EFFICACY AND TOLERABILITY OF A LOW-DOSE MEfloquine-Sulfadoxine-Pyrimethamine Combination Compared with Chloroquine in the Treatment of Acute Malaria Infection in a Population with Multiple Drug-Resistant Plasmodium falciparum


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Abstract. The efficacy and tolerability of single, low-dose mefloquine, sulfadoxine-pyrimethamine (MSP) combination was compared with chloroquine (CQ) for malaria treatment in a malaria-endemic area of Nigeria with multiple drug-resistant Plasmodium falciparum. The two drug regimens (MSP and CQ) were tested in a 12–month prospective population study. The patients were divided into two groups. Group 1 patients were treated presumptively, based on malaria symptoms. Group 2 patients were treated based on a parasitologic diagnosis using the World Health Organization seven-day in vivo test and extended to a 28-day follow-up period. Tolerance was assessed by the incidence and intensity of adverse events. One thousand nine hundred thirty-five patients visiting 10 health facilities, including the University of Calabar Teaching Hospital, were enrolled. The study showed that the low-dose MSP was efficacious, with day 7 response rates of 95% and 91% for (presumptive) Group 1 and (in vivo) Group 2, respectively, while CQ had day 7 response rates of 82% and 66% in Groups 1 and 2, respectively. The low-dose MSP was significantly (P < 0.0001) more efficacious, with faster fever and parasite clearance times than CQ in this area of CQ-resistant P. falciparum malaria. Eight patients treated with CQ, including seven severe cases (RII–RIII) were successfully re-treated with MSP. Adverse events were generally more common among those treated with MSP (29%) than those treated with CQ (17%). However, the adverse events caused by both drugs were mild to moderate and self-limited. The MSP combination appears to be a good substitute for CQ, in view of multiple drug resistance, especially in areas with severe (RII–RIII) malaria.

The malaria situation in Nigeria is deteriorating, and has been described as a moving target. Multiple drug-resistant Plasmodium falciparum, especially chloroquine (CQ)–resistant P. falciparum reported in this country, has complicated malaria chemotherapy. Most malaria treatment (80%) in malaria-endemic areas, such as Nigeria, is handled at home, without microscopic confirmation of the suspected malaria episode. We reported that mothers (64%) correctly recognized and treated malaria attacks in their children based on the symptoms. Presumptive malaria diagnosis and treatment is the basis of malaria control for primary health care facilities in Nigeria. Similarly, the World Health Organization (WHO) recommends that all febrile children in malaria-endemic areas should be treated, whether or not blood smears are microscopically examined, to quickly relieve the symptoms, prevent convulsive complications, and reduce transmission. Mefloquine-sulfadoxine-pyrimethamine (MSP) is effective and tolerable in the treatment of children, but it has not been used in a cross-sectional population study, particularly in respect to fever clearance in this area. We reported that fever regressed significantly faster with CQ than with sulfadoxine/pyrimethamine (one of the components of MSP). This delay in fever reduction is often perceived by patients as drug failure. Such patients resort to other antimalarial drugs or increase the dose of sulfadoxine/pyrimethamine (Ezedinachi ENU, unpublished data). If the MSP combination could quickly clear the fever, it could restore patients’ confidence and be a good alternative to CQ, whose effectiveness is compromised by CQ-resistant P. falciparum. The objective of this study was to evaluate the effectiveness and tolerability of low-dose MSP compared with CQ in a population study in view of increasing drug resistance in P. falciparum to CQ.

Patients and Methods

Study site. The study was conducted from January 1995 to January 1996 in 10 health facilities, including the University of Calabar Teaching Hospital in Calabar in the Cross River State of southeastern Nigeria. The study site is situated in the rain forest belt, where malaria infection is holoendemic and perennial, with intense transmission throughout the year. Human malaria is caused by four Plasmodium species. Plasmodium falciparum is the most common species in Nigeria, causing approximately 96% of all malaria infections, while P. malariae causes about 2%, and P. ovale is rare. Plasmodium vivax is usually not found in Africa (Salako LA, unpublished data). High humidity (80%) and a high mean temperature (35°C) favor the bionomics of the principal vectors (Anopheles gambiae and An. funestus). The overall prevalence rate of malaria infection in this population is 48%, while the P. falciparum CQ resistance rate is 53–62%.

