COMPARATIVE EFFICACY OF CHLOROQUINE AND SULFADOXINE-PYRIMETHAMINE FOR UNCOMPLICATED PLASMODEM FALCIPARUM MALARIA AND IMPACT ON GAMETOCYTE CARRIAGE RATES IN THE EAST NUSATENGGARA PROVINCE OF INDONESIA

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Abstract. The efficacy of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) was evaluated in 89 subjects greater than one year of age with uncomplicated P. falciparum malaria in the East Nusatenggara Province of Indonesia. Fever clearance time was longer in the SP group than in the CQ group. However, parasite clearance time was extended in subjects who received CQ compared with those who received SP. Major adverse events were not observed in either group, and no hospitalizations were required during the study. Treatment failure rates at day 28 were 69% for CQ and 8.5% for SP. In both treatment groups, gametocytemia developed during the follow-up period, but was more pronounced in the SP group, peaking at 94% on day 7. Regardless of treatment group, children < 10 years of age had significantly higher treatment failure rates than subjects ≥ 10 years of age (relative risk = 2.49), suggesting that acquired immunity influenced treatment outcomes in the presence of parasite drug resistance. Although a highly effective alternative to CQ for clearing infection, SP treatment also presented some potential drawbacks (e.g., increased and persistent gametocytemia). Replacement of CQ with SP as a first-line therapy, either alone or in combination with CQ, in those areas of Indonesia with high levels of CQ resistance should significantly improve treatment outcomes, particularly in vulnerable populations lacking clinical immunity. More efficacious and rapidly acting asexual stage treatments are generally associated with increased gametocyte clearance and combination therapy in areas where drug resistance is high or emerging may provide an additional means for reducing transmission.

INTRODUCTION

Plasmodium falciparum chloroquine (CQ) resistance has been reported in Indonesia for nearly 30 years.1–3 However, CQ remains the first-line treatment for uncomplicated P. falciparum in this country because of its relatively low cost, good safety, and tolerance profile, particularly its use in pregnant women and infants. The sulfadoxine-pyrimethamine (SP) combination is the second-line therapy when CQ treatment failure occurs; however, its use is more limited and cannot be used in pregnant women during the early trimester and it has generally poor efficacy against P. vivax infections. Since P. falciparum CQ resistance rates have continued to increase in Indonesia4 and the efficacy of CQ for treatment of P. vivax malaria decreases,5–9 new or revised antimalarial treatments regimens are desperately needed.

In the face of high levels of CQ treatment failures, some countries have replaced CQ with SP as the first-line treatment.10–12 In some areas with high CQ resistance, CQ in combination with SP has resulted in better parasitologic and hematologic recovery compared with CQ alone.13–16 Use of SP as a first-line therapy has not always been advantageous. Pinichpongse and others reported the rapid development of resistance against this anti-folate combination within five years of initiating widespread use in Thailand.10 Although this phenomenon has not been reported from other locations,11 the potential risk of rapid development of resistance must be considered before any decision is made to abandon CQ in favor of SP alone. Moreover, both clinical failures and a higher risk of developing severe malaria in children treated with SP alone compared with CQ have been reported in Africa.15–18 These observations indicate that caution is needed and highlight the need for site-specific, controlled clinical trials to assess the efficacy of alternative treatments under consideration before revising national malaria treatment policies.

The aim of this study was to compare the clinical and parasitologic efficacy of standard CQ and SP therapies in a malaria-endemic area to provide evidence-based information supporting the most appropriate first-line treatment of P. falciparum in specific areas of high transmission in Indonesia.

