COMPARISON OF SULFADOXINE-PYRIMETHAMINE WITH AND WITHOUT CHLOROQUINE FOR UNCOMPLICATED MALARIA IN NIGERIA

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ABSTRACT

While resistance to older antimalarials is increasingly common, newer antimalarials are still not widely available or affordable in much of Africa. Older antimalarials used in combination might be adequately effective in treating uncomplicated malaria. The objective of this study was to determine whether the combination of sulfadoxine-pyrimethamine (SP) and chloroquine (CQ) is superior to SP alone in the treatment of uncomplicated Plasmodium falciparum malaria in Nigerian patients. We recruited subjects with malaria, defined as the presence of fever and parasitemia > 2,000/μL, from the outpatient department of a Nigerian teaching hospital. We alternately assigned 280 subjects to receive SP with or without CQ. We assessed clinical and parasitologic responses on days 1, 2, 3, 7, and 14. A total of 114 in the SP + CQ group and 116 in the SP group completed the study. By day 3, 97 (75%) in the SP + CQ group and 52 (42%) in the SP group had cleared their parasitemia (P < 0.001); by day 14, 112 (98%) and 67 (58%), respectively, had cleared their parasitemia (P < 0.001). By day 3, 82 (63%) in the SP + CQ group and 20 (16%) in the SP group were symptom free (P < 0.001). When a modified World Health Organization clinical classification system was used, adequate clinical response occurred in 99 (87%) and 61 (53%) of those in the SP + CQ and SP groups, respectively. RI, RII, and RIII resistance to SP + CQ was 7.9%, 3.5%, and 1.8%, respectively, whereas resistance to SP was 23%, 17%, and 5%, respectively. Combined SP + CQ is superior to SP alone for treatment of uncomplicated malaria in Nigerian patients and may prolong the usefulness of these readily available and affordable drugs.

INTRODUCTION

Forty percent of the world’s population is at risk of malaria. The disease affects people of all ages and can have especially devastating effects on children, pregnant women, and non-immune travelers. About 500 million people have acute malaria annually, and 9 of 10 cases occur in sub-Saharan Africa. The proportion of outpatient attendance in African health facilities due to malaria ranges from 25% to 40%. Early diagnosis and effective treatment of acute infections is probably the most important element of the Roll Back Malaria partnership, but increasing resistance of Plasmodium falciparum to common antimalarial agents such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) has compounded the problem of malaria control. At least 11 African countries no longer use CQ as the first choice for malaria treatment. Although combination therapy has been used in some countries as first-line antimalarial treatment, monotherapy with CQ is still used as first-line treatment in Nigeria, the most populous nation in Africa. Because of increasing parasite resistance to first-line drugs, effective and affordable combination therapy may be indicated in Nigeria. In areas where CQ is still used, despite some degree of resistance, combining CQ with SP rather than using SP alone may improve parasite clearance, particularly in a semi-immune population.

Due to increasing CQ resistance in Nigeria, consideration must be given to an alternative first-line regimen. Unfortunately, resistance to SP also seems to be increasingly common in other parts of Africa, and data on SP resistance in Nigeria are sparse. Alternative agents are either expensive or unavailable. Combining CQ and SP is a feasible option in Nigeria, given the availability, cost, and differing mechanism of actions of these drugs. The superiority of such a combination would contribute to effective treatment of uncomplicated malaria and control of the disease. The objective of this study was to determine whether combined SP and CQ is superior to SP alone in treatment of uncomplicated P. falciparum malaria in Nigerian patients.

MATERIALS AND METHODS

This randomized, partially blinded study was carried out in the General Outpatient Department of the Jos University Teaching Hospital, located in central Nigeria, where malaria transmission occurs year round. We collected data for six months: three months in the rainy season (July–September 2001) and three months in the dry season (November 2001–January 2002). The Ethical Committee of the Jos University Teaching Hospital reviewed and approved the study, and informed consent was obtained from all adults and the parents of children.

Patients were eligible for enrollment if they presented with an axillary temperature ≥ 38°C and had parasitemia > 2,000 P. falciparum/μL. Patients were excluded prior to enrollment for any of the following reasons: fever determined to be due to another cause; history of sulfila allergy or intolerance to CQ; severe malaria indicated by severe anemia (hematocrit < 18%), cerebral malaria, or respiratory distress; or inability to take drugs orally.

We alternately assigned enrolled subjects, without consideration of age, to receive SP (Fansidar®; F. Hoffmann-LaRoche, Basel, Switzerland) with or without CQ. Fansidar® (500 mg of sulfadoxine plus 25 mg of pyrimethamine in each tablet) was given as follows: adults (age > 14 years old), 3 tablets; 31–45 kg, 2 tablets; 21–30 kg, 1.5 tablets; 11–20 kg, 1 tablet; 5–10 kg, 0.5 tablets. Chloroquine tablets with 300 mg base were given as follows: adults (age > 14 years) 600 mg once a day on days 0 and 1 and 300 mg on day 2; for children, 10 mg/kg on days 0 and 1 and 5 mg/kg on day 2. Administration of medication was supervised by one of the investigators. Paracetamol was given for high-grade fever (≥ 39°C), and promethazine was given to all patients who reported pruritus as a side effect of CQ. In cases of treatment failure, quinine was prescribed.