Six of the 10 health facilities are located in Calabar, the capital city of Cross River State, with a population of 320,862 people (1991 national census). Most of these people are civil servants, while the rest are traders, craftsmen, and fishermen. The other four health facilities are situated in three local government areas, with a total population of 322,019 people. The occupations of this second group are mostly subsistence farming, trading, fishing, and crafts, while the rest are civil servants, who work in schools, rubber plantations, and health facilities. These health facilities are staffed by state-registered nurses who are specifically trained as community health officers to work in primary health care facilities. They are trained by the Federal Ministry of Health to recognize and treat endemic diseases such as malaria based on clinical symptoms and to refer severe cases.
are supervised by primary health care coordinators who are medical doctors.

Two representatives were selected from each of the 10 study centers for training. The training workshops and seminars were organized at the University of Calabar Teaching Hospital. In the workshop, the protocol of the study was discussed and representatives practiced completion of the case report form. Similarly, other logistic modalities such as drug dosing and administration were determined and practiced until all participants were conversant with the protocol. The grading of adverse events was defined and explained. For supervision, the 10 centers were grouped into three, each headed by a physician (co-investigators) who visited respective centers every week for the first three months, then every month. The supervisors also distributed supplies to the centers and picked up the completed case report forms for data entry. Informed consent was obtained from all patients and from the guardians of minors. It was either written or witnessed oral consent depending on the level of education of the patients or guardians. The study was approved by the Ethical Committee of the University of Calabar Teaching Hospital, which was responsible for biomedical research involving human subjects.

**Study design.** This was an open prospective population study, with treatment randomized according to health facilities based on their geographic location. All patients participating at one health facility received one of the two drugs, i.e., each health center used either MSP or CQ, except the University of Calabar Teaching Hospital, where both drugs were used for an *in vivo* test.

The patients were divided into two groups. Group 1 was composed of patients treated presumptively, while Group 2 was composed of patients treated on the basis of a microscopically confirmed diagnosis, using the WHO seven-day *in vivo* test. Group 1 consisted of all patients visiting each of the health facilities who were suspected of having malaria. These were patients with symptoms such as fever, malaise, headache, weakness, and loss of appetite, without any other obvious cause of the illness. These are symptoms generally recognized and associated with malaria infection by the community. The patients were examined by the specially trained community health officers under the supervision of the team clinicians. Patients fulfilling the protocol criteria were enrolled daily until 200 patients per facility were recruited.

**Clinical assessment.** Four major clinical malaria symptoms were considered for this assessment: fever or a history of fever in the last 24 hr before presentation and/or a temperature ≥ 37.5°C, weakness/sleepiness, headache, and loss of appetite or not eating in the case of children. Clearance of these clinical symptoms were scored. For example, a history of febrile illness and/or an axillary temperature ≥ 37.5°C was scored as one unit if the patient or guardian provided a history of illness during the previous 24 hr (or since the last visit during the follow-up). For a patient assessed as being ill by the team clinician, an additional score of one unit was given. Patients who scored ≥ one unit on day 0 and zero on day 7 were considered to be a clinical response, while those who scored > 0 on day 7 were regarded as treatment failures.

All patients in Group 2 were screened for the malaria symptoms and bled by fingerpricks. Thick and thin blood films were made and stained with Giemsa. The films were examined with an oil-immersion light microscope (× 600). The thick films were used to count 500 asexual parasites against 1,000 leukocytes, or whichever was counted first, while the thin films were used to determine the *Plasmodium* species. A thick film was regarded as negative if 1,000 leukocytes were counted against no asexual parasites. Parasitemia was estimated by assuming that there were 6,000 leukocytes/μl (mean leukocyte count of the population). Patients with asexual *P. falciparum* parasitemias ≥ 1,000/μl were recruited for the study. These patients were allocated randomly (open randomization) into two subgroups: 1) MSP and 2) CQ as the patients arrived at the University of Calabar Teaching Hospital. The first patient to begin treatment with either of the two drugs was determined by a simple blindfold method; odd and even number selection was then used sequentially.

