A double-blind trial of a fixed combination of mefloquine plus sulfadoxine–pyrimethamine compared with sulfadoxine–pyrimethamine alone in symptomatic falciparum malaria

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A total of 100 male Zambian patients with symptomatic falciparum malaria were treated with either two tablets of mefloquine plus sulfadoxine–pyrimethamine (Fansimef) or three tablets of sulfadoxine–pyrimethamine (Fansidar) as a single dose. The patients were kept under observation from day 0 (day of treatment) to day 28 and all were cured. An S-type of response was seen in all patients; one patient in the Fansimef group inexplicably remained positive for Plasmodium falciparum trophozoites until day 6. There were no cases of recrudescence.

The rate of clearance of parasitaemia was similar in both groups. The rate of clearance of fever was marginally faster in the Fansimef group. Side-effects such as pruritus, diarrhoea and abdominal pain occurred after both drugs but were mild and transient; tolerance was slightly better with Fansimef. Severe orthostatic hypotension occurred in 20% of the Fansidar patients and in only 2% of the Fansimef patients; this was reversed by bed rest. Haematological and biochemical parameters were generally not modified in an undesirable manner by the administration of these drugs.

A combination of 500 mg sulfadoxine, a long-acting sulfonamide, and 25 mg pyrimethamine, a folate antagonist, is widely used (under the trade name Fansidar)4 in the treatment of chloroquine-resistant malaria (1, 2). Unfortunately, resistance of Plasmodium falciparum to this drug has been reported (3, 4). A fixed dose combination of 250 mg mefloquine, 500 mg sulfadoxine and 25 mg pyrimethamine per tablet (Fansimef),5 now available for the treatment of chloroquine-resistant malaria, has been found to be safe, well tolerated and effective in the treatment of drug-sensitive and drug-resistant falciparum malaria (5, 6). Two tablets as a single dose is the recommended treatment for symptomatic falciparum malaria in adult Zambians.

Drug resistance of P. falciparum has emerged in Zambia (7) and is spreading rapidly (Ekue et al., unpublished observations, 1984–85). The present study was carried out to compare the efficacy, safety and tolerance of two tablets of Fansimef and three tablets of Fansidar in adult male Zambian patients with symptomatic P. falciparum malaria.

MATERIALS AND METHODS

The study was carried out in the malaria transmission-free environment of the clinical trial wards of the Tropical Diseases Research Centre (TDRC), Ndola, Zambia. The protocol for the study was approved by the Zambian Ethical Committee and the WHO Secretariat Committee on Research Involving Human Subjects.

All the patients were recruited from the outpatient department of Ndola Central Hospital. Patients who had a positive Dill–Glazko urine test, severe illness or complications requiring treatment with antimalarial drugs by parenteral administration were excluded from the study.

The study was a prospective randomized double-blind clinical trial comparing two tablets of Fansimef and three tablets of Fansidar. A total of 100 patients
who had proven falciparum malaria and gave informed consent were admitted to the trial. Each patient received, in a double-blind random manner, either two tablets of Fansimef or three tablets of Fansidar. The drugs were administered by a medical practitioner and the mouth was inspected to ensure that the tablets had been swallowed. The patients received other drugs, such as analgesics (paracetamol), sedatives (diazepam), anthelmintics (pyrantel or albendazole), only on the advice of the principal investigator. The prescription of these drugs was kept to a minimum.

A detailed clinical history was taken from each patient; a past history of pruritus following the administration of antimalarial drugs was also inquired into. A full clinical examination was carried out before treatment on day 0. Body temperature, weight, height, chest radiograph, respiratory frequency, radial pulse rate, supine blood pressure and the blood pressure after standing for 3 minutes, and a 12-lead electrocardiograph were recorded. A range of haematological and biochemical tests including haemoglobin genotype and glucose-6-phosphate-dehydrogenase deficiency were carried out before treatment on day 0. Urinalysis, examination of stools for parasites and ova, and the Dill-Glazko test for 4-aminoquinolines in urine were also performed. The in vitro microtest for the susceptibility of *P. falciparum* to chloroquine and mefloquine was performed on finger prick blood from all the patients who entered the trial.

Patients were admitted to the trial on day 0. Routine questioning for symptoms and side-effects as well as clinical examinations were carried out daily from day 0 to day 7 and subsequently on days 14 and 28. Respiratory rates as well as the radial pulse and body temperature were recorded twice daily from day 0 until day 28. The supine blood pressure and the blood pressure after standing for 3 minutes were measured daily from day 0 to day 7, and subsequently weekly until day 28. Urinalysis and haematological and biochemical tests were performed on days 0, 4, 7, 14 and 28. A sample of venous blood was taken from each patient on day 7 for the estimation of the plasma levels of the trial drugs. Thick blood smears were stained with Giemsa and examined for malarial parasites daily from day 0 to day 7 and on days 14, 21 and 28.

