The Effect of Primaquine on Gametocyte Development and Clearance in the Treatment of Uncomplicated Falciparum Malaria With Dihydroartemisinin-Piperaquine in South Sumatra, Western Indonesia: An Open-Label, Randomized, Controlled Trial

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(See the Editorial Commentary by Dondorp on pages 694–6 and the Electronic Article by Das et al on pages e48–e58.)

Background. Artemisinin-based combination therapy is very effective in clearing asexual stages of malaria and reduces gametocytemia, but may not affect mature gametocytes. Primaquine is the only commercially available drug that eliminates mature gametocytes.

Methods. We conducted a 2-arm, open-label, randomized, controlled trial to evaluate the efficacy of single-dose primaquine (0.75 mg/kg) following treatment with dihydroartemisinin-piperaquine (DHP) on Plasmodium falciparum gametocytemia, in Indonesia. Patients aged ≥5 years with uncomplicated falciparum malaria, normal glucose-6-phosphate dehydrogenase enzyme levels, and hemoglobin levels ≥8 g/dL were assigned by computerized-generating sequence to a standard 3-day course of DHP alone (n = 178) or DHP combined with a single dose of primaquine on day 3 (n = 171). Patients were seen on days 1, 2, 3, and 7 and then weekly for 42 days to assess the presence of gametocytes and asexual parasites by microscopy. Survival analysis was stratified by the presence of gametocytes on day 3.

Results. DHP prevented development of gametocytes in 277 patients without gametocytes on day 3. In the gametocytemic patients (n = 72), primaquine was associated with faster gametocyte clearance (hazard ratio = 2.42 [95% confidence interval, 1.39–4.19], P = .002) and reduced gametocyte densities (P = .018). The day 42 cure rate of asexual stages in the DHP + primaquine and DHP-only arms were: polymerase chain reaction (PCR) unadjusted, 98.7% vs 99.4%, respectively; PCR adjusted, 100% for both. Primaquine was well tolerated.

Conclusions. Addition of single-dose 0.75 mg/kg primaquine shortens the infectivity period of DHP-treated patients and should be considered in low-transmission regions that aim to control and ultimately eliminate falciparum malaria.

Clinical Trials Registration. NCT01392014.

Keywords. primaquine; dihydroartemisinin-piperaquine; gametocyte P. falciparum; Indonesia.

The World Health Organization recommends that a single dose of primaquine (PQ) be added to standard blood schizonticidal therapy of Plasmodium falciparum malaria because of its gametocidal effect and
potential transmission-blocking activity [1]. Primaquine is a member of the 8-aminooquinolines approved by the US Food and Drug Administration in 1952 and one of the older antimalarials still in widespread use. Its use has received renewed attention with the increased interest in malaria elimination [2]. However, the use of PQ to reduce malaria transmission is controversial. Although it only adds $0.05 to the cost of therapy [3], PQ can cause severe and occasionally life-threatening hemolysis in patients with severe glucose-6-phosphate dehydrogenase (G6PD) deficiency. Moreover, the artemisinins themselves, which are part of artemisinin-based combination therapy (ACT), are very efficient in inhibiting the growth of asexual stages, thereby indirectly inhibiting the development of *P. falciparum* gametocytes by reducing the asexual stage progenitors [4, 5]. Furthermore, numerous in vitro studies suggest that artemisinin derivatives may directly inhibit the development of young *P. falciparum* gametocytes into mature gametocytes [6, 7]. Mature gametocytes can be present in the peripheral circulation for several weeks to allow ingestion by the mosquito vector [8]. Hence, antimalarial drug treatments that can reduce the development of these late-stage gametocytes may play a key role in the elimination of malaria transmission. However, some studies suggest that artemisinins alone or in combination with other drugs merely reduce the number of immature gametocytes and are not effective in eradicating all mature gametocytes; consequently, patients undergoing ACT may remain infectious for 2–4 weeks [9–14]. Thus, additional drugs such as PQ that act directly against mature gametocytes may be needed to eliminate transmission in communities [1, 15].

