RANDOMISED COMPARATIVE STUDY OF MEFLOQUINE, QINGHAOSU, AND PYRIMETHAMINE-SULFADOXINE IN PATIENTS WITH FALCIPARUM MALARIA

GUOQIAO LI KEITH ARNOLD
XINGBO GUO HWAXIANG JIAN
LINCHUN FU

Malaria Research Unit, Guangzhou College of Traditional Chinese Medicine, Guangdong, China; Roche Far East Research Foundation, Hong Kong

Summary A prospective trial in 80 patients randomly allocated to four antimalarial treatment regimens—mefloquine plus pyrimethamine-sulfadoxine ('Fansidar'); mefloquine plus qinghaosu; mefloquine, fansidar, and qinghaosu; and qinghaosu alone—was carried out on Hainan Island, China, in patients with chloroquine-resistant falciparum malaria. A radical cure with slight side-effects was obtained with mefloquine plus fansidar; the addition of qinghaosu greatly increased the rate of parasite clearance with no additional side-effects. Qinghaosu alone had a rapid rate of parasite clearance, no side-effects, but a high recrudescence rate. These antimalarial drugs seem to act at different stages of the asexual parasite cycle and their most efficient use may depend on when in the course of the disease they are given. Because of the continuing appearance of drug-resistant strains of *Plasmodium falciparum* combination drug therapy is now indicated, but which drugs and how best they should be used remains to be decided.

Introduction

CHLOROQUINE-RESISTANT falciparum malaria is found worldwide, and resistance to other available drugs, such as quinine and pyrimethamine-sulfadoxine ('Fansidar'), also occurs.[1,2] In-vitro and in-vivo resistance to mefloquine,[3,4] an effective single-dose drug, has been reported even though it has not yet been made available commercially. Qinghaosu is another effective antimalarial, especially in severely ill patients with high parasitaemia,[5] since it has a rapid onset of action and destroys asexual parasites at an early stage of development.[6] No resistance to this drug has yet been demonstrated, but it also is not available commercially.

In animal models resistance can be induced to mefloquine and fansidar when they are used alone, but the appearance of this resistance can be delayed by giving the drugs in combination.[7,8] Since the development of resistance to antimalarial drugs has become a serious problem, drug combinations need to be studied in the laboratory and in patients. Our clinical trial was undertaken to examine the efficacy and side-effects of combinations of mefloquine, fansidar, and qinghaosu.

Patients and Methods

Patients attending the Dong Fang District Hospital on Hainan Island between June, 1982, and June, 1984, were considered for entry into the trial. We admitted to the trial patients who had fever, a clinical diagnosis of malaria, and a positive peripheral blood smear with a *Plasmodium falciparum* asexual parasite count of more than 1000/μl (or >5000/μl if they had been febrile for > 5 days); who had not been treated; who were aged between 8 and 60 years; who had no other apparent serious disease; and who gave informed consent. The World Health Organisation has officially declared that falciparum malaria on Hainan Island is chloroquine resistant.

All patients were kept in hospital for a minimum of 7 days and returned for follow-up on days 14, 21, and 28. In hospital, axillary temperatures were taken every 4 h until the patient remained afebrile for 24 h; the temperature was then taken daily in the evening. Thick and thin blood smears were used for the initial diagnosis and asexual parasite count, and subsequently thick smears were taken every 4 h until three consecutive smears were negative. The time at which the first smear was negative was used to calculate the parasite clearance time. A thick blood smear was examined daily until the patient was discharged and then at the follow-up visits. Routine haematology, urine, and hepatic and renal function tests were done at the time of diagnosis and before discharge from hospital.

Patients were randomly allocated to four therapeutic regimens, each group comprising 20 patients. The assessment of response to treatment was based on asexual parasite clearance time and the time to become afebrile. Overall patient response was evaluated according to World Health Organisation criteria of S (radical cure) or RI–III (varying degrees of resistance). The treatment regimens are given in table I. The dosage was reduced to two thirds for patients aged 12–15 years and to half for those aged 8–11 years. All drugs were given under the direct supervision of one of us.

To compare the effect on the rate of asexual parasite clearance and asexual parasite development of the drugs in groups A–D with that of mefloquine or fansidar alone, 5 patients from each of the four groups plus another 5 patients given mefloquine (0·75 g) and 5 given fansidar (75 mg pyrimethamine plus 1·5 g sulfadoxine) were studied as follows. Indigenous patients (who are considered to be semi-immune) who had been ill for less than 5 days and who had asexual parasite counts between 10 000 and 100 000/μl were selected. The drugs were given from 6 to 10 h of the asexual parasite development cycle (tiny ring stage), and thick blood smears were taken every 4 h to examine asexual parasite development as previously described[6] and so that a parasite count could be done. This count was then plotted as a percentage of the parasite count at the time of drug administration. The time taken to achieve 95% asexual parasite clearance was determined.

Results

90 patients were studied—20 in each of the four treatment groups (A–D) plus one group of 5 patients receiving mefloquine alone and one group of 5 receiving fansidar alone. 69 were male and 21 female; the age range was 9–57 years (mean 23·0±11·0). All patients were febrile (temperature

TABLE I—TREATMENT REGIMENS

—	A	B	C	D
Mefloquine 0·75 g	×	×	×	
Fansidar*	×		×	
Qinghaosu 1·0 g		×	×	×†

*Pyrimethamine 75 mg, sulfadoxine 1·5 g, as a single oral dose.
†As a single oral 1·0 g dose initially, then 0·5 g twice daily on days 2 and 3

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TABLE II—EFFECT OF TREATMENTS

Group	Parasite clearance (h)		Defervescence (h)	
	Mean±SD	p*	Mean±SD	p*
A	82·3±27·6		23·6±16·8	
B	60·1±22·4	<0·05	22·0±12·9	NS
C	54·9±12·7	<0·01	13·6±11·6	<0·05
D	44·7±13·0	<0·01	15·5±11·0	NS

*For comparison with group A. NS = not significant.