MATERIALS AND METHODS

Study area. The investigation took place from November 2001 to March 2002 in an isolated, rural coastal area of Alor Island in the East Nusatenggara Province of Indonesia (Alor District = 8°6′–8°36′S, 123°48′–125°E), which is located within a zone with high endemicity for malaria. Malaria transmission is perennial but fluctuates according to local rainfall patterns. The wet season usually begins in late September, peaking in January–February and returning to a significant dry period at the end of April. Anopheles subpictus Grassi, which breeds in both brackish and freshwater, is considered the primary malaria vector.19 Malarialmetric surveys conducted in June 2001 showed a spleen rate of 62.5% (282 of 453) and a slide positive rate of 45.2% (205 of 453) in 453 children 6–10 years of age; however, less than 2% (4 of 205) of infections were symptomatic (i.e., fever). Plasmodium falciparum was the dominant species (61%), followed by P. vivax (29%) and P. malariae (10%).

Study subjects. During the study, 796 suspected malaria cases were evaluated at the local primary health center during normal malaria passive case detection activities. Finger prick blood samples were taken for malaria thick and thin blood smear examination. Thirty-seven percent (292 of 796) of the sampled people showed patent asexual parasitemia and were evaluated for enrollment. Study subject inclusion criteria followed the World Health Organization protocol for the in vivo 28-day test in low to moderate transmission zones.20 Criteria included clinical illness compatible with malaria, fever or his-
tory of fever within 24 hours of examination, and a *P. falciparum* mono-infection with an asexual stage parasite density of at least 1,000/μL of blood. Subjects were excluded when they presented with signs or symptoms of other illnesses or had evidence of severe malnutrition, severe or complicated malaria, and eczema and pemphigoid exanthems, conditions for which SP administration is contraindicated. Children less than one year of age and pregnant women were excluded from participation. A recent history of previous antimalarial drug use or the presence of an antimalarial drug in the urine was not considered grounds for exclusion in this study design. Based on study inclusion criteria, 154 volunteers were enrolled after signing informed consent forms: 114 subjects with *P. falciparum* and 40 with *P. vivax* mono-infections. A detailed report of *P. vivax* CQ treatment outcomes will be reported separately. Study subjects with *P. falciparum* were enrolled into one of two groups by block randomization of four: 57 volunteers each in the SP and CQ treatment arms. Ethical clearance for this study was obtained from the Committee of Medical Research Ethics of the Faculty of Medicine, University of Indonesia, Jakarta (No. 63/PT02.FK/ETIK/2001).

**Microscopy.** Blood smears (thick and thin) were stained with Giemsa and examined by microscopy at 1,000× magnification. The presence of asexual parasites and gametocytes was reported as the number of parasites per 200 white blood cells and factored by 40 to estimate number of parasites per microliter of peripheral blood.

**Treatment and follow-up.** Subjects were given either oral CQ tablets (chloroquine phosphate, Resochin® batch no. 29015T, expiration date 6/2004; PT Bayer, Cibubur, Indonesia) or oral SP tablets (Fansidar® batch no. JO32210, expiration date 6/2006; PT Roche, Bogor, Indonesia). Chloroquine was dispensed over a three-day period (25 mg base/kg: 10 mg/kg on days 1 and 2 and 5 mg/kg on day 3), and SP as a single dose (25 mg/kg of sulfadoxine and 1.25 mg of pyrimethamine/kg) of no more than three tablets per subject on day 1. All therapy was observed, and each subject was monitored for one hour after dosing by the health center’s staff. Subjects who vomited during this period were given another complete dose. When indicated, paracetamol (one dose given at the health center and another to be taken at home), was provided to febrile subjects with a temperature greater than 38.5°C to increase treatment compliance.

Subjects were observed for up to 28 days and were asked to return to the clinic on days 1, 2, 3, 7, 14, 21, and 28. During each follow-up visit, the axillary temperature was measured and a blood sample was obtained by finger prick for thick and thin blood smear examination, except on day 1 where only a clinical evaluation was conducted. Subjects who did not clear their parasitemia or developed recurrent parasitemia during the follow-up period were treated with oral quinine (10 mg/kg orally three times a day for seven days) and primaquine (15 mg of base orally once a day for five days). Measurement of glucose-6-phosphate dehydrogenase (G6PD) activity is not standard practice in Indonesia, and subjects were not screened for G6PD deficiency before initiating primaquine rescue therapy. Instead, they were asked to inform the study team and discontinue treatment immediately if they experienced passage of dark urine at any time during primaquine use.

