

A double-blind clinical trial of a combination of mefloquine, sulfadoxine and pyrimethamine in symptomatic falciparum malaria

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Fansimef is a combination of 250 mg of mefloquine, 500 mg of sulfadoxine, and 25 mg of pyrimethamine per tablet. A total of 150 adult male Zambian patients who had symptomatic Plasmodium falciparum parasitaemia were treated in a double-blind randomized fashion with either one, two or three tablets of Fansimef. All patients in the three treatment groups showed an S-type response. The rates of clearance of parasitaemia and fever were similar in all treatment groups. Tolerance was good at all dose levels. The main side-effects were abdominal discomfort, weakness and lassitude, dizziness, and pruritus, but these were mild, transient and required no specific treatment. Vomiting occurred only in 4% of patients given the highest dose of three tablets. The results of various haematological and biochemical investigations and urinalysis were not adversely altered by the administration of Fansimef.

Mefloquine, administered orally in doses of 750-1000 mg, has been shown to be effective in the treatment of both chloroquine-resistant and chloroquine-sensitive acute falciparum malaria (1, 2). However, it is feared that the use of mefloquine alone in clinical practice may soon lead to the development of resistance, since studies in mice and rats have already demonstrated that resistance of *Plasmodium berghei* to mefloquine could be induced relatively quickly and easily (3-5). The emergence of resistance could be delayed by the administration of antimalarials in combination (6).

Fansidar^a is a fixed 20:1 ratio combination of sulfadoxine and pyrimethamine, which has been used for many years for the successful treatment and suppression of malaria (7). It is a second-line drug of choice in the management of chloroquine-resistant falciparum malaria (8, 9). Unfortunately, increasing resistance of *P. falciparum* to sulfadoxine/pyri-

methamine has been reported from Brazil and Thailand and has also emerged in Africa (10, 11, J. M. K. Ekue et al., unpublished observations, 1983-84).

Fansimef,^a a combination of 250 mg of mefloquine, 500 mg of sulfadoxine, and 25 mg of pyrimethamine per tablet, was introduced in the hope that it would not only be effective in drug-resistant *P. falciparum* malaria but also delay the emergence of resistance to mefloquine.

In phase I studies, Fansimef was found to be well tolerated in healthy adult male volunteers in Zambia; adequate blood levels of each of the components were achieved after administration of three tablets to volunteers (J. M. K. Ekue et al., unpublished observations, 1982).

The present study was carried out to assess the tolerance and effectiveness of Fansimef at three dose levels in adult male Zambians with symptomatic *P. falciparum* parasitaemia.

MATERIALS AND METHODS

The study was carried out in the clinical trials wards of the Tropical Diseases Research Centre, Ndola, Zambia. The transmission of malaria is not possible in the mosquito-free hospital environment.

The protocol for the trial was approved by the

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Zambian Ethical Committee as well as by the World Health Organization Secretariat Committee on Research Involving Human Subjects.

All the patients who entered the trial were aged 12 years or over, and were recruited from the out-patients' department of Ndola Central Hospital.

The trial was prospective, randomized, and double-blind. Each patient was kept under observation in hospital from day 0 (when the drugs were administered) to day 35. A total of 150 patients with proven symptomatic asexual *P. falciparum* parasitaemia gave informed consent to participate in the trial.

Patients with serious infections or other complications needing parenteral treatment were excluded from the study.

Each patient was assigned to one of three groups, in a random double-blind manner. Tablets of Fansimef, together with identical placebo tablets, were administered as follows: patients in group 1 received one Fansimef plus two placebo tablets; those in group 2, two Fansimef plus one placebo tablet; and those in group 3 were given three Fansimef tablets.

The patients were treated with other drugs such as analgesics (aspirin), sedatives (diazepam), and anthelmintics only upon advice of the clinicians; 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 0 before the administration of the trial drugs and daily on days 1–7, then once a week until day 35. Clinical features such as symptoms, pulse rate, body temperature, and respiration were recorded daily. Blood pressure was measured daily on days 0 to 7 and then weekly up to day 35. The electrocardiogram, chest X-ray, measurement of height and body weight, the Dill-Glazko urine test for chloroquine, a qualitative urine test for glucose-6-phosphate dehydrogenase (G6PD), and determination of haemoglobin genotype were performed on day 0. The electrocardiogram was repeated on days 1, 4, 7, 14, 28, and 35 and the patients were reweighed on day 35. A series of haematological and biochemical investigations was carried out on days 0, 1, 4, 7, 14, 28, and 35. Urinalysis was performed daily on days 0 to 7 and also on days 14, 28, and 35. Stools were examined for blood and parasites on day 0. Blood smears were prepared and examined for malarial parasites daily from day 0 to day 7, then weekly until day 35.

RESULTS

Each of the three treatment groups comprised 50 patients aged between 12 and 49 years. Two patients

dropped out from each group (in total six patients) for reasons that were not related to the administration of the trial drugs. One patient in group 3 could not be assessed as he was found to have gametocytes only. Therefore, results were available for 48 patients in each of groups 1 and 2, and 47 in group 3.

The mean body weight in group 1 was 53.5 kg on day 0, and there was an average weight gain of 2.4 kg by day 35. The mean body weight in group 2 was 53.9 kg on day 0, with a mean weight gain of 1.3 kg by day 35. The equivalent values for group 3 were 54.3 kg and 3.3 kg. There were wide individual variations in weight but there was no significant difference in mean weight among the three groups during the period of observation.