**Adverse events.** Adverse events were defined as any change in the baseline (pre-treatment) condition of a patient. These were recorded on the case report form according to their frequency, severity/intensity, and whether they required...
intervention/treatment and for how long. To elicit adverse events, all patients were uniformly asked during the follow-up whether they noticed any change from their pre-treatment condition. Those regarded as adverse events by the clinician were graded as 1) mild if the discomfort did not affect normal activity, 2) moderate if the discomfort affected, but did not disrupt, normal activity, and 3) severe if the discomfort disrupted normal daily activity. Any serious adverse event was reported immediately to the supervising physician and the principal investigator.

**Blood levels of mefloquine and CQ.** Blood samples (100 μl) were randomly taken by fingerprick into a calibrated capillary tube from 20 enrolled patients. These blood samples were applied to filter paper, dried, and kept frozen at −20°C. Three sets of blood samples were taken from each patient on days 0, 3, and 7. The blood was analyzed at Falun Central Hospital (Falun, Sweden) to estimate mefloquine and CQ levels.

**Sample size and data analysis.** Sample size was generated with STATCALC in Epi-Info, version 6, as in population study using random sampling. The population to be represented was 642,881 people from the 10 communities served by the health centers. If the expected frequency of CQ-resistant *P. falciparum* was 10% and lowest frequency was approximately 2%, at a 95% confidence level the sample size will require approximately 54 cases. Data were analyzed separately for each group, using Epi-Info, version 6 software. Differences in proportion and means were compared separately using the chi-square test and Student’s *t*-test, respectively.

**RESULTS**

**Group 1 (presumptively treated patients).** A total of 1,810 patients were enrolled in this group: 957 (53%) were treated with MSP and 853 (47%) were treated with CQ. Table 1 summarizes the characteristics and treatment responses to both drugs. The patients treated with MSP had clinical response rate of 95%, while those treated with CQ had a rate of 83%. Figure 1 shows the proportional fever clearance of both drugs. Fever reduction in the MSP-treated patients was faster than in the CQ-treated patients. The overall clinical response to MSP on day 7 was significantly better than that to CQ (*P* < 0.0001) (Figure 1). Eleven (1%) patients treated with MSP and five (1%) patients treated with CQ were lost to follow-up, while 19 (2%) treated with MSP and 44 (5%) treated with CQ were withdrawn from the study. Three (0.3%) patients treated with MSP and 28 (3%) treated with CQ either refused treatment or further follow-up because of adverse events and were withdrawn from the study.

**Group 2 (in vivo test).** One hundred twenty-five patients were enrolled in this group: 68 (54%) were treated with MSP and 57 (46%) were treated with CQ. Table 2 summarizes the findings and shows the similarity in the demographic data of the subgroups (MSP and CQ). There was an increase in parasitemia 24 hr after start of treatment in both groups. Parasitemias on days 2/3 ≥ 25% of those on day 0 were found in five (9%) of the CQ-treated patients. Similarly, RII-RIII responses were found in seven (39%) of the 18 CQ treatment failures. The fever clearance times were 23 hr for MSP and 30 hr for CQ. The parasitemia clearance times were 38 hr for MSP and 43 hr for CQ (*P* < 0.001) (Table 2). Differences in the day 7 parasitologic S response rates (91% for MSP and 67% for CQ) were statistically significant (*P* < 0.0001) (Figure 2). Eight of the 18 CQ treatment failures (including the 7 RII-RIII cases) were successfully retreated with MSP but parasites reoccurred in one patient on day 14. One the six MSP RI treatment failures required retreatment and responded to CQ. The other five MSP-treated RI response patients cleared their parasitemias up to day 28. The remaining 31 patients treated with MSP followed-up to day 28 showed an S response. Two patients treated with CQ (no. 89 and 267) who showed an S response up to day 14 became parasitemic on day 21. One patient treated with MSP (no. 322) was withdrawn from the study because one of her parents gave her quinine 24 hr after the start of the study. Two siblings (no. 393 and 394) who received CQ were withdrawn from the study because their father refused to allow further follow-up, even by home visit, while the third patient treated with CQ traveled out of town and was withdrawn from the analysis. Figure 3 shows the absorption profile for mefloquine and CQ, which suggests that both drugs were well absorbed.

