval; 15% had sinus arrythmia; 9% had first-degree AV block; and 7% had abnormal T-waves. In the three-tablet group, sinus bradycardia was observed in 46% of patients; prolonged Q–T_c interval in 27%; sinus arrythmia in 19; and abnormal T-waves in 4%.

All the electrocardiogram changes were transient and symptomless, needed no specific treatment, and were considered clinically non-significant by a cardiologist not involved in the study.

DISCUSSION

The one-tablet dose regimen of MSP had to be abandoned at an early stage of the trial because of its high rate of RI response (37%). In Zambia, where *P. falciparum* is sensitive to all available antimalarial drugs, a cure rate (S response) of 100% has been reported for the one-tablet regimen (*12*). As expected, the multiresistant strains of *P. falciparum* in Thailand were less sensitive to MSP. In Gabon, systematic *in-vitro* testing of *P. falciparum* has indicated that, in some instances, strains of the parasite that are highly resistant to chloroquine exhibit also reduced sensitivity to mefloquine. Reduced sensitivity was also found among *P. falciparum* isolates tested in the Philippines (*6*).

The cure rate (S response) for the two-tablet group was 93%, while that of the three-tablet group was 97%. The incidence of RI response in the two-tablet group was 7%, compared to 2% for the three-tablet, but the difference was not statistically significant. The only patient with RI response on D_{13} in the three-tablet group vomited 5 minutes after taking the drug. In the absence of data on drug blood level, however, it is difficult to determine whether this arose because of drug failure or decreased total drug absorption; nevertheless, some of the drug was probably lost through vomiting. No RII or RIII response was observed in either group. Also, the mean rates of clearance of parasitaemia and fever were similar in both groups. The incidence of side-effects was comparable in both groups but was slightly greater in the three-tablet group, especially nausea, vomiting, diarrhoea, dizziness, and abdominal pain.

Adult male Thai patients with uncomplicated falciparum malaria who were administered two or three tablets of MSP, therefore, exhibited a cure rate of 93% or 98%, respectively. All patients tolerated the drug well, and the side-effects were mild and transient.

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RÉSUMÉ

TRAITEMENT DU PALUDISME SYMPTOMATIQUE À *P. FALCIPARUM* PAR LA MÉFLOQUINE, LA SULFADOXINE ET LA PYRIMÉTHAMINE: ESSAI EN DOUBLE INSU VISANT À DÉTERMINER LA POSOLOGIE LA PLUS EFFICACE

Dans une étude en double insu randomisée, 89 Thaïlandais adultes de sexe masculin souffrant de paludisme aigu à *Plasmodium falciparum* non compliqué ont reçu une dose orale unique de deux ou trois comprimés contenant chacun 250 mg de méfloquine, 500 mg de sulfadoxine et de 25 mg de pyriméthamine (MSP). Au cours d'une étude préliminaire, un groupe de patients avait reçu un comprimé de MSP, mais étant donné le taux élevé de réponse RI (37%), cette posologie n'a pas été adoptée dans l'étude principale. Le taux de guérison (réponse S) a été de 93% pour deux comprimés et de 98% pour trois comprimés. La durée moyenne de la parasitémie a été de 50 heures pour le groupe ayant reçu deux comprimés et de 29 heures pour le groupe ayant reçu trois comprimés, tandis que la durée moyenne de la fièvre a été de 43 heures et 40 heures respectivement. Les différences entre les groupes n'étaient pas statistiquement significatives. Dans les deux cas, la tolérance a été bonne. Les principaux effets secondaires ont été une gêne abdominale, des nausées, des vomissements, des vertiges et de la diarrhée; toutefois, ces effets ont été légers et passagers, et aucun traitement spécifique n'a été nécessaire. Les examens hématologiques et biochimiques, tout comme les analyses d'urine, n'ont révélé aucun changement lié à l'administration de comprimés de MSP. L'électrocardiogramme a mis en évidence une bradycardie sinusale ou une arythmie sinusale chez quelques patients, mais ces anomalies étaient passagères, ne s'accompagnaient d'aucun symptôme, et n'avaient aucune signification clinique.

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