A trained laboratory technician, unaware of treatment group assignment, prepared thick and thin blood films and identified P. falciparum malaria parasite species. Parasite density was determined by counting the number of parasites.
per 200 leukocytes in the thick smear. Parasite number was converted to a count per milliliter using a standard leukocyte count of 8,000/μL.

We repeated clinical assessment on days 1, 2, 3, 7, and 14. Neither clinicians nor patients were blinded to treatment group assignment. Symptoms of fever, headache, vomiting, malaise, and anorexia were recorded, as were evidence of adverse reactions such as rash. An examination was performed, including measurement of axillary temperature. Thick and thin films were examined on days 3, 7, and 14 for parasite clearance, and the hematocrit was determined.

The primary outcome was based on a slight modification of the World Health Organization (WHO) 14-day in vivo clinical classification system. Early treatment failure (ETF) was defined as the occurrence of any of the following on days 1–3: severe malaria/danger signs with parasitemia, temperature on day 3 > 38.0°C with parasitemia, or day 3 parasite density > 25% of day 0 parasite density. Late treatment failure (LTF) was defined as occurrence of any of the following on days 4–14: severe malaria/danger signs with parasitemia, or temperature > 38.0°C with parasitemia, or history of fever in previous 48 hours with increasing parasitemia. Adequate clinical response (ACR) was defined as completion of 14 days follow-up without meeting the criteria for ETF or LTF.

Patients were also classified according to the WHO parasitologic classification system as follows: RII resistance was defined as a day 3 parasite density > 25% of the day 0 parasite density. RII resistance was defined as a day 3 parasite density < 25% of the day 0 parasite density and a positive smear on day 7. RII resistance was defined as a day 3 parasite density < 25% of the day 0 parasite density, a negative smear on day 7, and a positive smear on day 14. Full sensitivity (S) was defined as a day 3 parasite density < 25% of the day 0 parasite density and negative smears on days 7 and 14 (even though this technique would miss cases of later recrudescence).

The proportion of patients responding to each regimen was compared using the chi-square statistic. A Student's t-test was used to compare mean values between groups. All analyses were performed with Epi-Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA). A P value < 0.05 was considered significant.

RESULTS

We evaluated 421 patients with fever, of which 280 (67%) had malaria parasitemia. Of the 146 children ≤ 14 years old with fever, 111 (76%) had parasitemia, while 169 (61%) of the 275 adults with fever had parasitemia (odds ratio = 2.0, 95% confidence interval = 1.2–3.2). Of the cases with parasitemia, 77% occurred during the rainy season and 23% during the dry season. Parasitemia was present in 136 males and 144 females; 169 (60%) were adults, and 111 (40%) were children. The ages of subjects ranged from 2 to 72 years, with a mean ± SD age of 23 ± 13 years. Of the 280 patients enrolled, 230 (82%) completed the study: 114 (81%) in the SP + CQ group and 116 (83%) in the SP alone group (Figure 1).

There were no important differences in baseline characteristics between the SP + CQ and SP groups (Table 1), except for a slightly greater mean temperature in the SP + CQ group (P < 0.01). Symptom resolution occurred significantly more rapidly and in a greater proportion of patients in the SP + CQ group than in the SP group (Table 2). Parasite clearance was significantly greater in the SP + CQ group than in the SP group at days 3, 7, and 14. By day 14, parasite clearance was 98% in the SP + CQ group and 58% in the SP group (P < 0.001). Eighty-seven percent of the parasites were fully sensitive to SP + CQ, and 54% were sensitive to SP (P < 0.001). The RII, RII, and RIII resistance to SP + CQ was 7.9%, 3.5%, and 1.8%, respectively. The RII, RII, and RIII resistance to SP was 23%, 17%, and 5%, respectively.

Among patients in the SP + CQ group, 87% had an ACR (Table 2) compared with 53% in the SP group (P < 0.001).

![Figure 1. Trial flow chart. SP = sulfadoxine-pyrimethamine; CQ = chloroquine.](image)

![Table 1. Baseline characteristics for the treatment groups at enrollment†](table)

*SP = sulfadoxine-pyrimethamine; CQ = chloroquine.
Both early and late treatment failures were more common in the SP group than in the SP + CQ group. In the SP + CQ group, 71 of 80 adults (89%) and 28 of 32 children (88%) had an ACR. In the SP group, 47 of 78 adults (60%) had an ACR compared with 17 of 40 children (43%; P = 0.07).

At enrollment, the hematocrit did not differ between the two groups, but after treatment it was significantly greater in the SP + CQ group than in the SP group. Parasitemia cleared in all patients who were given quinine. No deaths or progression to severe malaria were recorded. We observed no serious adverse reactions during the course of the study. Only 11% in the SP + CQ group were given promethazine because of pruritus.