In Indonesia, dihydroartemisinin-piperaquine (DHP) has been the first-line treatment for both uncomplicated *P. falciparum* and *Plasmodium vivax* infections since 2010. The risk of *P. falciparum* gametocytemia is higher after treatment with DHP than with other ACTs, possibly reflecting the relatively lower dose of artemisinins in DHP [16]. The national policy also includes the use of a single dose of PQ 0.75 mg/kg in addition to DHP; however, with the exception of the bigger health centers and hospitals, screening for G6PD deficiency is usually unavailable, limiting the implementation of the recommended doses. Further, the effectiveness of primaquine in reducing gametocytes has never been evaluated in DHP-treated patients in Indonesia. The present trial was designed to determine the risk-benefit profile of a single dose of PQ when given directly following treatment with DHP.

**MATERIALS AND METHODS**

**Study Site**
The study was conducted between December 2008 and March 2010 at Hanura Primary Health Center, Padang Cermin district, Lampung province (105°45’–103°48’E and 3°45’–6°45’S) located at the southern end of Sumatra. The health center was the only place in the immediate area providing artemisinin-based combination drugs for antimalarial treatment. Nearby abandoned shrimp cultivation ponds provide larval habitat for *Anopheles sundaicus*, an efficient and important malaria vector in the region [17]. Seasonal malaria transmission peaks following the rainy season between September and April. At the time of the study, artesunate-amodiaquine with a single dose of PQ was the first-line therapy for patients with *P. falciparum* infection. High-grade chloroquine resistance to both *P. falciparum* and *P. vivax* is well established in the area [18]. Community-based surveys showed that the study area had low malaria endemicity with a malaria prevalence of 1.8% across all age groups at the time of this study (Sutanto et al, unpublished data).

**Participants**
This was a single-center, open-label, 2-arm, randomized, controlled superiority trial in patients with fever or a history of fever within the past 24 hours with microscopically confirmed *P. falciparum* infection, regardless of the presence of gametocyte stages. Inclusion criteria consisted of (1) parasite density ≥1000 parasites/µL; (2) age ≥5 years; (3) normal glucose-6-phosphate dehydrogenase (G6PD) enzyme levels based on a qualitative test; (4) hemoglobin level ≥8 g/dL; (5) negative pregnancy test (assessed by human chorionic gonadotropin urine test) or not breastfeeding; (6) no signs of severe malnutrition; (7) no other chronic diseases; (8) no history of allergy to the study drugs; (9) ability to return for 42 days of follow-up. A history of previous antimalarial drug use was not an exclusion criterion. The protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Indonesia, Jakarta.

**Procedures**
Subjects received a standard 3-day course of DHP (fixed-dose tablets of 40 mg dihydroartemisinin and 320 mg piperaquine; D-ARTEPP, Guilin Pharmaceutical Co, Ltd) with primaquine (DHP + PQ arm) or without it (DHP-only arm). The daily DHP regimen was based on weight (>41 kg: 3 tablets; 31–40 kg: 2 tablets; 18–30 kg: 1 tablet). The total dose of dihydroartemisinin ranged 4–10.9 mg/kg, and piperaquine ranged 32–87.3 mg/kg. In the DHP + PQ arm, a single dose of PQ (15 mg base, PT Phapros Tb) was given on day 3 to achieve a dose of 0.75 mg/kg, rounded to the nearest half tablet. The mean dose was 0.74 mg/kg (range, 0.5–0.94 mg/kg). Modeling has suggested that the greatest impact of primaquine on gametocytes can be achieved by administrating primaquine on day 8 after the start of symptoms [19]. Self-treatment and corresponding delay in seeking care from health centers are common in Indonesia, such that many patients attend clinic.
several days after the onset of symptoms. We therefore chose to administer PQ on day 3 to maximize the delay of PQ administration while minimizing the impact on compliance.

