

MALARIA CHEMOTHERAPY TRIAL AT A MINIMAL EFFECTIVE DOSE OF MEFLOQUINE/SULFADOXINE/PYRIMETHAMINE COMPARED WITH EQUIVALENT DOSES OF SULFADOXINE/PYRIMETHAMINE OR MEFLOQUINE ALONE

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Abstract. In murine malaria the addition of mefloquine to sulfadoxine/pyrimethamine has been shown to exert an additive effect and to significantly slow the emergence of resistance to the individual components. In a pilot study carried out in Gabon, a reduced dosage of the triple combination with a mean of 1 mg/kg of mefloquine/2 mg/kg of sulfadoxine/0.1 mg/kg of pyrimethamine (Fansimef®; Roche, Basel, Switzerland) had previously been shown to achieve high cure rates in *Plasmodium falciparum* malaria. To evaluate the additive effect, a randomized, double-blind trial in school children with mild *P. falciparum* malaria was performed in Gabon. Two hundred thirty-one patients evaluated received a single dose of either the triple combination with a mean of 1.07 mg/kg of mefloquine/2.14 mg/kg of sulfadoxine/0.11 mg/kg of pyrimethamine (group MSP), or 1.07 mg/kg of mefloquine alone (group M), or 2.14 mg/kg of sulfadoxine/0.11 mg/kg of pyrimethamine alone (group SP). In the MSP group and the SP group, 67% and 69% of the patients were parasitologically cured, respectively, compared with only 13% in the M group ($P < 0.001$). A significantly higher parasitemia was found in the M group compared with the MSP group or the SP group on days 2 and 3 after the start of treatment. The high efficacy of the low dose sulfadoxine/pyrimethamine regimen was the most surprising finding of this study.

Chloroquine-resistant *Plasmodium falciparum* malaria has rapidly spread throughout sub-Saharan Africa. In Gabon, chloroquine-resistant *P. falciparum* was first reported in 1984¹ and resistance has dramatically increased since. Although chloroquine is still widely used, we found resistance rates of 100% in vitro² and more than 90% in vivo in Gabonese children.³ Clearly, the need for an effective, cheap, and easily administered antimalarial drug is urgent, especially in face of the estimated two million deaths due to malaria each year.⁴ The combination of sulfadoxine/pyrimethamine has become the drug of choice in some areas with chloroquine-resistant malaria. Despite a 30% resistance rate in vitro,² we have recently found a very high cure rate using sulfadoxine/pyrimethamine in Gabonese school children with *P. falciparum* malaria.⁵ Recent reports of sulfadoxine/pyrimethamine-resistant *P. falciparum* malaria in Nigeria⁶ and Zaire⁷ raised the fear of its spreading to other parts of Africa. Thus, interest in drug combinations has been renewed, since this might be one way to slow the emergence of malaria parasites that show resistance to individual components of the mixtures. The triple combination of mefloquine, sulfadoxine, and pyrimethamine (MSP) was shown to significantly slow the development of resistant strains in vitro⁸ and in the mouse model.^{9,10} Furthermore, in the latter reports, the investigators showed that mefloquine has an additive effect when given together with sulfadoxine/pyrimethamine.

These findings underlined the justification of a fixed combination, with each tablet containing 250 mg of mefloquine, 500 mg of sulfadoxine, and 25 mg of pyrimethamine. We decided to evaluate the degree of additivity between mefloquine and sulfadoxine/pyrimethamine in a two-staged clinical field trial, in an area where both sulfadoxine/pyrimethamine⁵ as well as mefloquine¹¹ in their standard regimen

showed very high efficacy for treating school children with *P. falciparum* malaria. In a pilot study,¹² we determined the minimal effective dose of the triple combination in school children with *P. falciparum* malaria. Even at a surprisingly low dosage with a mean of 1 mg/kg of mefloquine/2 mg/kg of sulfadoxine/0.1 mg/kg of pyrimethamine, corresponding to about one-twelfth of the recommended dosage, all patients were radically cured by day 28. In a second stage, we compared at this reduced dosage the triple combination versus the individual components alone in a prospective, double-blind study.