### DISCUSSION

Two-thirds of Nigerian patients presenting to a general outpatient department with fever had laboratory evidence of malaria. Children with fever were more likely to have malaria parasitemia than adults. The combination of SP + CQ more rapidly resolved symptoms and more effectively cleared parasitemia than SP alone in both semi-immune adults and children with malaria. We have shown that SP alone is not a suitable choice as first-line treatment of malaria in Nigerian children, where SP + CQ more effectively cleared symptoms than SP given alone. Resistance to SP is an important concern because this antimalarial is considered a first-line agent in areas of CQ resistance in Africa. Strategies to prolong the usefulness of SP would clearly be beneficial. Treatment with combinations of antimalarials provides an alternative when single-agent chemotherapy is inadequate.

We observed adequate clinical response in 87% of patients receiving the SP + CQ combination. A randomized open label clinical trial in Manila, the Philippines reported a nearly identical cure rate of 87.5% with the SP + CQ combination (P < 0.05). In Ibadan, Nigeria, sequential treatment for three days with CQ and chloroquine (CP), followed by a single dose of SP, was effective and well tolerated in children with acute, uncomplicated *P. falciparum* malaria. Parasite clearance at day 14 was 98% in the CQ + CP group and 100% in those receiving CQ + SP + CP. A recent study in Kampala, Uganda reported sensitivities to combinations of SP + CQ and SP + amodiaquine of 83% and 99%, respectively, and the SP + amodiaquine combination was clearly superior to SP + CQ. However, SP + CQ has been the first-line therapy in Uganda. In Nigeria, the availability of amodiaquine is limited, and the cost ($US) is about $10.00 per course compared with $0.40 for SP and $0.06 for CQ. Artemisinin-class combination therapies have also been advocated as the optimal malaria therapy for Africa, but this option is also currently limited by cost and availability. Our findings indicate that combination therapy with SP and CQ may be a reasonable interim first-line therapy in Nigeria.

Concern has been raised that increasing gametocytemia with incompletely effective treatment might actually promote the spread of resistant disease. Even clinical treatment success can be accompanied by transmission of CQ-resistant *P. falciparum* gametocytes. Increased gametocyte carriage rates have been documented in Nigerian children with malaria resistant to CQ and SP. We did not determine the level of gametocytes either at enrolment or during the follow-up, so we were unable to address the possibility of persistent gametocytemia in our patients.

Acquired immunity to malaria is generally greater in areas of intense transmission, creating a complex relationship between infection, illness, and treatment. Infected individuals seek treatment only when they become symptomatic and the likelihood of treatment seeking increases with the severity of symptoms. Under conditions of high transmission, a much smaller proportion of infected people seek and obtain treatment, even with a well functioning health system (e.g., only 5% in western Kenya). Consequently, resistant parasites can increase in absolute numbers and spread within the population. Combination therapy that includes CQ has the advantage of rapid symptomatic response resulting in greater patient satisfaction with treatment and increased likelihood of seeking future treatment. The low cost of combined SP + CQ further increases the likelihood of obtaining effective treat-

### Table 2

<table>
<thead>
<tr>
<th>Treatment outcomes*</th>
<th>SP + CQ (n = 114)†</th>
<th>SP (n = 116)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>31 (20%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 2</td>
<td>76 (56%)</td>
<td>4 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 3</td>
<td>82 (63%)</td>
<td>20 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 7</td>
<td>97 (80%)</td>
<td>62 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 14</td>
<td>108 (95%)</td>
<td>83 (72%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit day 14 (mean ± SD)</td>
<td>36.3 ± 4.0</td>
<td>35.0 ± 3.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Parasite clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>97 (75%)</td>
<td>52 (42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 7</td>
<td>106 (88%)</td>
<td>62 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 14</td>
<td>112 (98%)</td>
<td>67 (88%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parasite sensitivity</td>
<td>Sensitive</td>
<td>99 (87%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RI</td>
<td>9 (8%)</td>
<td>27 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RII</td>
<td>4 (3%)</td>
<td>20 (17%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RIII</td>
<td>2 (2%)</td>
<td>6 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early treatment failure</td>
<td>7 (6%)</td>
<td>26 (22%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late treatment failure</td>
<td>8 (7%)</td>
<td>28 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adequate clinical response</td>
<td>99 (87%)</td>
<td>61 (53%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*SP = sulfadoxine-pyrimethamine; CQ = chloroquine.
† Number of subjects at day 14.
ment in Nigeria, where patients must directly pay for their treatment. In addition, the concurrent use of insecticide-treated bed nets offers hope of restoring sensitivity to CQ and SP by reducing drug pressure.25,26

Rapid emergence of resistance against SP is already evident in Nigeria and other parts of Africa, threatening child survival in regions where no substitute for SP is available. Combination SP + CQ is an effective, inexpensive, easily administered regimen that may delay the progression of CQ and SP resistance. Until the affordability and availability of amodiaquine or artemisinin-class combination therapies are within the reach of the majority of Nigerians, combined SP + CQ is a reasonable option for malaria treatment.

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