EFFICACY OF MEFLOXINE AND SULFADOXINE-PYRIMETHAMINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* INFECTION IN MACHINGA DISTRICT, MALAWI, 1998

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Abstract. In response to the spread of chloroquine-resistant *Plasmodium falciparum*, Malawi changed its first-line antimalarial drug in 1993 from chloroquine to sulfadoxine-pyrimethamine (SP). Surveillance data has suggested that resistance to SP may be increasing. We compared the efficacy of SP with a potential successor, mefloquine (MQ). By use of a modified World Health Organization in vivo protocol, children infected with *P. falciparum* were randomized to receive SP (sulfadoxine 25 mg/kg) or MQ (15 mg/kg). We observed combined RII and RIII parasitologic failures of 20.0 and 22.0% in the SP and MQ arms, respectively. Among those in the MQ arm, the relative hazard of failing with a Day 2 drug level < 500 ng/mL was 10.6 times higher than those with levels ≥ 500 ng/mL. Given the decreased efficacy of the first-line antimalarial drug and the high failure rates of MQ at this lower dosage, Malawi should consider assessing the efficacy and feasibility of alternative drugs to treat uncomplicated falciparum malaria.

INTRODUCTION

The spread and intensification of drug-resistant *Plasmodium falciparum* malaria in Africa has been called an impending disaster. Resistance to chloroquine, the first-line therapy most commonly used throughout sub-Saharan Africa, is now widespread. Countries with high levels of resistance have witnessed increased childhood morbidity and mortality. In response to high levels of chloroquine resistance, in 1993, Malawi became the first country in Africa to change its national treatment policy and recommend sulfadoxine-pyrimethamine (SP) as the first-line therapy for uncomplicated falciparum malaria.

Soon after this change in policy, the Malawian National Malaria Control Programme began receiving anecdotal reports of failure of patients to respond to SP therapy, but early studies continued to show high efficacy. By 1998, however, one study showed that only 49.5% of children were aparasitemic 14 days after treatment with SP (Kachur SP unpublished data). This led the National Malaria Control Programme to begin to assess potential alternatives to SP. Furthermore, the Malawian National Malaria Programme received a report of a mefloquine (MQ) prophylaxis failure in a Peace Corps volunteer with adequate blood drug levels stationed in Machinga District. In this context of rising SP resistance and reported MQ prophylaxis failure, we assessed therapy with SP and a potential successor, MQ.

PATIENTS AND METHODS

Study site. The study was conducted in July–September 1998 in an outpatient clinic located in the Machinga District Hospital situated near the Shire River in southern Malawi. More than 90% of malaria infections are caused by *P. falciparum*, with the remaining caused by *P. malariae* and a very small amount by *P. ovale*. This area of Malawi has 3 distinct seasons: rainy season in December–March, a dry, cool season in April–July, and a dry, hot season in August–November.

Patients. A modified 14-day World Health Organization (WHO) in vivo protocol for assessing the efficacy of antimalarial drugs in areas of intense transmission was used. Children aged 6–59 months with a documented axillary temperature ≥ 37.5°C and a pure *P. falciparum* infection between 2,000 and 250,000 asexual parasites/mm³ were eligible for inclusion if their parent or guardian gave informed consent. Children with signs of nonmalarial fever or chronic medical conditions, severe malaria, or reported history of allergy to antimalarial or sulfa drugs were excluded. Previous antimalarial use was not a reason for exclusion.

The study was approved by the United States Centers for Disease Control and Prevention institutional review board and the Malawian National Health Sciences Research Committee. The guidelines of the Centers for Disease Control and Prevention, the United States Department of Health and Human Services, and Malawian National Health Sciences Research Committee that govern research involving human subjects were followed.

TREATMENT. All enrolled children underwent a thorough history and physical examination by the staff clinical officer and were randomized to receive either SP (sulfadoxine 25 mg/kg) or MQ (15 mg/kg) in an unblinded fashion. The children were given the medication orally under supervision and monitored for 30 min. If the child vomited, a second full dose was administered. Children who vomited the mediation twice were given an alternative drug (SP for those vomiting MQ and quinine for those vomiting SP) and excluded from the study. If the alternative drug was vomited, they were hospitalized for parenteral treatment.