PATIENTS AND METHODS

The study took place at the Albert Schweitzer Hospital in Lambarene, Gabon. From January 1995 to January 1996, all malaria patients up to the age of 15 years seeking treatment at the hospital were included in the study if they fulfilled the following criteria: 1) proven mono-infection with *P. falciparum* with a parasitemia between 1,000 and 100,000/μl of blood (assessed by Giemsa-stained thick blood smear); 2) weight between 15 and 44 kg; 3) clinical symptoms and a recent history of fever $> 37.5^{\circ}\text{C}$; 4) absence of signs for severe malaria, such as severe anemia, cerebral malaria, or hypoglycemia, or coinfections; 5) no history of recent treatment with antimalarial drugs, confirmed by testing urine samples for chloroquine and quinine (Wilson and Edeson test) and for sulfonamides (Lignin test); and 6) informed consent given by parents or legal guardians. The study was approved by the Ethics Committee of the International Foundation of the Albert Schweitzer Hospital.

Two hundred fifty-two patients were admitted into the study. After being stratified for three weight classes (15.0–24.4 kg, 24.5–34.4 kg, and 34.5–44.0 kg), they received on

day 0 in a randomized, double-blind fashion a single capsule of the drug. To account for potential temporal imbalance in recruiting the different weight classes, recruitment was divided into four blocks, each containing equivalent numbers of patients in each class. Patients in the MSP group received 31.25 mg of mefloquine, 62.5 mg of sulfadoxine, and 3.125 mg of pyrimethamine (Fansimef®; Roche), patients in group M received 31.25 mg of mefloquine (Lariam®; Roche), and patients in the SP group received 62.5 mg of sulfadoxine and 3.125 mg of pyrimethamine (Fansidar®; Roche).

Clinical and parasitologic follow-ups were performed every 24 hr until patients were free of symptoms, signs, fever, and parasites, and again on days 7, 14, 21, and 28. The patients were considered cured if the thick blood smear became negative in the first week and remained negative up to day 28, indicating clinical and parasitologic cure. Low-grade resistance (RI) was defined as absence of parasitemia and symptoms during the first week, followed by reappearance of parasitemia during follow-up. Nonresponse was defined as either a failure to clear parasites during the first seven days or an increase in parasitemia after day 2 (at least 1,000 parasites/ μ L above the lowest observed value) or a parasitemia of more than 25% of the initial parasitemia and no clinical improvement on day 2. Both nonresponders and patients with low-grade resistance were successfully treated with a regular dose of the combination (12.5 mg/kg of mefloquine, 25 mg/kg of sulfadoxine, and 1.25 mg/kg of pyrimethamine).

Venous blood samples were taken on day 3 and before therapy of patients who were not cured to determine the concentration of mefloquine, its major metabolite, carboxymefloquine, and sulfadoxine by high-performance liquid chromatography. After drawing the blood, plasma was extracted, stored, and shipped to Falun, Sweden on dry ice until analysis. The lower limits of detection were 0.15 μ mol/L for mefloquine, 0.20 μ mol/L for carboxymefloquine, and 10 μ mol/L for sulfadoxine.

The sample size was calculated to detect a difference between groups of 20% at a hypothetical maximal efficacy of 90% with a statistical significance of $\alpha = 0.05$ and a power of 80%. To account for unexpectedly low efficacy as a potential consequence of the low drug dosages, contingent interim analysis after completion of the first 36 patients was planned in case of an overall nonresponder rate $\geq 33\%$. Unblinding of the drug code was performed after completing and locking of the database.

Statistical analysis was performed by the Mann-Whitney U test and the Kruskal-Wallis test, and the chi-square test was used for proportional data. The data shown were obtained by per-protocol analysis (see Results for criteria); however, no significant differences in the major efficacy parameters (parasitologic response, course of parasitemia) occurred when intention-to-treat analysis was performed instead.

RESULTS

A total of 231 of the 252 patients were monitored for 28 days or until recrudescence and 21 (8%) were excluded from the per-protocol analysis because of either vomiting within 60 min after drug intake (5), antimalarial treatment at home

during follow-up (4), coinfection with *P. malariae* (4), failure to return for follow-up (7), or intercurrent disease (1). Overall, six, eight, and seven patients from the MSP, M, and SP treatment groups, respectively, were excluded and considered unassessable for efficacy analysis. The three treatment groups were similar in terms of demography, clinical signs, symptoms, and parasitemia (Table 1).