All treatment doses were given as directly observed therapy by the healthcare attendants. If the patient vomited within 30 minutes, the same dose was repeated. If drug vomiting reoccurred, the subject was excluded. Before taking the tablets, each subject ate biscuits provided by the study. Both manufacturers provided certificates of analysis for the batches used in the study, and fulfilled standards for good manufacturing practices in China and Indonesia, respectively.

Subjects with fever (≥38.5°C using tympanic membrane measurement) received acetaminophen (paracetamol). Subjects were requested to return to the health center on days 1, 2, 3, 7, 14, 21, 28, 35, and 42, and any other day in between if they felt ill. At each scheduled visit (except on day 1) a finger-prick blood sample was collected for malaria blood smears and dried blood blots for parasite genotyping (100 µL of blood on Whatman FTA filter paper). Patients found to be parasitemic on day 7 or later were treated with quinine (3 × 10 mg/kg/day for 7 days). Compliance or outcome following treatment with quinine was not monitored.

Thick and thin blood smears were stained with 3% Giemsa solution for 40 minutes. The number of asexual parasites was counted against 200 leukocytes and expressed per microliter assuming a leukocyte count of 8000 cells/µL blood. If <10 parasites were detected in the first 200 leukocytes, counting was continued against 500 leukocytes. If no parasites were detected, 100 fields were examined before a smear was declared negative. The counting of sexual-stage parasites was always against 500 leukocytes. Blood smears were read independently by 2 laboratory technicians, in the field (unblinded to the treatment allocation) and in the central laboratory in Jakarta (blinded). In case of disagreement, a third reader (blinded) reread the slide and final results were based on the third reader’s evaluation. Parasite densities were determined using the average parasite counts from both technicians. Hemoglobin levels were assessed on days 0, 7, 14, 21, 28, 35, and 42 using a HemoCue system (Hb 201+, Angelholm, Sweden). G6PD deficiencies were assessed on days 0, 7, and 42 using a HemoCue system (Hb 201+, Angelholm, Sweden). G6PD deficiency was defined using qualitative assays based on the fluorescent spot test (Trinity Biotech, cat no. 203-A).

Molecular analysis to distinguish reinfections from recrudescences of *P. falciparum* was performed at the Eijkman Institute, Jakarta, by genotyping GLURP, MSP2, and MSP1 in paired samples of treatment failures [20, 21].

**Randomization and Masking**

A computerized randomization sequence was prepared in advance. Block sizes of 4 were used to ensure equal distribution across the study arms by time. Allocation concealment was achieved by using prenumbered opaque and sealed envelopes. Eligible subjects were randomized sequentially by drawing successive envelopes according to their order on the patient list at the healthcare center.

**Outcomes and Sample Size**

The main objective was to determine the effect of the standard single dose of primaquine in addition to the completed 3-day treatment with DHP on gametocyte carriage. This was done by comparing the overall risk of gametocyte carrierage on day 7 and then weekly till day 42, to measure the combined effect on gametocyte development and clearance (primary endpoint). This 2-arm trial required 165 patients per arm to detect a 7% absolute reduction in the prevalence of gametocytes following the week after treatment with primaquine from 9% in the DHP-only arm to 2% in the DHP + PQ arm with 80% power and a 2-sided α of .05. The anticipated gametocyte prevalence of 9% was based on the day 7 prevalence in an earlier study with DHP (Sutanto et al, unpublished data). We planned to recruit 200 patients per arm, to allow for 17.5% loss to follow-up, but recruitment was stopped earlier because the success rate of follow-up was higher than anticipated.

We also assessed the impact on gametocytes using the following secondary endpoints: (1) the gametocyte clearance rates by day 42 in patients with gametocytes on day 3, (2) the incidence of gametocyte development by day 42 in patients who were gametocyte free on day 3, and (3) gametocyte densities between days 3 and 42 inclusive. Other endpoints included the effect of primaquine on recurrence of the asexual stages of *P. falciparum*, polymerase chain reaction (PCR) adjusted and unadjusted for reinfections.

Adverse events were evaluated using a questionnaire prompting for symptoms of headache, weakness, nausea, vomiting, abdominal pain, diarrhea, itching, and paresthesia.