Blood was taken for baseline quantitative parasite counts and hemoglobin levels with a Hemocue® machine (Hemocue AB, Angelholm, Sweden). Parasite density was calculated by counting the number of asexual parasites per 300 white blood cells on Giemsa-stained thick blood smears, assuming a white blood cell count of 8,000/μL of blood. The smears were read in a blinded manner by 2 microscopists, and if densities differed by > 20%, a third microscopist examined the blood smear. The final parasite density was an average
of the 2 closest counts. Slides were considered negative if no parasites were found after examining 100 high-power fields.

**Follow-up.** Children were asked to return for follow-up on Days 2, 3, 7, and 14. Parents were asked about the presence of fever, vomiting, diarrhea, and use of additional medications or treatments since the last visit, and they were asked whether they perceived their child to be improving. At each visit, a brief physical examination, including axillary temperature, was performed, and blood was taken for thin and thick smears. On Day 2, serum SP and MQ levels were taken. Children who failed to respond to treatment received an alternative drug.

Outcomes were evaluated by parasitologic, clinical, and hematologic response. Standard WHO definitions for parasitologic response were used, although late RI (Days 15–28) could not be assessed and was combined with sensitive reactions for this 14-day trial. Clinical outcomes were defined as early treatment failure (ETF), late treatment failure (LTF), or adequate clinical response (ACR). We assigned children to the ETF category if they had either an axillary temperature ≥ 37.5°C and a Day 2 parasite density greater than a Day 0 density, an axillary temperature ≥ 37.5°C and parasites present on Day 3, or a Day 3 parasitemia greater than or equal to 25% of the Day 0 parasite density. We assigned children to the LTF category if asexual parasites appeared in any child with an axillary temperature ≥ 37.5°C between Days 4 and 14. Children whose responses were classified as an ACR remained afebrile with or without parasitemia by the end of the 14-day follow-up period. Children who had an axillary temperature ≥ 37.5°C but no parasites noted on thick blood smear were also assigned to the ACR group. Any child with parasitemia at the end of the 14-day follow-up period received an alternative antimalarial drug per national policy guidelines.

**Drug levels.** Concentrations of MQ in plasma were measured by solid-phase extraction and high-performance liquid chromatography. Sulfadoxine levels were measured by liquid-liquid extraction and high-performance liquid chromatography analysis methods. The intra-assay coefficients of variation were 3% at 500 ng/mL and 1% at 50 μg/mL for MQ and SP, respectively.

**Statistical analyses.** The sample size was calculated to estimate prevalence of SP parasitologic failures on the basis of recent reports from Malawi and to detect a 1-g/dL difference in hemoglobin levels between MQ and SP with 5% level of significance and 80% power, assuming an estimated 10% of children would be lost to follow-up during the study.

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**RESULTS**

**Study population.** A total of 492 children presented to the outpatient department with fever and were screened. Of these children, 120 met enrollment criteria and 102 (85%) were enrolled in the study. The parents of the remaining 18 (15%) children declined to participate in the study. Forty-eight children were randomized into the SP group and 54 into MQ group. The median ages, weight, temperature, sex distribution, mean hemoglobin levels, and geometric mean parasite density in the 2 groups were comparable (Table 1). Ten children were lost to follow-up, leaving 92 (90%) whose clinical outcomes were evaluated. Three children who did not meet the parasitologic RII failure definition were classified as ETF, and one child classified as RII did not receive a clinical classification; thus, 90 (88%) of the 102 children entered in the study had parasitologic outcomes that could be evaluated.

**Clinical response.** The clinical response to therapy is summarized in Table 2. Of the 43 children evaluated in the SP group, 5 (11.6%) were classified as ETF, 3 (7.0%) as LTF, and 35 (81.4%) as ACR. Forty-nine (90.7%) of the 54 children enrolled in the MQ group were evaluated. Four (8.2%) experienced ETF, 1 (2.0%) LTF, and 44 (89.8%) were determined to have ACR.

**Parasitologic response.** Ninety (88.2%) of the 102 children enrolled were able to be evaluated for parasitologic response (Table 3). A total of 4 (10.0%) of 40 treated with SP and 8 (16.0%) of 50 children taking MQ experienced RII failures. A further 4 (10.0%) children treated with SP and 3 (6.0%) of those treated with MQ developed RII failure. Thus, when RII and RI are combined, we observed 20.0 and 22.0% moderate- to high-grade parasitologic failures in the SP and MQ arms, respectively. Six (15.0%) children in the SP group and 5 (10.0%) in the MQ arm were classified as early RI failure. At the end of the 14-day follow-
up period, 26 (65.0%) of 40 children taking SP and 34 (68.0%) of 50 children taking MQ were classified as late RI/S.