In the MSP group and the SP group, 52 (67%) of 78 and 53 (69%) of 77 patients were parasitologically cured, respectively, as compared with only 10 (13%) of 76 in the M group. Thirty-one patients (41%) showed recrudescent parasitemias in the M group, whereas 22 (28%) and 18 (23%) patients in the MSP and SP groups, respectively, showed recrudescences after day 7. The rate of nonresponders was markedly higher in the M group with 35 patients (46%) compared with only four (5%) and six (8%) in the MSP and SP groups. These differences between the M group versus the MSP and SP groups were highly significant ($P < 0.001$), whereas there was no significant difference between the MSP and SP groups. Moreover, the distribution of cure and resistance in the three treatment groups did not differ significantly among the three weight classes, although a trend to lower cure rates can be seen at higher weight in the M group (Table 2). In the patients with a sensitive or a low-grade resistance response, there were no differences in parasite clearance time, fever clearance time, or duration of symptoms (Table 3).

Figure 1 shows the course of parasitemia in the three treatment groups. There was no significant difference on day 0 or day 1. From day 2 onward the parasitemia in the M group was significantly higher than in the other groups ($P < 0.001$), whereas no significant differences between the MSP group and the SP group throughout the first week were found.

Table 4 shows the association between plasma drug level and response. High levels of carboxymefloquine on day 3 were significantly associated with cure in the MSP group ($P = 0.028$), but only as a trend in the M group ($P = 0.15$). Mefloquine levels did not predict parasitologic outcome in either group. Furthermore, there was no association between response to treatment and sulfadoxine levels in either the MSP group or the SP group.

Adverse events were defined as signs or symptoms occurring or worsening during the course of treatment and follow-up. In all cases they were assessed as mild and possibly related to the drug. The adverse events consisted mainly of abdominal pain and diarrhea, and were evenly distributed throughout the three treatment groups with 9, 10, and 15 adverse events in the MSP, M, and SP groups, respectively.

DISCUSSION

The biggest surprise of the present study was the high efficacy of the low dose sulfadoxine/pyrimethamine regimen. The patients in the highest weight class, in which 75% of the children were cured, received on average one-sixteenth of the recommended dosage of 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine. The dynamics of parasite and fever clearance were comparable with a previous study in Lambarene in school children who received a full regimen of sulfadoxine/pyrimethamine.⁵ The mean du-

TABLE 1
Clinical and demographic data on admission

Patient parameter	Treatment groups*		
	MSP (n = 78)	M (n = 76)	SP (n = 77)
Demographic data†			
Age (years)	9.9 (2.9)	9.8 (2.8)	9.7 (2.9)
Male/female	29/49	43/33	40/37
Height (cm)	138 (17)	136 (17)	135 (17)
Weight (kg)	29 (8)	29 (9)	29 (9)
Clinical signs†			
Axillar temperature (°C)	38.0 (1.1)	37.8 (1.1)	37.8 (1.1)
Systolic blood pressure (mm of Hg)	111 (11)	115 (10)	110 (12)
Diastolic blood pressure (mm of Hg)	70 (9)	72 (10)	70 (11)
Heart rate	109 (16)	106 (17)	107 (18)
Percentage of patients with			
Recent history of fever	100	100	100
Headache	90	88	86
Fatigue	63	69	54
Abdominal pain	47	65	54
Vomiting	47	51	39
Nausea	41	36	32
Body aches	31	30	42
Diarrhea	10	3	6
Parasitemia (parasites/μl)‡	19,067	16,848	17,247
Range	1,000–100,000	1,000–100,000	1,000–100,000

* M = mefloquine; S = sulfadoxine; P = pyrimethamine.

† Except for the male/female ratios, values are the mean (SD).

‡ Values are the geometric mean.

ration of symptoms was 2.3 days for the full regimen compared with 2.8 days for the reduced dosage. The present results are also in agreement with a study from Tanzania, where a 100% cure rate was achieved using one-quarter of the recommended dose in asymptomatic school children with *P. falciparum* parasitemia.¹³

The evidence of the high efficacy of this drug is encouraging. In tropical Africa, malaria attacks are often self-diagnosed and self-treated, and drugs are often taken in a fraction of the recommended dosage due to financial reasons. The fact that no relationship between the plasma level of sulfadoxine and parasitologic outcome could be found is

TABLE 2
Efficacy of the treatment groups in all patients and in the three weight classes