**Statistical Analysis**

Modified intent-to-treat analysis of the effect of PQ was used, and the evaluable population included all patients that were seen on day 3. Patients who withdrew, were lost to follow-up, or had protocol deviations before day 3 inclusive were excluded from the analysis; however they were included if these events occurred after day 3.

Data were analyzed using Stata software, version 10.0. Differences in gametocyte prevalence were compared using the prevalence ratio (PR) and corresponding 95% confidence interval (CI), along with P values using χ² test or Fisher exact test. The therapeutic response to treatment was assessed by calculating the cumulative risks of recurrence of asexual parasites (unadjusted and PCR adjusted for reinfections by genotyping) and compared by survival analysis using the Kaplan-Meier product limit formula [22]. In the PCR-unadjusted
analysis, recurrences were treated as treatment failures and all other events (withdrawal, protocol deviations, occurrence of *P. vivax*) resulted in censoring at the time of that event, or at the time of their last follow-up visit in case of loss to follow-up. A similar strategy was used for the PCR-adjusted analysis except that patients with new *P. falciparum* infections were censored at

*Figure 1.* Trial profile. *All 374 patients who provided informed consent and were screened for glucose-6-phosphate dehydrogenase deficiency were found to have normal levels of enzyme activity. **Five subjects failed screening; 4 had mixed infections with *Plasmodium vivax* and 1 was infected by *P. vivax* instead of *Plasmodium falciparum*. ***Seven individuals allocated to the dihydroartemisinin-piperaquine (DHP)–only arm were accidently given DHP plus primaquine (DHP + primaquine [PQ]) owing to human error. To maintain the balance within the block randomization, 7 subjects randomized to the DHP + PQ group within the same blocks of 4 were also excluded. Abbreviation: DHP, dihydroartemisinin-piperaquine.*
RESULTS

Evaluable Population
A total of 374 individuals were randomized; 186 received DHP-PQ and 188 DHP-only. Of the 374, 25 (6.6%) were excluded from analysis (15 and 10 subjects from the DHP + PQ and DHP-only groups, respectively; Figure 1). Thus 171 subjects in the DHP + PQ group and 178 subjects in the DHP-only group contributed to the modified intent-to-treat analyses (who had completed the follow-up period). No one developed microscopically patent gametocytes among the patients who were gametocyte free on day 3. Among those who were gametocytemic on day 3, patients in the DHP-only group remained gametocytemic for longer (hazard ratio [HR], 2.42 [95% CI, 1.01–5.71], P = .049; Figure 3). The geometric mean gametocyte densities were lower in the DHP-only group (157/µL vs 260/µL, P = .036).

Table 1. Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Without Gametocytes on Day 3</th>
<th>With Gametocytes on Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects, No.</td>
<td>171</td>
<td>178</td>
</tr>
<tr>
<td>Male/female</td>
<td>107/64</td>
<td>107/71</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>20 (11–31)</td>
<td>17 (10–30)</td>
</tr>
<tr>
<td>Body weight, kg, median (IQR)</td>
<td>45.0 (25.0–55.0)</td>
<td>45.0 (24.0–55.0)</td>
</tr>
<tr>
<td>Body temperature, °C, mean (SD)</td>
<td>35.7 (0.7)</td>
<td>35.7 (0.6)</td>
</tr>
<tr>
<td>History of duration of illness, d, median (IQR)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL, mean (SD)</td>
<td>13.3 (2.19)</td>
<td>13.3 (2.08)</td>
</tr>
<tr>
<td>Density of asexual stage on day 3, per µL, mean (SD)</td>
<td>NF</td>
<td>NF</td>
</tr>
<tr>
<td>Gametocytemia on day 3, No. (%)</td>
<td>41 (24.0)</td>
<td>31 (17.4)</td>
</tr>
<tr>
<td>Gametocyte density on day 3, per µL, median (IQR)</td>
<td>128 (52–260)</td>
<td>196 (88–552)</td>
</tr>
<tr>
<td>History of self-treatment prior to health center, No. (%)</td>
<td>39 (22.8)</td>
<td>32 (18.5)</td>
</tr>
</tbody>
</table>

