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A phase II/III double-blind, dose-finding clinical trial of a combination of mefloquine, sulfadoxine, and pyrimethamine (Fansimef) in falciparum malaria

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Fansimef is a combination of 250 mg mefloquine (base), 500 mg sulfadoxine, and 25 mg pyrimethamine per tablet. One hundred and fifty adult male Brazilian patients at Belém (Pará), who had peripheral blood smears positive for Plasmodium falciparum, *with or without clinical symptoms of falciparum malaria, were treated in a double-blind randomized fashion with either one, two or three tablets of Fansimef. Of those receiving one tablet (48 patients), 81% were cured and 19% exhibited RI recrudescences. All the patients receiving two or three tablets of Fansimef (49 patients in each group) were cured. The rates of initial clearance of parasitaemia and fever were similar in all treatment groups. Tolerance was good at all dose levels. The main side-effects included nausea, vomiting, dizziness, diarrhoea and abdominal pain, but these were mild and transient and required no specific treatment. The incidence of vomiting and nausea was highest in patients given the three-tablet dose. The results of various haematological, biochemical and urine analyses were not adversely altered by the administration of Fansimef.*

For the treatment of chloroquine-resistant and chloroquine-sensitive acute falciparum malaria, mefloquine administered orally in a dose of 750–1000 mg was found to be effective and well tolerated (*1*, *2*). Studies on induced resistance in mice and rats infected with *Plasmodium berghei* have shown that use of mefloquine alone quickly resulted in resistance (*3–5*). In this model the emergence of resistance could be delayed by administration of a combination of mefloquine, sulfadoxine and pyrimethamine (*6*).

Fansidar is a fixed combination of sulfadoxine and pyrimethamine (20:1 ratio) and has been successfully used as a second line drug for the suppression and treatment of *P. falciparum* infections resistant to chloroquine (*7–9*). However, in recent years increasing resistance of *P. falciparum* to sulfadoxine/pyrimethamine has been reported from Brazil and Thailand (*10*, *11*) and, in 1983–84, also from Africa (J. M. K. Ekue et al., unpublished observations).

Fansimef (a combination of 250 mg mefloquine (base), 500 mg sulfadoxine and 25 mg pyrimethamine per tablet) has been introduced, with the hope that it will not only be effective in multidrug-resistant *P. falciparum* but would also delay the development of resistance of *P. falciparum* to mefloquine. Phase I studies with Fansimef have shown the drug to be well tolerated in Zambia (J. M. K. Ekue et al., 1982, unpublished observations) and Belém, Brazil (*12*). Further phase II and III studies, including dose-finding studies, have been carried out in Zambia (*13*) and Thailand (Harinasuta et al., 1985, unpublished observations; Pinichpongse et al., 1984, unpublished observations).

The object of the present study was to assess the tolerance and effectiveness of Fansimef at three dose levels in adult Brazilian men with *P. falciparum* infection, with, or without, clinical symptoms of falciparum malaria.

MATERIALS AND METHODS

The study was carried out at the Clinical Trials Centre, Barros Barreto Hospital, Belém, Pará. Belém

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is free of malaria transmission. The protocol of the trial was approved by the local ethical committee as well as by the WHO Secretariat Committee on Research Involving Human Subjects.

All the patients who entered the trial were aged between 17 and 53 years and came mainly from the Paragominas and Marabá areas. The trial was prospective, randomized and double-blind. The patients stayed on the ward from day -1 (the day before drug administration) to day 63. A total of 150 patients with proven *P. falciparum* infection and a parasitaemia of more than 400 asexual forms per μl blood, with or without clinical symptoms, gave informed consent to participate in the trial. Patients with serious infections or complicated malaria needing parenteral treatment were excluded from the study. So were patients suffering from intercurrent diseases or pathological conditions that could have interfered with the conduct of the clinical trial.

Each patient was assigned to one of three groups in a random double-blind design. Tablets of Fansimef, together with identical placebo tablets were administered as a single, oral dose as follows: patients in group 1 received one Fansimef plus two placebo tablets; patients in group 2 received two Fansimef plus one placebo tablet; patients in group 3 received three Fansimef tablets. The patients received other drugs such as analgesics (paracetamol) and anthelmintics if considered necessary by the clinician: any such medication was noted on the patient's record form.