	Treatment groups*		
	MSP (n = 78)	M (n = 76)	SP (n = 77)
All patients (15.0–44.0 kg) (1.07 mg/kg M; 2.15 mg/kg S; 0.11 mg/kg P)†			
Parasitologic cure (%)	52 (67)	10 (13)	53 (69)
Low-grade resistance (%)	22 (28)	31 (41)	18 (23)
Non-response (%)	4 (5)	35 (46)	6 (8)
Weight class 1 (15.0–24.4 kg) (1.58 mg/kg M; 3.16 mg/kg S; 0.16 mg/kg P)†			
Parasitologic cure (%)	18 (69)	4 (15)	18 (69)
Low-grade resistance (%)	7 (27)	17 (65)	6 (23)
Non-response (%)	1 (4)	5 (19)	2 (7)
Weight class 2 (24.5–34.4 kg) (1.09 mg/kg M; 2.18 mg/kg S; 0.11 mg/kg P)†			
Parasitologic cure (%)	18 (69)	5 (18)	17 (63)
Low-grade resistance (%)	7 (27)	7 (25)	7 (26)
Non-response (%)	1 (4)	16 (57)	3 (11)
Weight class 3 (34.5–44.0 kg) (0.79 mg/kg M; 1.57 mg/kg S; 0.08 mg/kg P)†			
Parasitologic cure (%)	16 (62)	1 (5)	18 (75)
Low-grade resistance (%)	8 (31)	7 (32)	5 (21)
Non-response (%)	2 (8)	14 (64)	1 (4)

* M = mefloquine; S = sulfadoxine; P = pyrimethamine.

† Mean drug concentration administered.

TABLE 3

Efficacy parameters of cured patients and patients with low-grade resistance in the three treatment groups

	Treatment groups*		
	MSP (n = 74)	M (n = 41)	SP (n = 71)
Parasite clearance time, days†	3 (1–6)	3 (2–7)	3 (2–5)
Fever clearance time, days†	1 (0–6)	1 (0–6)	1 (0–6)
Duration of symptoms, days†	2 (1–5)	2 (1–5)	2 (1–5)

* M = mefloquine; S = sulfadoxine; P = pyrimethamine.

† Values are the median (range).

consistent with a trial performed in Thailand,¹⁴ an area with *P. falciparum* highly resistant to sulfadoxine/pyrimethamine. Mefloquine, on the other hand, showed poor results at this reduced dosage. Even in the lowest weight class a radical cure was seen in only 15% of the malaria patients. Similar results were obtained in a dose finding study in east Africa, in which six of 14 children were not cured by one-eighth of the standard dose, while the parasites were found to be highly sensitive to mefloquine in vitro.¹⁵

Plasmodium falciparum parasites in our study area were shown to be highly sensitive to 15 mg/kg of mefloquine in vivo,¹¹ and in three recent in vitro studies in 1992,² 1994, and 1996 (Kremsner PG, unpublished data). Considerable interindividual differences in pharmacokinetic parameters after mefloquine treatment have been reported, with additional differences between healthy volunteers¹⁶ and malaria patients.¹⁷ To minimize the influence of variations during the absorption phase, we decided to measure the drug concentration on day 3. In the present study no correlation between mefloquine plasma levels and outcome was found. This is consistent with some reports,^{18,19} but is in contrast to another study, which found a strong relationship between clinical outcome and the plasma concentration after treatment.²⁰ This may be in part due to differences in the patient group and the study area, or depend on the administered dose, since one study showed a significantly lower drug level in treatment failures who received a dose of 25 mg/kg, but did not show such difference in the group that received 15 mg/kg.²¹ However, drug levels associated with parasitologic cure in previous studies, e.g. 500 or 1,000 µg/L, are approximately twice the highest measured value of the present study (291 µg/L). Interestingly, we found an association between treatment response and high plasma levels of carboxymefloquine, the major metabolite of mefloquine. This association reached statistical significance in the MSP group. However, the rel-

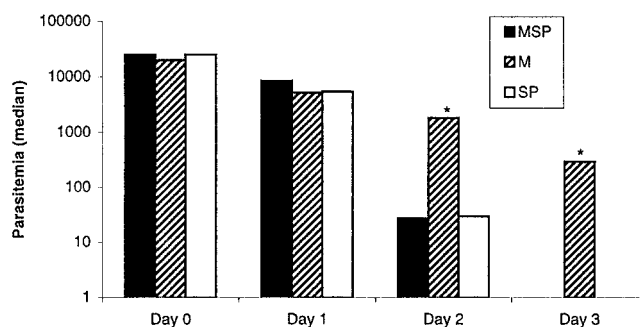


FIGURE 1. Median parasitemia on admission and during the first three days after treatment. M = mefloquine; S = sulfadoxine; P = pyrimethamine. * $P < 0.001$, M versus MSP or SP.