**Tolerability and adverse events.** Table 3 summarizes the adverse events in all patients. These were more common in those treated with MSP (273, 29%) than in those treated with CQ (146, 17%) (*P* < 0.0001). The most serious adverse events affected the central nervous system in 15% of those treated with MSP and 9% of those treated with CQ. Three (0.3%) treated with MSP and 28 (3%) treated with CQ refused treatment or follow-up due to adverse events. Among the MSP-treated patients with adverse events, dizziness in 99 (10%), headache in 20 (2%), and insomnia in 25 (3%) were most common, while in the CQ-treated patients, itching in 58 (7%), dizziness in 22 (3%), and headache in 20 (2%) were most common. The outcome of the adverse events in the MSP-treated patients was mild in 216 (23%), moderate

<table>
<thead>
<tr>
<th>Number treated</th>
<th>MSP</th>
<th>CQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>957 (52.9)</td>
<td>853 (47.1)</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD age (years) 25.8 ± 16.4 25.8 ± 19.3

Mean ± SD weight (kg) 50.9 ± 22.6 51.2 ± 20.7

Mean ± SD height (cm) 147.5 ± 32 139.2 ± 32

Mean ± SD temperature (°C) 39.1 ± 0.37 38.3 ± 0.7

Pulse rate/min 87.9 ± 33.8 86.3 ± 19.5

Mean ± SD systolic blood pressure 112.22 ± 16.5 113.77 ± 20.9

Mean ± SD diastolic blood pressure 72.14 ± 12.24 70.15 ± 14.02

No. cured on day 7 910 (95.04) 705 (82.6)

No. lost to follow-up 11 (1.14) 5 (0.53)

No. of withdrawals 19 (1.96) 44 (5.14)

No. of failure cases 47 (4.96) 148 (17.4)

No. refusing treatment at follow-up 3 (0.26) 28 (3.32)

Fever clearance time (hr) 23 30.4

*Values in parentheses are percentages. P < 0.0001; χ² = 57.*
117

EFFICACY OF ANTIMALARIALS IN A POPULATION STUDY

FIGURE 1. Fever reduction in malaria patients treated with mefloquine-sulfadoxine-pyrimethamine (MSP) and chloroquine (CQ), respectively. (P < 0.001). Temp. = temperature.

in 34 (4%), and severe in six (1%), while in CQ-treated patients, the outcome of adverse events was mild in 63 (7%), moderate in 60 (7%), and severe in 14 (2%). Itching accounted for most of the withdrawals in the CQ-treated group. The adverse events did not require any specific treatment in both groups.

TABLE 2

Characteristics of the in vivo test (Group 2) patients and treatment response to mefloquine-sulfadoxine-pyrimethamine (MSP) or chloroquine (CQ)

<table>
<thead>
<tr>
<th></th>
<th>MSP</th>
<th>CQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>68</td>
<td>57</td>
</tr>
<tr>
<td>Mean ± SD age (years)</td>
<td>16.3 ± 13.8</td>
<td>10.98 ± 11.7</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>1–58</td>
<td>1–59</td>
</tr>
<tr>
<td>Mean ± SD weight (kg)</td>
<td>40.7 ± 25.7</td>
<td>28.2 ± 20.0</td>
</tr>
<tr>
<td>Mean ± SD height (cm)</td>
<td>132.5 ± 32</td>
<td>118.4 ± 32</td>
</tr>
<tr>
<td>Geometric mean parasite density (range)</td>
<td>13,323 (1,020–37,500)</td>
<td>13,367 (1,650–361,200)</td>
</tr>
<tr>
<td>Mean ± SD day 0 temperature (°C)</td>
<td>37.5 ± 4.2</td>
<td>38.04 ± 0.08</td>
</tr>
<tr>
<td>No. with an increased parasitemia after 24 hr</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No. with parasitemia on days 2/3 ≥25% of day 0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No. followed to day 7</td>
<td>67</td>
<td>54</td>
</tr>
<tr>
<td>No. lost to follow-up</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No. of failures (%)</td>
<td>6 (8.9)</td>
<td>18 (34)</td>
</tr>
<tr>
<td>Cure rates (%)</td>
<td>92.5</td>
<td>66.0</td>
</tr>
<tr>
<td>No. with parasites on day 7</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>No. with parasites on day 14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No. with RI-RHII*</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Parasite clearance time (hr)†</td>
<td>38.4</td>
<td>43.4</td>
</tr>
</tbody>
</table>

* Severe failure cases. RI = reduced but persistent parasitemia up to day 7; RII = no pronounced change in parasitemia on day 2.
† P < 0.001.