Treatment outcomes were characterized as either cure, early treatment failure (ETF), or late treatment failure (LTF). Subjects were classified as having ETF if they met any of the following criteria during the first three days (days 1, 2, and 3) of treatment: 1) development of severe malaria on days 1, 2, or 3 in the presence of parasitemia; 2) parasitemia on day 3 with an axillary temperature ≥ 37.5°C; 3) a parasite count on day 2 ≥ 75% of that on day 0; or 4) parasitemia on day 3 ≥ 25% of the count on day 0. Subjects were categorized as having ETF if they developed one of the following criteria during the follow-up period beginning on day 4 (days 4–28): 1) signs of severe malaria in the presence of parasitemia; or 2) parasitemia with or without fever. Subjects were classified as having adequate clinical and parasitologic response if they did not meet any of the criteria for ETF or LTF during the 28 days of follow-up.

Other measured outcomes included fever and parasite clearance times. Fever clearance was defined as reduction of temperature below 37.5°C after initiation of treatment. Because temperatures were measured only once a day, comparison between the CQ and SP treatment groups was limited to daily intervals for rate of fever clearance and mean fever clearance time. Similarly, parasite clearance, i.e., negative blood smear for asexual parasites, was measured in day intervals from initiation of treatment. Treatment failures because of persistent parasitemia (ETF and LTF) were excluded from parasite clearance time calculations because rescue therapy would interfere with assessment of the primary treatment.

**Presence of antimalarial drug in urine.** The concentrations of CQ and SP in urine were measured qualitatively using the Dill Glazko and Lignin tests, respectively. Two milliliters of a subject’s urine were mixed with 10 drops of Dill Glazko reagent in a 10-mL tube. A change of color from yellow to violet indicated presence of chloroquine in the sample. For Lignin tests, 1–2 drops of a subject’s urine were placed on clean tissue paper, followed by the addition of one drop of 25% HCl solution. Appearance of a yellow to orange color indicated presence of a sulfonamide in the urine.

**Statistical analysis.** Data were analyzed using SPSS version 11.0 (SPSS, Inc., Chicago, IL) software. Discrete data were analyzed using either a chi-square test, with or without Yates’ correction, or Fisher’s exact test. Continuous data were compared using Student’s t-test after Levene’s test for homogeneity of variance, or when failing the homogeneity test, the Mann-Whitney test for analysis of non-parametric data. The level of statistical significance was set at $P < 0.05$.

**RESULTS**

**Subject characteristics.** Among 114 study subjects, 15 in the CQ group and 10 in the SP group did not complete the study. Eight subjects in the CQ group and 5 in the SP group dropped out for personal reasons, most commonly, movement to a new home outside the study area. An additional 7 subjects in the CQ group and 5 in the SP group developed *P. vivax* infection after study treatment and therefore were excluded from further participation. The number of subjects lost to follow-up between the CQ and SP groups were not significantly different ($P > 0.05$, Table 1). The number of individuals for whom a study outcome could be assessed was 42 and 47 for the CQ and SP groups, respectively.

Both treatment groups were comparable in distribution of age, sex, body weight, axillary temperature, and parasite den-
sity (Table 1). Before treatment, approximately 20% of the subjects in each group had evidence of CQ in their urine, while no subject demonstrated a sulfonamide. The small difference in febrile case incidence between treatment groups was not statistically significant.