A history was taken from each patient and a detailed clinical examination was carried out according to a standard protocol. Clinical measurements and various laboratory investigations were also carried out serially. The patients were examined on day -1, again on day 0 before the administration of the trial drugs, daily on days 1-7, and then weekly up to day 63. Clinical features such as symptoms, pulse rate, body temperature and respiration were recorded daily. Blood pressure was measured daily on days -1 to 7 and then weekly up to day 63. The electrocardiogram, chest X-ray, measurement of body weight and height, and the Dill-Glazko and Bratton Marshall urine test for chloroquine and sulfonamides, respectively, were performed on day -1. The electrocardiogram was repeated on days 1, 4, 7, 14, 28 and 63 and the patients were reweighed on day 63. A series of haematological and biochemical tests were carried out on days -1, 0, 1, 4, 7, 14, 28 and 63. Haematological tests included haemoglobin, erythrocyte volume fraction (haematocrit), red blood cell count, reticulocyte count, total and differential white blood cell counts, and platelet count. Biochemical investigations included serum glucose, creatinine, albumin, SGOT, SGPT, bilirubin, calcium, sodium, potassium, iron, phosphates, chloride, magnesium, urea and alkaline phosphatase measurements. Urine analysis was performed daily from day -1 to day 7 and also on days 14, 28 and 63. Stools were examined for blood and intestinal parasites on day -1. Blood smears were prepared and examined for malaria parasites four times a day (at 06h00, 12h00, 18h00 and 24h00) until two days after the clearance of asexual forms, and daily from this day to day 63.

The incidence of drug side-effects, such as nausea, vomiting, diarrhoea, abdominal pain and dizziness, was determined by questioning the volunteers prior to and following treatment. These criteria are therefore subjective.

RESULTS

Each of the three treatment groups comprised 50 patients aged 17-53 years. In group 1, two patients dropped out for personal reasons, one on day 28 and the other on day 32, leaving 48 patients who completed 63 days. One patient each from groups 2 and 3 dropped out for personal reasons on day 35 and day 39 respectively, leaving 49 patients in each group completing the 63-day study period.

The mean body weight in group 1 was 56.5 kg on day 0, and there was an average weight gain of 4.5 kg by day 63. The equivalent values for group 2 were 57.8 kg and 3.6 kg, and for group 3, 57.7 kg and 4.0 kg. There were wide individual variations in weight, but no significant difference in mean weight among the three groups during the study period.

Clinical findings

In all cases, blood pressure and the respiratory system were normal and remained so, after administration of the trial drug. In some cases the pulse rate was higher during fever and came down when the body temperature became normal. There were no cases of sinus bradycardia. No disturbances of the central nervous system were found, except for transient dizziness in 10% of patients in group 2 and 8% of patients in group 3.

Splenomegaly was observed in 37-40 patients in each group on day -1, with a mean enlargement of 1.4 Hackett units; the numbers with spleen enlargement on day 63 were 6 in group 1, 3 in group 2, and one in group 3. Hepatomegaly was present on day 0 in 36 patients in group 1, 40 in group 2, and 37 in group 3. In most cases, the liver size was normal by day 63.

Laboratory investigations

In all three groups, the values for haemoglobin, erythrocyte volume fraction (haematocrit), red and white blood cell counts and reticulocytes were

comparable before treatment. No drug-related adverse changes were seen. In a number of patients the eosinophil counts were high — probably related to a high rate of helminth infection in this group. No significant drug-related changes were seen in the results of urine analysis in any of the three groups.

Values of all biochemical investigations mentioned earlier, i.e., fasting serum glucose, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum calcium, serum sodium, serum potassium, serum iron, serum creatinine, serum magnesium, serum albumin and plasma urea, were within the normal range and were not modified in any undesirable manner after administration of the trial drug.

Parasitological response

Table 1 shows the details of clearance of parasitaemia and mean parasite counts in the three treatment groups.

Group 1 (one tablet). Of the 48 patients who completed the trial, ten were positive for *P. falciparum* asexual forms on day 3. From day 5 until day 63, 39 patients remained negative. An "RI" type of response was observed in 9 patients, of whom one was positive on each of days 18, 23, 25, 29, 31, 32, 35 and two were positive on day 48. Thus, there was an "S" type response in 81% of the patients and an "RI" type response in 19%. The mean parasite clearance time was 59.9 ± 18.2 hours. All RI cases received 2 tablets of mefloquine (500 mg) and responded satisfactorily and remained free from parasitaemia until the end of the study.

Group 2 (two tablets). All 50 patients were positive for *P. falciparum* asexual forms on day 0, two on day 4, and one up to day 6. From day 7 to 63 no patient was positive (one patient left on day 39 who had no parasitaemia from day 4 onwards (S/RI? response)). The mean parasite clearance time was 54.6 ± 23.6 hours.

Group 3 (three tablets). All 50 patients were positive for *P. falciparum* asexual forms on day 0, one case on day 4, and one on day 5. From day 6 to 63 all patients remained negative (one patient, who had cleared by day 3, had no parasitaemia until day 35 when he left (S/RI? response)). The mean parasite clearance time was 53.7 ± 20.9 hours.