**RESULTS**

A total of 100 patients (50 in each group) were studied. All of them completed the 28-day study period and examinations, except for one patient in the Fansidar group who had to leave the hospital on day 17 for personal reasons. The patients were aged between 12 and 58 years.

The average body weight in the Fansimef group was 53 kg on day 0 and 55 kg on day 28; there was an overall mean weight gain in most patients of 2 kg. The equivalent average body weights in the Fansidar group were 54 kg on day 0 and 56 kg on day 28 with an overall mean weight gain of 2 kg.

**Clinical findings**

In all patients, no abnormality was found in the respiratory and urinary systems before and after the administration of the trial drugs.

On day 0 (before drug administration), 27 patients in the Fansimef group and 36 patients in the Fansidar group had fever. After drug administration, the mean durations of fever were similar: 42.48 ± 19.2 hours in the Fansimef group and 54 ± 23.04 hours in the Fansidar group. All patients had normal body temperature from day 3 to day 28.

Fever-related tachycardia was seen in some patients in both treatment groups and the radial pulse returned to normal levels with decrease in body temperature. Symptomless bradycardia occurred in 18 patients after the administration of Fansimef and in 16 cases after the administration of Fansidar. The pulse rates reverted to normal spontaneously and no treatment was needed.

One patient in the Fansimef group had first-degree atrioventricular block and two patients had nonspecific T-wave inversion in chest lead V2 before treatment on day 0. The changes were symptomless and unaffected by the administration of Fansimef, and the electrocardiographs showed normal sinus rhythm by day 28. In the Fansidar group, three patients (6%) had first-degree atrioventricular block and another three had T-wave inversion in chest leads V2 and V3 before treatment on day 0; one patient showed ventricular ectopic beats until day 14. All these electrocardiographic changes were symptomless, required no specific treatment, and were unaffected by the administration of Fansidar; normal sinus rhythm was restored by day 28.

A total of 20 patients in the Fansimef group had spleno-megaly on day 0, which was still present in 10 patients on day 28. The corresponding figures for the Fansidar group were 19 patients on day 0 and 6 patients on day 28. Before treatment on day 0, there was hepatomegaly (3 cm below the costal margin) in one patient in the Fansimef group and in two patients (mean 0.04 cm) in the Fansidar group. There was no hepatomegaly in any patient after day 2.

Ten patients (20%) in the Fansidar group developed severe orthostatic hypotension (blood pressure unrecordable after standing for 3 minutes), beginning 8 hours to 3 days before the administration
of the drug and lasting for 1 to 3 days. The blood pressure became immediately normal on assumption of the supine position. These patients did not have the orthostatic hypotension on day 0 before treatment. The remaining patients had normal blood pressures both in the supine and standing positions. Patients with hypotension had dizziness on standing upright. No treatment was needed except bed rest for the duration of the episodes of severe orthostatic hypotension. Only one patient developed severe orthostatic hypotension after the administration of Fansimel; the remaining 49 patients in this group had normal blood pressures at all times.

One patient in the Fansimel group was diagnosed as having mild anxiety on day 20 and was treated with diazepam by oral administration. This patient complained of visual hallucinations and was found to be tense, apprehensive and worried, but orientated in time, place and person. There was no similar previous history and the patient denied the use of drugs or alcohol.

**Laboratory investigations**

In both groups, the values for haemoglobin, erythrocyte volume fraction (haematocrit), red and white blood cell counts, and reticulocyte and differential white blood cell counts were comparable before and after the administration of the trial drugs. No drug-related adverse changes were seen. Eosinophil counts were raised in a number of patients in both groups and this was probably related to the 50–60% prevalence of helminth infection in these patients. The erythrocyte sedimentation rates ranged between 31 and 43 mm/h on day 0 in both groups and fell to values of 14–17 mm/h by day 28; some patients had unexplained high values. No adverse drug-related changes were revealed in the results of urinalysis in both groups.

The values of fasting serum glucose, serum total bilirubin, serum alkaline phosphatase, serum creatinine and serum proteins were all generally within normal limits and were not adversely modified by the administration of the trial drugs. One patient who received Fansidar had a normal aspartate aminotransferase (SGOT) on day 0; this was elevated on days 1, 4 and 7 and returned to normal on day 14 and day 28. Two other patients had values within the normal range. One Fansimel-treated patient had a single raised alanine aminotransferase (SGPT) value on day 7 and another patient had a raised value on day 14; a third had raised values on days 0 (before treatment), 4, 7, and 14; all patients at all other times had values within the normal range until day 28.