Response to CQ and SP. Among 17 febrile subjects treated with CQ, 94% (16 of 17) cleared fever by day 1 compared with only 68% (15 of 22) of the subjects treated with SP. The mean fever clearance time was longer in the SP group compared with CQ group (1.33 days versus 1.06 days; \(P = 0.048\)). Of the 42 CQ and 47 SP treatment subjects, 8 and 2 treatment failures, respectively, were excluded from parasite clearance analysis because of persistent parasitemia. Parasite clearance time was greater in the CQ group compared with the SP group (mean \(\pm\) SD = 3.88 \(\pm\) 1.93 days versus 3.00 \(\pm\) 1.34 days, \(P = 0.027\)). The parasite clearance rates in the CQ group on days 2, 3, and 7 were 18% (6 of 34), 74% (25 of 34), and 100% (34 of 34), respectively, while the SP group clearance rates on the same days were 36% (16 of 45), 91% (41 of 45), and 100% (45 of 45), respectively.

During the entire study, no significant adverse events were observed in subjects. One child in the SP group developed nausea without emesis during drug administration. By day 1, the child showed clinical improvement and was later classified as having an adequate clinical response at the end of the 28-day follow-up period. No subject demonstrated signs or symptoms of severe malaria after beginning either treatment, and none require in-patient hospitalization. Among subjects requiring follow-up rescue therapy for primary treatment failure, none developed clinical signs suggestive of primaquine-induced hemolytic anemia.

**In vivo 28-day test.** The 28-day cumulative incidence of CQ treatment failure was 69%; 7% (3 of 42) were classified as ETF, and the remaining 26 failures as LTF occurring between days 7 and 28 (Table 2). Only four treatment failures (8.5%) occurred in the SP treatment group by day 28. One subject experienced ETF and 3 had LTF, 2 on day 7 and 1 on day 28. The cure rate with SP was 91.5% (43 of 47).

To assess for a possible association between age and treatment outcome, regardless of treatment group, treatment outcomes were compared between subjects < 10 years of age (n = 34) and those \(\geq\) 10 years of age (n = 55) (Table 3). Treatment failures occurred more frequently in the younger age group (relative risk 2.49, 95% confidence interval = 1.43–4.32).

**Development of gametocytes after drug administration.** At the beginning of treatment, the gametocyte carriage rate was similar between the CQ and SP groups (Figure 1). Both treatment groups experienced an increasing gametocyte carriage rate after treatment, but to a much higher degree in the SP group compared with the CQ group. Gametocyte carriage

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### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CQ Group</th>
<th>SP Group</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>42</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD age, years (range)</td>
<td>16.4 ± 12.7 (2.6–56)</td>
<td>14.3 ± 9.7 (1.1–56)</td>
<td>0.388</td>
</tr>
<tr>
<td>Children &lt; 10 years old</td>
<td>45.2% (19/42)</td>
<td>31.9% (15/47)</td>
<td>0.1965</td>
</tr>
<tr>
<td>Males</td>
<td>50% (21/42)</td>
<td>46.8% (22/47)</td>
<td>0.699</td>
</tr>
<tr>
<td>Mean ± SD axillary temperature, °C (range)</td>
<td>37.2 ± 1.1 (35.2–39.4)</td>
<td>37.5 ± 1.2 (36–40)</td>
<td>0.181</td>
</tr>
<tr>
<td>Fever rate</td>
<td>40.5% (17/42)</td>
<td>46.8% (22/47)</td>
<td>0.699</td>
</tr>
<tr>
<td>Mean ± SD parasite density/μL of blood (range)</td>
<td>7,487 ± 2,700 (1,000–56,720)</td>
<td>10,186 ± 3,600 (1,000–193,040)</td>
<td>0.210</td>
</tr>
<tr>
<td>Mean ± SD body weight, kg (range)</td>
<td>37.2 ± 19.4 (10–75)</td>
<td>33.2 ± 16.1 (7.7–76)</td>
<td>0.576</td>
</tr>
<tr>
<td>Positive urine test result</td>
<td>Dill Glazko (CQ)  20% (8/40)</td>
<td>23.9% (11/46)</td>
<td>0.6626</td>
</tr>
<tr>
<td></td>
<td>Lignin (SP)  0% (0/40)</td>
<td>0% (0/46)</td>
<td>–</td>
</tr>
<tr>
<td>Incomplete follow-up</td>
<td>Drop out  14% (8/57)</td>
<td>8.8% (5/57)</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>Withdrawn  8.8% (5/57)</td>
<td>8.8% (5/57)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* CQ = chloroquine; SP = sulfadoxine-pyrimethamine.