Body temperature

Fever before treatment on day 0 was noted in 24 patients in group 1, 24 in group 2, and 28 in group 3. Similar mean rates of fever clearance were seen in the three groups: 31.2 ± 15.8 hours for group 1, 37 ± 27.4 hours for group 2, and 30.2 ± 13.4 hours for group 3. Differences between the groups were not significant.

Table 1. Clearance of parasitaemia and mean parasite count in patients given mefloquine/sulfadoxine/pyrimethamine (Fansimef)

	Group 1 (one tablet)			Group 2 (two tablets)			Group 3 (three tablets)		
Day of treatment	Number positive	Percentage positive	Mean parasite count (per mm^3 blood)	Number positive	Percentage positive	Mean parasite count (per mm^3 blood)	Number positive	Percentage positive	Mean parasite count (per mm^3 blood)
0	50[a]	100	13 471	50[b]	100	14 603	50[c]	100	21 484
1	50	100	6 658	50	100	4 385	49	98	7 749
2	36	72	299	30	60	125	29	58	318
3	13	26	24	9	18	24	8	16	44
4	2.0	4.0	1.0	3.0	6.0	3.5	2.0	4.0	9.5
5	0	0	0	1.0	2.0	0.5	1.0	2.0	1.0
6	0	0	0	1.0	2.0	0	0	0	0
7	0[d]	0	0	0	0	0	0	0	0

[a] Two patients dropped out on days 28 and 32 respectively.

[b] One patient dropped out on day 35.

[c] One patient dropped out on day 39.

[d] Among a total of 9 patients positive for asexual forms of *P. falciparum*, an RI response was observed in one patient on each of days 18, 23, 25, 29, 31, 32, 35 and in two patients on day 48.

Table 2. Incidence of side-effects noted in patients given mefloquine/sulfadoxine/pyrimethamine (Fansimef)

Side-effect	No. of patients		
	Group 1[a]	Group 2[a]	Group 3[a]
Nausea	7 (14)[b]	7 (14)	15 (30)
Vomiting	1 (2)	2 (4)	8 (16)
Diarrhoea	8 (16)	7 (14)	8 (16)
Dizziness	0 (0)	5 (10)	4 (8)
Abdominal pain	1 (2)	3 (6)	5 (10)
Central nervous system involvement	0 (0)	0 (0)	0 (0)
Pruritus	1 (2)	1 (2)	1 (2)
Rash	0 (0)	0 (0)	0 (0)
Tremor of the hands	0 (0)	1 (2)	0 (0)
Tinnitus	0 (0)	0 (0)	1 (2)

[a] There were 50 patients in each group; one tablet of Fansimef was given in group 1, two in group 2, and three in group 3 patients.
[b] Figures in parentheses are percentages.

Side-effects

The main subjective side-effects that could be attributed to the trial drug were nausea, vomiting, diarrhoea, abdominal pain and dizziness (Table 2). The incidence of nausea and vomiting was similar in groups 1 and 2 but higher in group 3. The incidence of diarrhoea was similar in all three groups. Dizziness, which had a similar incidence in groups 2 and 3, was not seen in group 1. Abdominal pain seemed to be dose related. The side-effects were mostly mild, of short duration and required no specific treatment.

DISCUSSION

The objective of this study was to compare the clinical effectiveness, safety and tolerance of three doses of Fansimef (one, two or three tablets) which were given as a single oral dose to patients who were positive for asexual forms of *P. falciparum*, with or without clinical malaria fever.

The cure rate (S-response) was 81% in group 1, and 100% in groups 2 and 3. (In groups 2 and 3, one patient dropped out on days 39 and 35, respectively, whose response could have been S/RI). An RI type of response was seen in 19% of patients in group 1, between days 18 and 48. No RII or RIII responses were seen in any of the groups. The mean rate of clearance of *P. falciparum* asexual forms was 56 hours, the rates being similar in all three treatment groups (59.8, 54.6 and 53.7 hours, respectively). By day 3, the extent of clearance was 79% for group 1, 94% for group 2, and 96% for group 3. By day 4, the percentage clearance was 96% for group 1, and 98% for groups 2 and 3. Fever clearance rates in the three groups were also similar: 31.2, 36.96 and 30.19 hours for groups 1, 2 and 3, respectively.

Tolerance was good at all dose levels, but effectiveness was less with the one-tablet dose which had 19% RI-type responses, compared to the 100% cure rate (S-type) with doses of two and three tablets.

The side-effects were mild and transient and not significantly different in the three groups, except for nausea and vomiting which were higher with the three-tablet dose. The incidence of vomiting was 16% with three tablets of Fansimef, which was similar to that seen in other studies (U. K. Sheth, unpublished data), except for the Zambian study (*13*) which had a low incidence of 4%. In another outpatient study in Thailand, the incidence of vomiting following three tablets of Fansimef was 24% (E. B. Doberstyn, personal communication). The incidence of dizziness following the three-tablet dose of Fansimef was 8%, which is similar to the 6% observed in Bangkok (Harinasuta et al., 1986, unpublished observations), whereas the Zambian study reported an incidence of 22% (*13*).