**Hematologic response.** Overall, both groups observed an increase from Day 0 to Day 14 in mean hemoglobin levels. The hemoglobin increased (1.82 ± 2.29 g/dL) in the SP group compared with (1.64 ± 1.67 g/dL) in the MQ arm (P = 0.70).

**Factors influencing parasitologic outcomes.** There was no evidence that age, weight, nutritional status (weight for age), temperature, parasite density, initial hemoglobin level, or history or subsequent episodes of vomiting or diarrhea contributed to an increased risk of parasitologic failure. Serum drug levels of MQ were obtained on Day 2 for 43 (79.6%) of the 54 children enrolled. The mean ± standard deviation serum MQ concentration was 633 ± 343 ng/mL. Levels of MQ below the therapeutic level of 500 ng/mL were strongly associated (RH, 10.59; 95% CI, 2.80, 40.03) with parasitologic failure. Sulfadoxine drug levels were assessed for 39 (81.3%) of the 48 children entered into the SP group of the study. The mean ± standard deviation serum sulfadoxine level was 74.6 ± 24.5 μg/mL. Sulfadoxine levels less than the therapeutic level of 60 μg/mL were suggestive of increases in parasitologic failures (RH, 3.63; 95% CI, 0.62, 21.47); however, the increase was not statistically significant.

**Adverse drug effects.** Eight patients initially randomized to the MQ group vomited the drug within the first 30 min and were readministered the 15 mg/kg dose. Five of these children vomited a second time, were given an alternative antimalarial drug, and were excluded from the study. Only one child vomited SP and was successfully readministered the medication. There were no differences during follow-up visits between the SP and MQ groups in terms of the mother’s perception of child’s condition and report of fever or diarrhea. On Day 2 of follow-up, the caretakers of 10 (22.2%) of 45 children randomized to SP and 4 (7.5%) of 53 children in the MQ group (P = 0.047) reported vomiting since the last clinic visit. Between Days 3 and 7, the reported vomiting decreased to 4 (10.3%) of 39 and 0 (0.0%) of 47 (P = 0.039) children taking SP and MQ, respectively.

**Discussion.** Chloroquine, long the mainstay therapy for uncomplicated *P. falciparum* used by malaria control programs in sub-Saharan Africa, is losing its efficacy in many locations. Since Malawi changed national policy in March 1993 and began to recommend SP as the first-line treatment for uncomplicated falciparum malaria, there has been active discussion regarding the merits of this change. Was the change made too soon? Would SP resistance develop quickly? What drug would replace SP once resistance emerged? Could African countries afford the next drug? Eight years after Malawi’s change, these questions remain central to the discussion surrounding antimalarial drug policy in sub-Saharan Africa.

We found substantial amounts of moderate- to high-level parasitologic failures in both the SP and MQ arms (Figure 1). These data confirm an increase in the overall level of RII and RIII SP parasitologic failures that has occurred since the countrywide initiation of SP. Although data suggest that subtherapeutic blood levels of SP contributed to the failure rate, a substantial number of patients with adequate Day 2 drug concentration experienced parasitologic failure. The clinical response to SP was better than the parasitologic response; however, a large proportion of children still developed fever and parasitemia by the end of the 14-day study.

There was a larger proportion of MQ parasitologic and clinical failures than expected, given that MQ has had very limited use in Malawi. Although this study showed parasitologic failures strongly associated with subtherapeutic blood levels (Figure 2), there were 3 RII and 1 RI failures in children with MQ levels ≥ 500 ng/mL. Only one of these

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**Table 2**

Day 14 clinical response

<table>
<thead>
<tr>
<th>Response</th>
<th>Sulfadoxine-pyrimethamine (%)</th>
<th>Mefloquine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 60 μg/mL (n = 26)</td>
<td>≥ 60 μg/mL (n = 43)</td>
</tr>
<tr>
<td></td>
<td>&lt; 500 μg/mL (n = 13)</td>
<td>≥ 500 μg/mL (n = 26)</td>
</tr>
<tr>
<td>Early treatment failure</td>
<td>1 (12.5)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Late treatment failure</td>
<td>2 (25.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Adequate clinical response</td>
<td>5 (62.5)</td>
<td>22 (84.5)</td>
</tr>
</tbody>
</table>