Venous blood was taken from each patient on day 7 and the plasma was separated and stored for the estimation of the plasma concentrations of the trial drugs. The in vitro microtest for the sensitivity of *P. falciparum* to chloroquine and mefloquine was performed on fingerprick blood from each patient on day 0 (before treatment). The test was successful in 50% of cases in that there was a significant growth of schizonts in the control wells. Five patients who received Fansimel had falciparum infections which showed in vitro resistance to chloroquine. The *P. falciparum* isolates of two of the patients who received Fansidar showed a relatively low sensitivity to mefloquine in vitro.

**Parasitological response**

Table 1 shows the parasitological response in the Fansimel and Fansidar treated groups.

**Fansimel group.** Of the 50 cases, only two were positive for *P. falciparum* asexual forms by day 3 and one case persisted to be positive on days 4, 5 and 6. From day 7 to day 28 no cases were positive. Parasitaemia was cleared in 98% on day 3 and in 100% on day 7 only owing to a persistence of parasites in one patient. The mean asexual *P. falciparum* clearance time was 60.96 ± 17.2 hours. None of the 50 patients had *P. falciparum* gametocytes on day 0. Gametocytes were present in four cases on day 1, ten cases on day 4, seven cases on day 7, and persisted in one case until day 28.

**Fansidar group.** Of the 50 patients, only two were positive for *P. falciparum* asexual forms by day 3; no cases were positive from day 4 to day 28. Parasitaemia was cleared in 98% on day 3 and 100% on day 4. The mean asexual parasite clearance time was

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>Fansimel group*</th>
<th>Fansidar group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number positive</td>
<td>Count (per mm³)</td>
</tr>
<tr>
<td>0</td>
<td>50</td>
<td>59 460</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>60 000</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>9 450</td>
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<td>4 320</td>
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<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fifty patients in each group.
Table 2. Adverse effects of Fansimex and Fansidar in patients with falciparum malaria

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Fansimex* (2 tablets)</th>
<th>Fansidar* (3 tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (2)†</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (12)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (14)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>18 (36)</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Behaviour disorder</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus/raekh</td>
<td>10 (20)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1 (2)</td>
<td>10 (20)</td>
</tr>
</tbody>
</table>

† Fifty patients in each group.
‡ One case of first-degree atrioventricular block and 2 cases of T-inversion in V2 before treatment.
§ One case of ventricular ectopic beats, 3 of T-wave inversion in V2–V3, and 3 of first-degree atrioventricular block before treatment.

58.56±16.8 hours. There were no patients with *P. falciparum* gametocytes on day 0. Three patients had gametocytes on day 1, nine on day 4, 17 on day 7, and five on day 28.

Side-effects

The incidence of side-effects that could be attributed to the trial drugs is shown in Table 2. A total of 71% of the patients in the Fansimex group and 70% of the patients in the Fansidar group gave a history of pruritus following the administration of antimalarial drugs, mostly after chloroquine. The main side-effects of Fansimex were pruritus (20%), diarrhoea (14%) and abdominal pain (12%). One patient developed a neuropsychiatric reaction and another one developed severe orthostatic hypotension after the administration of Fansimex. The main side-effects after Fansidar were severe orthostatic hypotension (20%), pruritus (12%) and abdominal pain (12%).

The severe orthostatic hypotension after the administration of Fansidar or Fansimex will be described in detail elsewhere. The other side-effects were mostly mild and of short duration and required no specific therapy.

DISCUSSION

The aim of this study was to compare the clinical effectiveness, safety and tolerance of two tablets of Fansimex and the standard dose of three tablets of Fansidar for the treatment of symptomatic falciparum malaria in the adult Zambian population. Previous experiments had shown that one, two or three tablets of Fansimex were equally safe and efficacious in symptomatic falciparum malaria (5).

The cure rate in patients who completed the 28-day period of observations was 100% in both treatment groups. All patients had an "S" type of response. There were no cases of recrudescence. One patient in the Fansidar group was negative for *P. falciparum* asexual parasites from day 2 to day 17 when he had to leave the hospital and he was deemed to have an "S" type of response. Another patient in the Fansimex group remained positive for *P. falciparum* trophozoites from day 0 to day 6; he may have absorbed Fansimex poorly but the blood levels of mefloquine, sulfadoxine and pyrimethamine were not known. The mean clearance time of parasitaemia was 60±19.2 hours after Fansimex and 58.56±16.8 hours after Fansidar.