DISCUSSION

The MSP drug combination appears to have improved the effectiveness of sulfadoxine/pyrimethamine. Fever reduction was more rapid and overall fever clearance up to day 28 was significantly greater in the MSP-treated patients than in those treated with CQ.
treated with CQ (Figure 1). This confirmed the similar findings in southwestern Nigeria by Sowounmi and Oduola. We have reported slower fever reduction when sulfadoxine-pyrimethamine is used alone compared with CQ, which could erode patient confidence. The efficacy and tolerability of MSP has been reported in children. In this study, only six (9%) of the MSP-treated patients (three adults 14, 28, and 35 years of age and three children 1, 2, and 5 years of age) showed an RI response. The 35-year-old patient required re-treatment and responded to CQ. The rest of the patients including the 31 followed-up to day 28 remained aperasitemic. Thirteen (72%) of the 18 CQ treatment failures, including the seven (54%) with RII-RIII responses, were successfully re-treated with MSP. These seven RII-RIII responses were children (mean age = 3 years). The clinical response rate to CQ has decreased from 94% (1990) to 83%.

This study appears to confirm the effectiveness of low-dose MSP in a cross-sectional survey in an area with multiple drug-resistant P. falciparum. Mefloquine-associated adverse effects have been reported to increase significantly with an increase in dose, and lowering the dose could improve its tolerability. There were no psychosis or psychiatric adverse events reported among Africans when a standard MSP dose was used. However, patients perceived the adverse events (dizziness, insomnia, headache) in this study as disturbing. Headache was reported by 84% of the malaria patients in this population. Although itching occurred in both groups of patients, there were no skin eruptions often associated with a sulfonamide. Both MSP and CQ appeared to be well absorbed, suggesting good bioavailability (Figure 3).

Antimalarial drugs in Nigeria are often used to treat fevers suspected to be due to malaria infection (presumptive treatment), which is also the basis for the malaria control in the primary health care system. This study showed that the patients in both groups who were treated with MSP had similar clinical response rates (95% and 91%, respectively; $P > 0.05$). It appeared to validate the use of presumptive treatment in an area with holoendemic malaria. The MSP com-

**FIGURE 2.** Parasitologic response of Plasmodium falciparum malaria to mefloquine-sulfadoxine-pyrimethamine (MSP) compared with chloroquine (CQ), as shown by parasite density clearance time (38.4 hr for MSP and 43.4 hr for CQ). ($P < 0.0001$).

**FIGURE 3.** Absorption and elimination curves of mefloquine (MSP) and chloroquine (CQ) on days 0, 1, and 7.
Combination as a single-dose treatment could positively impact patient compliance due to its rapid reduction of fever, which could reduce the incidence of malaria complication due to febrile convulsions. Although in vitro resistance of *P. falciparum* to mefloquine had been reported before its introduction and use in Nigeria, the MSP drug combination appears to be fully efficacious in vivo, suggesting that mefloquine may delay the onset of resistance to sulfadoxine/pyrimethamine. More studies are required to confirm this. Similarly, Okoye and others reported good effectiveness and tolerability of a reduced dose of mefloquine in pregnant women. Although MSP appears to be a good substitute for chloroquine in an area with CQ-resistant *P. falciparum*, its affordability by the low socioeconomic rural population (75% of Nigerians) is a cause for concern. Further studies are required to compare the cost and benefits of MSP against the risk of recurrent malaria due to the drug-resistant *P. falciparum* (RII-RIII) and the development of resistance to sulfadoxine/pyrimethamine. Clinicians should weigh the risk of recurrent severe malaria in children against the cost of effective antimalarial drugs.

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