*P* < 0.001

**Table 3**

Day 14 parasitologic response

<table>
<thead>
<tr>
<th>Response</th>
<th>Sulfadoxine-pyrimethamine (%)</th>
<th>Mefloquine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 60 μg/mL (n = 8)</td>
<td>≥ 60 μg/mL (n = 24)</td>
</tr>
<tr>
<td></td>
<td>&lt; 500 μg/mL (n = 14)</td>
<td>≥ 500 μg/mL (n = 26)</td>
</tr>
<tr>
<td>RII</td>
<td>1 (12.5)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>RI</td>
<td>1 (12.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Early RI</td>
<td>3 (37.5)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Sensitive/late RI</td>
<td>3 (37.5)</td>
<td>18 (75.0)</td>
</tr>
</tbody>
</table>

* Not all children had serum levels taken; thus, total numbers are larger than the sum of subsets.

† The P value was calculated comparing total column of sulfadoxine-pyrimethamine versus total column of mefloquine failure rates (Fisher’s exact test).
children experienced a clinical failure (ETF); however, the parasites eventually cleared by the end of 14 days.

Five of the children initially randomized to receive MQ vomited the medication twice and were excluded from the study. Of the 3 children who vomited MQ once and were successfully redosed, there was one RIII failure (serum MQ 271.5 ng/mL), one RII (serum MQ 200.1 ng/mL), and one sensitive (serum MQ not obtained). Had the other 5 children been successfully redosed, the overall parasitologic failure rate may have been higher.

In this study, MQ at 15 mg/kg, the dose recommended by WHO for areas without known MQ resistance, led to unacceptable levels of treatment failure even before the drug was being widely used. Increasing the dose to 25 mg/kg, especially given in split doses (15 and 10 mg/kg), can increase absorption\textsuperscript{23} but may be further problematic because of associated vomiting.\textsuperscript{24} Although fever has also been linked with increases in vomiting,\textsuperscript{24,25} reduction of the fever in children aged < 15 years does not lower the incidence of early vomiting.\textsuperscript{26} Addition of the antiemetic metoclopramide has been shown to accelerate the absorption of MQ and increase maximum concentrations.\textsuperscript{27} In a previous study performed in Malawi, there was no difference in parasitologic failures between children given MQ 15 mg/kg and those taking MQ 25 mg/kg\textsuperscript{28}; therefore, it is uncertain if an increase in dose would improve the parasitologic outcome; however, this warrants further study.

Our findings highlight several obstacles to the use of MQ as a first-line drug for the treatment of uncomplicated \textit{P. falciparum} infections in tropical sub-Saharan Africa, where most patients are children aged < 5 years. Aside from the small percentage of MQ-resistant parasites, these obstacles in children include difficulty in administering the drug, problems with vomiting afterward, and erratic absorption leading to subtherapeutic blood levels.

Malawi is faced with a major public health challenge. As the first country in Africa to change first-line antimalarial therapy to SP nationwide, they are now experiencing high- to moderate-grade parasitologic failures with SP. Although 81.4% of the children continue to experience an adequate clinical response 5 years after implementation of SP, the increasing levels of parasitologic and clinical failures suggest that Malawi needs to act now to consider alternative antimalarial therapies for the future.

Therapeutic options beyond SP are limited. Apart from MQ, chlorproguanil-dapsone (CD) shows promise as an effective drug.\textsuperscript{29,30} However, there are concerns that SP resistance may affect the efficacy of CD. Both SP and CD have been shown to select for mutations at Ile51, Arg59, and Asn108 of dihydrofolate reductase, which are associated with \textit{in vitro} resistance to pyrimethamine and cycloguanil.\textsuperscript{31} Atovaquone plus proguanil has been found to be an extremely effective treatment for uncomplicated falciparum malaria,\textsuperscript{32-35} but the cost per treatment is prohibitive for most sub-Saharan African countries. Recent studies have shown the combination of SP and artesunate to be an effective therapy.
against uncomplicated *P. falciparum* infection in African children under very controlled settings.\textsuperscript{36} It is unclear how efficacious this combination would be in areas with high levels of SP monotherapy resistance. When patients in Thailand experienced high levels of MQ failures, combining MQ with artesunate reduced the failure rate from 31\% to 2\%.\textsuperscript{37}

Given the increasing resistance to SP, the apparent early MQ resistance, and the overall operational problems associated with MQ treatment, Malawi should assess the efficacy and feasibility of alternative drugs other than MQ. Chlorproguanil-dapsone or artemisinin derivatives combined with another antimalarial drug (e.g., SP or CD) may be future options for the treatment of uncomplicated falciparum malaria in Malawi.

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