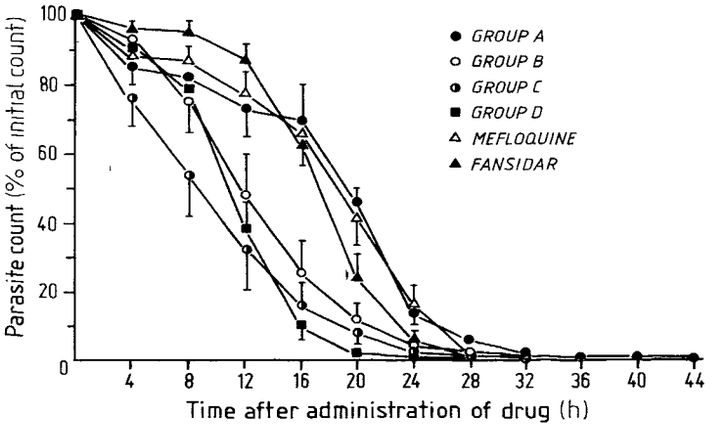
>37·6°C); in 52 the liver was palpable and 46 had splenomegaly. Asexual parasite counts ranged from 1840/μl to 353 157/μl (mean 57 414/μl); 31·1% had counts <10 000/μl, 47·8% between 10 000 and 50 000/μl, 15·5% between 51 000 and 100 000/μl, and 5·6% >100 000/μl.

Parasite clearance was significantly faster in the groups whose treatment included qinghaosu than in the group (A) not receiving qinghaosu (table II). The time taken to become afebrile was significantly shorter in group C than in group A and slightly but not significantly shorter in groups B and D than in group A (table II).

In group A *P vivax* was seen in 1 patient on day 21 and in another on day 28. Complete *P falciparum* asexual parasite clearance with no recrudescence within 28 days (S) was the result in all patients in groups A, B, and C. In 3 patients in group D *P vivax* parasitaemia developed before day 21, and in 7 of the remaining 17 patients *P falciparum* was present in the blood smear on day 28 (RI). The time to achieve 95% parasite clearance was 20 h for group D, 24 h for groups B and C and the group taking fansidar only, 28 h for the group taking mefloquine only, and 32 h for group A (see figure).

The tiny ring forms matured into the small and large ring forms during the first 24 h with mefloquine or fansidar alone but only tiny and small ring forms were seen with qinghaosu at 20 h. Intradermal smears, which we have shown to be comparable with bone-marrow smears (unpublished), showed late trophozoites and schizonts at 28 and 36 h in fansidar-treated patients but not in mefloquine-treated patients, in whom only large ring forms were seen. No parasites were seen in qinghaosu-treated patients at 28 and 36 h.

Side-effects were few and self-limiting. 1 patient had abdominal pain and 1 headache and vertigo in group A; 2 patients had nausea and vomiting and 1 patient abdominal pain and diarrhoea in group B; and 2 patients had nausea and



Effect of mefloquine, qinghaosu, and fansidar alone and in combination on rate of *P falciparum* parasite clearance.

Absolute parasite count at 0 h taken as 100% and later parasite counts were plotted as a percentage of that count. Each point is mean±SEM for 5 patients in treatment group.

1 patient vomiting in group C. There were no side-effects in group D.

Laboratory tests showed no substantial abnormalities in any of the patients other than those usually seen in patients with falciparum malaria, such as a low haemoglobin level early in the course of the illness.

Discussion

In this randomised, comparative therapeutic trial in 80 patients with falciparum malaria a combination of mefloquine and fansidar and this combination with qinghaosu resulted in radical cures, with some self-limiting side-effects in a few patients. Qinghaosu alone, although rapidly effective in clearing parasitaemia and producing no side-effects, had a recrudescence rate of 41·2% (7 of 17 patients since the 3 vivax-relapsing patients were retreated).

Fansidar had a slow onset of action and the asexual parasites continued to develop from the early ring forms into late trophozoites and schizonts. This finding implies that fansidar attacks the parasite late in its development cycle, after the nucleus divides at the late trophozoite-schizont stage, which could explain the long time taken to become afebrile in the fansidar-treated group (57·2 h). Qinghaosu acts early in the asexual parasite development cycle, by destroying the tiny and small ring forms; mefloquine acts (at the large ring and early trophozoite stage) later than qinghaosu but earlier than fansidar. In patients treated not with drugs but with acupuncture 80–90% clearance occurs at about 36 h (unpublished), since the large ring forms leave the peripheral circulation as if untreated, and the parasite count rapidly rises again as the next cycle develops, because the trophozoites and schizonts in the tissues are not destroyed.

Since different drugs appear to act at different stages of parasite development, perhaps for greatest effect antimalarial drugs should be given at different times and even repeated to ensure that the necessary concentration of drug is present in the body at the relevant stage of parasite development.

Because of the continuing appearance of drug-resistant strains of *P falciparum* it is probably going to be necessary to use drug combinations. Although the combinations that should be used remain to be decided, one fixed combination given as a single dose and shown to be effective and safe is mefloquine plus fansidar.[9] Whether such combinations will prevent the further development of resistance will be known only after they have been in clinical use for some time.

Correspondence should be addressed to K. A., PO Box 98595, Tsim Sha Tsui Post Office, Hong Kong.

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