Abbreviations: DHP, dihydroartemisinin-piperaquine; IQR, interquartile range; NF, not found; PQ, primaquine; SD, standard deviation.
Figure 2. Gametocyte prevalence and prevalence ratio of the 2 regimens (black bar = dihydroartemisinin-piperaquine (DHP) plus primaquine; white bar = DHP alone) during the 42-day follow-up period. Abbreviations: CI, confidence interval; DHP, dihydroartemisinin-piperaquine; PQ, primaquine.

Figure 3. Kaplan-Meier survival curves of gametocyte clearance by treatment regimen. Abbreviations: CI, confidence interval; DHP, dihydroartemisinin-piperaquine; PQ, primaquine.
Table 2. Tolerance of Dihydroartemisinin-Piperaquine (DHP) Plus Primaquine vs DHP Alone by Day 7

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>DHP + PQ, No. (%)</th>
<th>DHP-only, No. (%)</th>
<th>PR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>13/97 (13.4)</td>
<td>18/96 (18.8)</td>
<td>0.71 (.37–1.38)</td>
<td>.312</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13/93 (14.0)</td>
<td>11/96 (11.5)</td>
<td>1.22 (.58–2.58)</td>
<td>.603</td>
</tr>
<tr>
<td>Nausea</td>
<td>1/139 (0.7)</td>
<td>4/150 (2.7)</td>
<td>0.27 (0.03–2.40)</td>
<td>.205</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1/163 (0.6)</td>
<td>1/168 (0.6)</td>
<td>1.03 (.07–16.34)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4/156 (2.6)</td>
<td>4/170 (2.4)</td>
<td>1.09 (.28–4.28)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1/163 (0.6)</td>
<td>3/172 (1.7)</td>
<td>0.35 (0.04–3.35)</td>
<td>.623</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0/170 (0.0)</td>
<td>0/177 (0.0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2/161 (1.2)</td>
<td>2/170 (1.2)</td>
<td>1.06 (1.5–7.41)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Evaluable population includes only patients without the symptoms on day 3. Abbreviations: CI, confidence interval; DHP, dihydroartemisinin-piperaquine; PQ, primaquine; PR, prevalence ratio.

[95% CI, 111–222] vs 330/µL [95% CI, 197–554]; geometric mean ratio 0.47 [95% CI, .26–.88], P = .018.

Therapeutic Response on Asexual Stages by Day 42

Primaquine did not affect asexual stages of *P. falciparum*. The PCR-unadjusted recurrence rates were 1.3% (2 subjects) and 0.6% (1 subject) in the DHP + PQ and DHP-only groups, respectively (HR, 0.87 [95% CI, .39–1.97], P = .913). Molecular genotyping suggested that all 3 recurrences were due to reinfections.

**Hemoglobin Measurements and Adverse Events**

Hemoglobin levels were much the same between the 2 study arms (day 0: mean difference [MD], −0.09 g/dL [95% CI, −.54 to .36]; day 7: MD, −0.02 g/dL [95% CI, −.43 to 0.39]; day 42: MD, −0.03 g/dL [95% CI, −0.39 to 0.33]). The main complaints reported on day 7 were headache, fatigue and weakness, nausea and vomiting, abdominal pain, diarrhea, pruritus, and paresthesia, with similar numbers in both arms (Table 2).

**DISCUSSION**

Dihydroartemisinin-piperaquine effectively treated falciparum malaria and successfully prevented the appearance of new gametocytes detectable by microscopy. The addition of a single dose of PQ reduced gametocyte densities and enhanced gametocyte clearance and shortened the median clearance time by about 1 week, resulting in overall lower gametocyte carriage. By day 14, gametocytes were undetectable in all but 1 patient (0.6%) taking DHP + PQ compared to 9.6% (17 patients) taking DHP alone. Primaquine had no additional effect against asexual blood stages of *P. falciparum*. These results are consistent with previous reports in symptomatic malaria patients treated with artemisinins or ACTs showing that a single dose of PQ suppresses and quickly eliminates persistent mature blood-stage gametocytemia that were not affected by the artemisinins [12, 23–24].