Clinical findings

In all cases, the blood pressure and respiratory system were normal and remained normal after administration of the trial drug. Mild sinus bradycardia occurred in 6 patients from group 1, 5 patients from group 2, and 6 patients from group 3. There were no clinical symptoms and the pulse rate reverted to normal without any specific treatment.

Sinus tachycardia, associated with pyrexia, was seen in 22 patients in group 1, 22 patients in group 2, and 28 patients in group 3 before the administration of the trial drugs on day 0.

First-degree atrioventricular block was seen before treatment in three patients (two in group 2 and one in group 3) and developed between day 7 and day 35 in one patient in group 3. Before treatment, a Wolff-Parkinson-White syndrome was seen in one patient in group 2, a suspected myocarditis in one patient in group 3, and a generalized electrocardiographic T-wave inversion in one patient in group 3. None of these patients showed any adverse effects after drug administration.

Only one patient had neuropsychiatric symptoms after the administration of the trial drug; the patient in question developed an acute anxiety reaction on days 3 to 7, and was treated with diazepam and chlorpromazine. His relatives took him out of the hospital on day 8 against medical advice. Follow-up investigations revealed that the patient was under severe mental stress before he developed the attack of acute malaria.

There was splenomegaly in 20–22 patients in each group on day 0. The numbers with splenic enlargement on day 35 were 3 in group 1, 2 in group 2, and 4 in group 3.

Five patients (three in group 1 and one each in groups 2 and 3) had slight hepatomegaly on day 0; in most cases, liver size soon reverted to normal. One patient in group 1 developed slight hepatomegaly between days 2 and 35.

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Table 2. The incidence of side-effects after administration of sulfadoxine/pyrimethamine/mefloquine

Side-effect	Group 1 (%)	Group 2 (%)	Group 3 (%)
Nausea	0	6	4
Vomiting	0	0	4
Abdominal pain	12	14	4
Diarrhoea	4	2	4
Dizziness	10	14	22
Weakness/lassitude	18	14	14
Pruritus	10	8	6
Rash	0	0	2

doses of Fansimef (a combination of 250 mg of mefloquine, 500 mg of sulfadoxine, and 25 mg of pyrimethamine per tablet). One, two, or three tablets were given as a single oral dose to patients with *P. falciparum* malaria.

The cure rate (S-response) was 100% in all treatment groups. The mean rate of clearance of *P. falciparum* parasitaemia was 2.5 days, and similar rates were seen in all treatment groups (2.5, 2.5, and 2.4 days, respectively). By day 3, the extent of clearance of parasitaemia was 97.9% for group 1, 95.8% for group 2, and 95.7% for group 3.

The rates of clearance of fever in the three groups were also similar: 1.9 days for group 1, 2.2 days for group 2, and 2.3 days for group 3.

Tolerance was good at all dose levels. Side-effects were mild and transient and showed similar incidence in all treatment groups. The main side-effects were abdominal discomfort, weakness and lassitude, dizziness, and pruritus. During a previous study, mefloquine produced vomiting in 11.9% of cases (1). In the present study with Fansimef, the incidence of vomiting was low and occurred only in the group given the highest dose (4%).

Haematological and biochemical investigations

and urinalysis did not reveal any adverse effects after the administration of Fansimef at any of the three dose levels.

Fansimef was found to be well tolerated, safe, and effective in the treatment of symptomatic falciparum malaria in a single oral dose of one, two, or three tablets. Similar responses were seen at all three dosage levels. In Zambia, where the emergence of drug-resistant malaria is not yet a major problem and where most of the malarial parasites are sensitive to standard doses of chloroquine, a dose of two tablets would appear to be appropriate for the treatment of falciparum malaria; this will ensure a margin of safety for cases that may require slightly higher blood drug concentrations.

The sensitivity of *P. falciparum* to antimalarials is changing rapidly (12) and it is important to ensure the rational use and deployment of new drugs. Attention is drawn to the recommendations of a WHO Scientific Group (13), that the use of mefloquine and its combinations by communities in endemic areas should be restricted to the treatment of acute malaria attacks that are likely to be due to multiple drug-resistant *P. falciparum*, and that fully curative doses should be used at all times.

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RÉSUMÉ

ESSAI CLINIQUE À DOUBLE INSU D'UNE ASSOCIATION DE MÉFLOQUINE, SULFADOXINE ET PYRIMÉTHAMINE DANS LE PALUDISME SYMPTOMATIQUE À *P. FALCIPARUM*

Un total de 150 adultes zambiens de sexe masculin, présentant une parasitémie à *Plasmodium falciparum* symptomatique, ont été traités par une unique administration orale d'un, de deux ou de trois comprimés de Fansimef (contenant chacun 250 mg de méfloquine, 500 mg de sulfadoxine et 25 mg de pyriméthamine). Il s'agissait d'une étude prospective, randomisée, à double insu. Tous les malades ont été choisis parmi les sujets fréquentant la consultation externe de l'hôpital central de Ndola. Ils ont été inclus après avoir donné leur consentement éclairé et ont été gardés en observation pendant 35 jours en milieu hospitalier

à l'abri des moustiques.

Le taux de guérison (réponse S) a été de 100% dans tous les groupes de traitement. Les taux de disparition de la parasitémie et de la fièvre ont été similaires. La tolérance a été bonne pour les trois doses. Les effets secondaires étaient bénins, transitoires et n'ont demandé aucun traitement spécifique. Les plus courants étaient: douleur abdominale, vertige, faiblesse et fatigue ainsi que prurit. Les vomissements étaient rares (4%) et n'ont été observés que chez les malades recevant la dose la plus élevée. La fréquence des effets secondaires a été la même pour les trois doses.

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