Haematological and biochemical investigations and urine analysis did not reveal any adverse effects after the administration of Fansimef at any of the three dose levels.

Fansimef was thus found to be well tolerated, safe and effective at a dose of two and three tablets in the treatment of infection. The response at the one-tablet dose was unsatisfactory with a cure rate of only 81%. In Brazil, where *P. falciparum* is highly resistant to chloroquine, and is becoming increasingly resistant to sulfadoxine plus pyrimethamine as well as to quinine, a three-tablet dose of Fansimef for treatment of malaria may be considered adequate.

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RÉSUMÉ

ÉTUDE CLINIQUE DE PHASE II/III EN DOUBLE INSU VISANT À DÉTERMINER LA POSOLOGIE DE L'ASSOCIATION DE MÉFLOQUINE, SULFADOXINE ET PYRIMÉTHAMINE (FANSIMEF) DANS LE PALUDISME À *P. FALCIPARUM*

Le Fansimef est une association de 250 mg de méfloquine base, 500 mg de sulfadoxine et 25 mg de pyriméthamine. La présente étude avait pour objet d'évaluer la tolérance au Fansimef et l'efficacité de ce produit à trois différentes posologies chez des Brésiliens adultes de sexe masculin atteints de paludisme à *Plasmodium falciparum*, avec ou sans symptômes cliniques. L'étude a été menée à Belém (Pará), dans une région indemne de transmission. Les patients qui ont participé à l'étude étaient âgés de 15 à 53 ans et venaient principalement des régions de Paragominas et Marabá.

Les patients ont été répartis en trois groupes de façon aléatoire, en vue d'une étude en double insu. Des comprimés de Fansimef et des comprimés placebo d'apparence identique étaient administrés en une prise unique, de la façon suivante: les 50 patients du groupe 1 recevaient un comprimé de Fansimef plus deux comprimés placebo; les 50 patients du groupe 2 recevaient deux comprimés de Fansimef plus un comprimé placebo; les 50 patients du groupe 3 recevaient trois comprimés de Fansimef. L'étude a duré 63 jours. Deux patients du groupe 1, un patient du groupe 2 et un patient du groupe 3 ont abandonné avant la fin pour des raisons personnelles.

Sur les 48 patients du groupe 1 (un comprimé de Fansimef) qui ont participé à l'étude jusqu'à la fin, 81% ont été guéris, tandis que 19% ont présenté des recrudescences de type RI. Les 49 patients du groupe 2 (deux comprimés de Fansimef) et les 49 patients du groupe 3 (trois comprimés de Fansimef) qui ont suivi le traitement complet ont tous été guéris. Le temps moyen de disparition de la parasitémie a été de 59,9 ± 18,2 heures dans le groupe 1, 54,6 ± 23,6 heures dans le groupe 2, et 53,7 ± 20,9 heures dans le groupe 3. Le temps moyen de disparition de la fièvre a été de 31,2 ± 15,8 heures pour le groupe 1, 37,0 ± 27,4 heures pour le groupe 2 et 30,2 ± 13,4 heures pour le groupe 3. Le temps de disparition de la parasitémie et le temps de disparition de la fièvre ont donc été du même ordre dans chacun des trois groupes.

La tolérance a été bonne à toutes les posologies. Les principaux effets secondaires constatés ont été des nausées (14%, 14% et 30% dans les groupes 1, 2 et 3, respectivement), des vomissements (2%, 4% et 16% respectivement), des vertiges (0%, 10% et 8% respectivement), de la diarrhée (16%, 14% et 16% respectivement) et des douleurs abdominales (2%, 6% et 10% respectivement). Seuls les cas de nausées et de vomissements ont été nettement plus nombreux chez les patients ayant reçu trois comprimés. Les effets secondaires ont été généralement modérés et de courte durée, et aucun traitement spécifique n'a été nécessaire. L'administration de Fansimef n'a eu aucun effet défavorable sur les résultats des divers examens hématologiques et biochimiques et des analyses d'urine.

En conclusion, il est apparu que l'administration de deux ou trois comprimés de Fansimef constituait un traitement bien toléré, sûr et efficace de l'infection à *P. falciparum*. L'administration d'un seul comprimé a donné des résultats non satisfaisants, le taux de guérison n'ayant été que de 81%. Au Brésil, où *P. falciparum* est très résistant à la chloroquine et de plus en plus résistant à l'association sulfadoxine-pyriméthamine, ainsi qu'à la quinine, on peut considérer que l'administration de trois comprimés de Fansimef constitue un traitement satisfaisant du paludisme.

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