Concerns exist about the potential for a one-off dose of PQ to induce hemolysis, especially in G6PD-deficient individuals [25]. A recent study from Tanzania suggested that coadministration of artemisinins with PQ may be associated with mild asymptomatic hemolysis and transient reductions in hemoglobin concentrations even in individuals with the wild-type genotype [26]. This study used genotyping and screened for the most common mutation associated with G6PD deficiency in Tanzania (G6PD A). As 140 mutations are known to be potentially associated with G6PD deficiency, one possible explanation suggested by the authors is that patients with less common mutations causing G6PD deficiency may have been misclassified. Functional screening tests based on enzyme activity that measures the NADPH production capacity of G6PD, such as used in our study, do not have this limitation. We found that mean hemoglobin concentrations by day 7 and 42 were similar in both groups in this selected sample. However, the sample size was too small to draw more definitive conclusions about the safety of a single dose of 0.75 mg/kg PQ, as the study was not designed with safety as primary endpoint and excluded patients with G6PD deficiency.

There is typically a 7- to 15-day delay after the initial acute attack for mature *P. falciparum* gametocytes to become apparent. The timing of the single dose of primaquine is therefore important, especially because with a half-life of about 8 hours, primaquine is effective only for a few days. In Thailand, gametocytemia peaked 3 days after start of treatment with artemisinins, and gametocytes emerged in about one-quarter of patients after treatment [27]. The median duration of the history of fever prior to treatment was 5 days, consistent with models by Lawpoolsri et al predicting a maximum gametocytemia 8 days after the onset of symptoms [19]. In Indonesia, similar delays in seeking care are common. We therefore provided PQ the day after the last dose of DHP to maximize the delay of PQ administration.

There are several study limitations: This was an unblinded study, so all parties involved were potentially aware of the treatment allocation. Second, we omitted 14 patients from the analysis because 7 patients randomized to the DHP-only group were accidentally provided PQ. The allocation sequence concealment was good, and there was no indication that this was due to preferential treatment by study staff. Third, our study reflects the impact on microscopically detectable gametocytemia and does not exclude the persistence of subpatent gametocytemia detectable by PCR. Our results, however, are consistent with one previous treatment trial in Tanzania suggesting a marked benefit of primaquine in clearing submicroscopic gametocytes in symptomatic children receiving...
sulphadoxine-pyrimethamine-артемесунат [24]. By contrast, another trial in Sudan that aimed to eliminate submicroscopic gametocytes in asymptomatic carriers during the dry season found no effect of PQ [28]. They hypothesized that ACT alone is sufficient to clear gametocytes in asymptomatic carriers of submicroscopic infections, but that PQ is required in patients with acute malaria with higher parasite densities.

Although haphazardly implemented, the use of single-dose PQ to reduce malaria transmission of falciparum malaria is widely recommended. As countries move from malaria control to elimination, a better understanding of the risks and benefits of adding single-dose PQ to ACT has become increasingly important [23]. Because a relatively high proportion of patients had detectable gametocytes upon enrollment (21%), sick malaria patients constitute a significant source of transmissible malaria in this low-transmission areas. The addition of PQ could thus have a major effect on malaria transmission from treated patients by shortening the period of infectivity, consistent with previous observations in Myanmar [23] and other studies looking at the added value of PQ when provided in addition to ACT or artemisinins [24]. Combined, these findings support recommendations that in settings where screening for G6PD deficiency is feasible, a single gametocidal dose of PQ should be added to ACT in low-transmission regions that aim to control and ultimately eliminate falciparum malaria [1]. Further research is needed of PQ as an adjunctive gametocidal therapy under more programmatic conditions where routine screening for G6PD may not be feasible, including dose-finding studies to determine the minimal safe and effective dose [29].

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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