During the first week after treatment the frequency of *P. falciparum* gametocyteaemia was similar in both groups, but between day 7 and day 28 it was substantially higher in the Fansidar group compared with the Fansimex group (P<0.05 for day 7). In previous studies, the mean clearance time of parasitaemia was found to be about 2.5 days after mefloquine, chloroquine or Fansimex (5, 8; Ekue et al., personal observations). These results are comparable to our present findings and hence the claim that Fansidar and Fansimex are slow-acting in symptomatic falciparum malaria could not be confirmed (1, 9, 10).

The rate of clearance of fever was slightly faster after Fansimex (42.48±19.2 hours) than after Fansidar (54.00±23.04 hours) but the difference was not statistically significant. Both drugs were fairly well tolerated. The side-effects (pruritus, abdominal pain and diarrhoea) were mild and transient. The incidence was nearly similar in both treatment groups. About 70% of the patients in both groups gave a past history of pruritus following the administration of antimalarial drugs. In a double-blind clinical trial carried out two years previously, 45% of the patients developed pruritus after they received chloroquine (8); this probably shows that the incidence of drug-related pruritus is increasing in the population. In the Fansimex-treated group, one patient developed a behaviour disorder on day 20 and was treated with diazepam. This was similar to the observations in Zambia and Thailand after the administration of mefloquine or drug combinations that contained mefloquine (5, 6, 8).

Severe orthostatic hypotension occurred in 20% of patients who received Fansidar compared with only 2% in patients who received Fansimex. This finding
was unexpected and had not been described previously. All patients showing orthostatic hypotension responded to bed rest for up to 3 days (as the only measure). Much of the dizziness which occurs during the drug treatment of symptomatic malaria may be due to unrecognized orthostatic hypotension. Severe orthostatic hypotension after Fansidar, Fansimef and chloroquine will be described in detail elsewhere, and further studies have been planned to elucidate this unexpected finding.

Urinalysis and haematological and biochemical tests were not affected in an undesirable manner by the administration of the trial drugs, except in one patient who had raised SGOT levels on days 1, 4 and 7 after receiving Fansidar but reached normal levels by day 14. The serum bilirubin levels were normal. Unfortunately, viral hepatitis could not be excluded in this patient.

In vitro microtests for the susceptibility of *P. falciparum* to chloroquine and mefloquine were carried out on fingerprick blood from each patient before drug administration on day 0. Only 50% of the microtests were successful. It appears that very young ring forms, which represent the majority of parasites in many cases of symptomatic falciparum malaria, are not generally conducive to a successful growth of schizonts in the *in vitro* microtests. However, the results showed that Fansimef was effective in chloroquine-resistant malaria, confirming the results of previous workers (6, 11). Fansidar was also shown to be effective in infections with *P. falciparum* that showed a relatively low sensitivity to mefloquine and this confirms our previous findings (Ekue et al., unpublished observations, 1985).

ACKNOWLEDGEMENTS

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RÉSUMÉ

ESSAI COMPARATIF EN DOUBLE INSU D'UNE ASSOCIATION EN PROPORTIONS FIXES MÉFLOQUINE PLUS SULFADOXINE-PYRIMÉTHAMINE ET DE SULFADOXINE-PYRIMÉTHAMINE SANS MÉFLOQUINE DANS LE PALUDISME SYMPTOMATIQUE À FALCIPARUM

Cent Zambiens de sexe masculin présentant un paludisme symptomatique à falciparum ont été traités soit avec deux comprimés de méfloquine plus sulfadoxine-pyriméthamine (Fansimef), soit avec trois comprimés de sulfadoxine-pyriméthamine (Fansidar), administrés en une dose unique. Les malades ont été gardés en observation du jour 0 (jour du traitement) au jour 28: tous ont guéri. Dans tous les cas on a observé une réponse de type S; un malade du groupe traité par le Fansimef est resté inexplicablement positif pour les trophozoïtes de *Plasmodium falciparum* jusqu’au jour 6. On n’a observé aucun cas de recrudescence.

Le taux de disparition de la parasitémie était le même dans les deux groupes. La fièvre tombait un peu plus rapidement chez les malades traités par le Fansimef. Des effets secondaires tels que prurit, diarrhée et douleurs abdominales ont été observés avec les deux médicaments, mais ils étaient légers et transitoires; la tolérance était légèrement meilleure avec le Fansimef. Chez 20% des sujets traités par le Fansidar, mais chez 2% seulement des sujets traités par le Fansimef, on a observé une hypotension orthostatique sévère, avec tension non mesurable au bout de trois minutes en position debout; cet effet disparaissait après repos au lit en décubitus dorsal. D’une façon générale, le traitement était sans effets indésirables sur les paramètres hématologiques et biochimiques.

REFERENCES