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### Table 2

In vivo 28-day cumulative incidence of uncomplicated *Plasmodium falciparum* treatment failure in subjects randomized to receive CQ or SP

<table>
<thead>
<tr>
<th>Group</th>
<th>ETF</th>
<th>LTF</th>
<th>ACPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ</td>
<td>7.1% (3/42)</td>
<td>31% (13/42)</td>
<td>69.1% (29/42)</td>
</tr>
<tr>
<td>SP</td>
<td>2.1% (1/47)</td>
<td>91.5% (43/47)</td>
<td>89.5% (23/26)</td>
</tr>
</tbody>
</table>

† Number of subjects developing recurrent asexual stage parasitemia during interval.

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### Table 3

In vivo 28-day test results grouped by age and regardless of treatment provided (CQ or SP)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Failure</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>58.8% (20/34)</td>
<td>41.2% (14/34)</td>
</tr>
<tr>
<td>≥10</td>
<td>23.6% (13/55)</td>
<td>76.4% (42/55)</td>
</tr>
</tbody>
</table>

* CQ = chloroquine; SP = sulfadoxine-pyrimethamine.
the SP treatment success rate observed in this trial is 50%, with failure rates greater than 50% in certain areas of the country. In eastern Africa, where SP has been used as first-line therapy for uncomplicated \textit{P. falciparum} infection since 1993, treatment success rates have remained high and, according to country health officials, still recommend its use.10 Similarly, high SP cure rates have been reported in Ghana and Gabon.16,24 In contrast, other countries in Africa have experienced relatively poor outcomes when using SP alone against \textit{P. falciparum}, with failure rates as high as 66% in Zaire and 74% in Tanzania.25,26 High level resistance to SP by \textit{P. falciparum} has also been reported from South America.27,28 These variable findings affirm the need for well-controlled clinical trials to assess area-specific efficacy of SP for the treatment of uncomplicated \textit{P. falciparum} malaria.

In Alor in the eastern part of Indonesia, we confirmed >91% efficacy of SP for the treatment of uncomplicated \textit{P. falciparum} malaria. With the exception of fever clearance time, SP was found superior to CQ for the treatment of \textit{P. falciparum} in this study population. The shorter fever clearance time observed in the SP group may be related to the known anti-inflammatory properties of CQ.29,30 With the exception of one study conducted in Papua (formerly Irian Jaya), where SP treatment failure rates were greater than 50%,31 the SP treatment success rate observed in this trial is similar to that observed in other SP treatment trials conducted in eastern Indonesia.32–34 In western Indonesia, reasonably good efficacy is reported for SP in central Java (78% treatment success at day 28)35 which contrasted dramatically with a 83% failure rate observed for SP treatment of uncomplicated \textit{P. falciparum} malaria in Nias Island in northern Sumatra.36

The success of antimalarial treatment is influenced by many factors. The putative role of genetic mutations impacting parasite drug handling have been described.37 Drug metabolism as well as host immune status can influence treatment outcomes,38 with the role of immunity clearing parasitemia having been documented.39–40 Several studies have also examined the impact of host age and malaria exposure (number of prior infections), as indicators of acquired immunity, on the clearance of infection after CQ treatment.41,42 In Alor, subjects greater than 10 years old were significantly more likely to clear infection after CQ treatment than their younger counterparts (interestingly, in the SP group three of four treatment failures were in individuals ≥10 years old). In a location with high-level CQ resistance, continued CQ monotherapy would therefore place young children, who generally lack sufficient clinical immunity, at greater risk of severe morbidity and mortality.