evance of this finding is unclear because this substance has been reported to be ineffective against *P. falciparum*.²²

The follow-up time of four weeks bears the risk of reinfection, which may lead to a false high recrudescence rate. However, comparison of admission and recrudescence isolates by genotype analysis using three highly polymorphic *P. falciparum* genes (merozoite surface antigens 1 and 2, and the glutamate rich protein) showed a low genuine reinfection rate of 5% that was evenly distributed throughout the treatment groups, as anticipated from other studies performed in that area.^{3, 5, 11, 12}

The study area lies in a hyperendemic zone where the level of acquired immunity against *P. falciparum* increases with age.²³ This is most probably the reason for the even distribution of cure and noncure among the weight classes, even though the dosages received differed by a factor of two between the highest and lowest weight class.

At these very low doses used, the addition of mefloquine clearly had no advantage in efficacy over sulfadoxine/pyrimethamine alone. Thus, the proposed additive effect of the two components demonstrated in animal experiments¹⁰ could not be confirmed clinically because there was no trend towards a higher cure rate when mefloquine was added. The results suggest that the weight ratio of the components in the fixed triple combination may not be optimal. However, this does not preclude the existence of clinical and parasitologic additivity between mefloquine and sulfadoxine/pyrimethamine per se, but means that the weight ratio of the two components would need to be shifted in favor of more mefloquine. In fact, results of an earlier study from Tanzania in

TABLE 4
Plasma drug levels in the three treatment groups

Drug	Response†	Treatment groups*		
		MSP (n = 78)	M (n = 76)	SP (n = 77)
Mefloquine (µM)	Cure	0.33 (0.15)	0.36 (0.11)	—
	Noncure	0.32 (0.13)	0.34 (0.16)	—
Carboxymefloquine (µM)	Cure	0.52 (0.23)‡	0.57 (0.27)	—
	Noncure	0.39 (0.16)‡	0.46 (0.21)	—
Sulfadoxine (µM)	Cure	38.2 (11.8)	—	39.2 (11.0)
	Noncure	36.3 (10.0)	—	39.0 (13.3)

* M = mefloquine; S = sulfadoxine; P = pyrimethamine. Values are the mean (SD). — = not determined.

† Noncure = non-response plus low-grade resistance.

‡ $P = 0.028$.

asymptomatic *P. falciparum* infections support this view (Handschin J, unpublished data).

The important rationale of mefloquine/sulfadoxine/pyrimethamine usage in Africa, where resistance to the individual components is rare, is the proposed ability of the combination to slow the spread of multiple drug-resistant malaria.^{8–10} Since there is reason to believe that once introduced, resistance to sulfadoxine/pyrimethamine or to mefloquine will spread throughout Africa with similar speed as seen in Asia and South America, the widespread use of the combination for the treatment of mild malaria has been suggested.²⁴ However, resistance to mefloquine developed rapidly, despite the strict usage of the triple combination, on the Thailand-Myanmar border, where, at the time it was introduced, resistance to sulfadoxine/pyrimethamine was already widespread.²⁵ The fixed triple combination has previously been shown to have a high in vitro and in vivo efficacy in Africa.²⁶ However, using mefloquine/sulfadoxine/pyrimethamine widely at subtherapeutic doses, as is often done with many drugs in developing countries, bears a considerable risk of provoking resistance in *P. falciparum*. Thus, for successful prevention of development of resistance against the single component, an optimized triple combination first has to be developed and introduced before the emergence of considerable sulfadoxine/pyrimethamine or mefloquine resistance in Africa.

Acknowledgments: We thank M. Nkeyi and A. Ndzengue for excellent technical assistance and C. Crevoisier (F. Hoffmann-La Roche, Basel, Switzerland) for helpful comments. The database was established and statistical input was provided by Clin-Pharma Research Ltd. (Birsfelden, Switzerland) (J. F. K. Hoogkammer and M. Ouwerkerk); plasma drug level analysis was done by Y. Bergqvist (Falun, Sweden); and polymerase chain reaction genotype analysis was done by D. Walliker and L. D. Ranford-Cartwright (Edinburgh, United Kingdom).

Financial support: This trial was sponsored by F. Hoffmann-La Roche Ltd., Tropical Medicine Unit (Basel, Switzerland).

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