When considering the public health implications of antimalarial treatment regimens for prevention of transmission, drug choice can have important relevance. Neither CQ nor SP have any significant gametocytocidal activity;43,44 however, post-treatment gametocytemia has been shown to be influenced by these drugs.45–46 In our study, gametocyte carriage rates were significantly higher and persisted longer after treatment with SP compared with CQ. These findings are similar to other reports when comparing SP and CQ monotherapy against \textit{P. falciparum}.45–48 \textit{Plasmodium falciparum} gametocyte rates are highest when SP is used against SP-resistant infections, and persistent gametocytemia may be related to longer parasite clearance times associated with select dihydrofolate reductase mutations, even if SP ultimately cures infection.49 These findings markedly contrast an earlier study showing gametocyte carriage rates significantly lower in the SP group one month following treatment compared with either CQ or amodiaquine.50 Studies of post-treatment gametocyte infectivity in mosquitoes have not resolved these conflicting reports. Although a sporontocidal effect of SP has been reported, gametocytes from SP-treated blood yield higher infectivity rates in \textit{An. arabiensis} and \textit{An. gambiae} than those from CQ-treated blood.51 However, in another SP and CQ treatment trial in which all circulating gametocytes cleared by day 28, pre-clearance infectivity of \textit{An. arabiensis} was shown to be enhanced by CQ and suppressed by SP.52 Based on these conflicting results, further investigations of the impact of SP on gametocyte carriage and infectivity of mosquitoes are needed. Combination treatment regimens incorporating SP with another chemotherapeutic agent significantly reduces gametocyte carriage rates. Combinations of CQ or amodiaquine and SP can significantly reduce gametocyte rates when compared with treatment with either CQ or SP alone.12,50 In central Java, where \textit{P. falciparum} resistance to CQ and SP has approached 47% and 22%, respectively,53 combining SP with CQ has dramatically reduced the odds of treatment failure compared with CQ alone, although the gametocyte carriage rates were not significantly reduced (Maguire JD, unpublished data). However, a single dose of primaquine (45 mg of base) added to either regimen (CQ or CQ plus SP) signifi-
cantly reduced gametocyte carriage rates and clearance times. Combining SP with drugs such as artesunate that have reputed gametocytocidal activity can also reduce carriage rates post-treatment.44,47,48 Combination treatments such artesunate plus SP, CQ plus SP or CQ plus SP plus primaquine may provide inexpensive, well-tolerated alternatives to current treatment regimens in regions with high level resistance to monotherapy. Not only could combination therapy improve cure rates, but such treatments could also potentially reduce transmission and the overall malaria burden in communities.

Combination therapy with CQ and SP has been adopted as the first-line treatment for uncomplicated P. falciparum infections in several Asian and Pacific countries (Malaysia, Papua New Guinea, and Vanuatu).51 Concomitant CQ and SP administration appears superior in improving both parasite and fever clearance times over sequential treatment.52 Although not an ideal combination, CQ plus SP, because of its relatively low cost, availability, ease of administration, safety and efficacy profile, and better gametocyte suppression effects may be a preferable first-line treatment compared with SP alone in CQ-resistant areas.12,18,53

In Alor, SP was shown to be highly efficacious for the treatment of uncomplicated P. falciparum malaria compared with CQ alone. Since SP-resistant P. falciparum is an increasing concern in Indonesia,35,36,54 use of combination CQ plus SP therapy for uncomplicated P. falciparum malaria may provide a far more effective alternative to currently recommended monotherapy regimens in the face of multidrug resistance. Further evaluation of this combination for efficacy and impact on gametocyte carriage rates is required before a nation-wide treatment revision can be recommended. In areas where combination therapy now seems most appropriate, compulsory periodic reassessment using an in vivo test format would be highly recommended to monitor drug efficacy.

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