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## High-dose Primaquine Regimens against Relapse of *Plasmodium vivax* Malaria

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### Abstract

*Plasmodium vivax* causes debilitating but usually non-lethal malaria in most of Asia and South America. Prevention of relapse after otherwise effective therapy for the acute attack requires a standard daily dose of primaquine administered over 14 days. This regimen has < 90% efficacy in Thailand, and is widely regarded as ineffective because of poor compliance over the relatively long duration of dosing. We evaluated the efficacy, safety, and tolerability of alternative primaquine dosing regimens combined with artesunate among 399 Thai patients with acute, symptomatic *P. vivax* malaria. Patients were randomly assigned to one of six treatment groups: all patients received artesunate, 100 mg once a day for 5 days. Groups 1–5 then received primaquine, 30 mg a day for 5, 7, 9, 11, and 14 days, respectively. Group 6 received primaquine, 30 mg twice a day for 7 days. The 28-day cure rates were 85%, 89%, 94%, 100%, and 96%, respectively. Treatment of *P. vivax* malaria with artesunate for 5 days followed by high-dose primaquine, 30 mg twice a day for 7 days, was highly effective, well-tolerated, and equivalent or superior to the standard regimen of primaquine therapy.

### INTRODUCTION

*Plasmodium vivax*, the predominant species of malaria parasite, has a relapse mechanism that results in the reappearance of parasitemia arising from the pre-erythrocytic hepatic-stage hypnozoite.<sup>1</sup> This parasite affects millions of persons living in tropical areas and is an important cause of morbidity in Central and South America and Asia.<sup>2</sup> In Thailand, the current standard treatment for *P. vivax* malaria is chloroquine, 1,500 mg over 3 days, followed by primaquine, 15 mg a day for 14 days. The acute phase of a *P. vivax* infection has been successfully treated with chloroquine in Thailand<sup>3</sup> but not in eastern Indonesia.<sup>4</sup> Many studies in Thailand have demonstrated that the standard regimen of primaquine showed relatively high relapse rates.<sup>3–6</sup> Because higher doses of primaquine showed good

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efficacy against relapse in Thailand,<sup>7-9</sup> the observed poor efficacy of the standard regimen is often attributed to an intrinsic tolerance of primaquine by parasites in the region,<sup>4,10,11</sup> such as the well-known tolerance of the Chesson strain of *P. vivax* from New Guinea.<sup>12</sup>

Primaquine, an 8-aminoquinoline, has been the drug of choice for radical cure of *P. vivax* malaria since 1950. Although therapeutic application of primaquine is restricted because of its reported adverse events,<sup>13-17</sup> it is the only drug currently available to prevent relapse of *P. vivax* malaria. Numerous studies have shown relatively poor efficacy against relapse without supervision of compliance to the 14-day regimen. The regimen is widely viewed as impractical among malaria control officers. In light of the remarkably good safety and tolerability of a 30-mg regimen given for prophylaxis against malaria over prolonged periods,<sup>7,18</sup> some workers suggested abbreviated, higher-dose regimens of primaquine may improve the effectiveness of primaquine against relapse.<sup>19</sup>

Artesunate, a sodium salt of the hemisuccinate ester of artemisinin, has proven efficacious for treatment of blood stage *P. vivax* malaria.<sup>7,17,18</sup> Because chloroquine-resistant *P. vivax* malaria continues to develop and mixed infections with *P. falciparum* and *P. vivax* are not uncommon, especially in Southeast Asia,<sup>8,20,21</sup> artesunate may be a possible alternative treatment for acute *P. vivax* malaria in the future. This strategy, a single treatment for *P. falciparum* and *P. vivax* malaria, avoids risks to patients that hinge upon correct species diagnosis, i.e., receiving ineffective chloroquine therapy for a dangerous drug-resistant infection with *P. falciparum* diagnosed as *P. vivax* malaria.

The use of artesunate in the studies reported here offered the important advantage of avoiding the confounding effects of a drug such as chloroquine with its relatively long plasma half-life.<sup>22-24</sup> Lingering chloroquine in the blood suppresses relapse after ineffective primaquine therapy.<sup>25</sup> The rapid excretion of artesunate enabled us to assess the efficacy of primaquine against relapse within 28 days.<sup>26</sup> The objectives of this study were to determine the efficacy, safety, and tolerability of artesunate with selected regimens of primaquine and the parasite and fever clearance times.

## PATIENTS AND METHODS

The study was reviewed and approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Bangkok, Thailand). Before enrollment in the study, written informed consent was obtained from all patients. The study was a randomized, open-label, prospective study. Patients admitted to the Bangkok Hospital for Tropical Diseases were recruited if they were slide-positive for *P. vivax*, 12-60 years of age, weighed more than 30 kg, and agreed to remain in the hospital for 28 days. Reasons for exclusion included pregnancy, history of antimalarial drug treatment within the preceding two weeks, mixed *P. vivax* and *P. falciparum* infections, unwillingness to remain hospitalized for 28 days, and a glucose-6-phosphate dehydrogenase (G6PD) deficiency.

All patients received artesunate, 600 mg over 5 days and were then randomly assigned into 1 of 6 groups. Groups 1-5 received 30 mg of primaquine daily over durations of 5, 7, 9, 11, and 14 days, respectively. Group 6 received primaquine, 30 mg twice a day (60 mg a day) for 7 days.

Laboratory tests included a complete blood count and blood chemistry (liver and renal function tests), and urinalysis was performed prior to treatment and repeated weekly until patients were discharged. Hematologic tests were performed using ADVIA 120 (Bayer, Leverkusen, Germany) and the biochemistry tests were performed using INTEGRA 400 (Roche, Basel, Switzerland). A qualitative test of G6PD activity was performed using a rapid fluorescent spot (Beutler) test.<sup>27-29</sup> Thick and thin blood films were obtained from

finger pricks and stained with Giemsa. Blood smears were examined every 12 hours from initiation of treatment until they were negative on two consecutive occasions; thereafter blood smears were examined daily until patients were discharged. Blood films were considered negative if no parasites were seen in 200 oil-immersion fields on a thick blood film. Parasitemias (asexual parasite/microliter of blood) were determined by counting the number per 200 leukocytes (thick film) or the number per 1,000 erythrocytes (thin film). Parasite clearance time was expressed in hours from the start of treatment until the parasite counts decreased below the level of detection for at least 24 hours.

Vital signs except blood pressure were measured every four hours. Blood pressure was measured daily. Monitoring of signs and symptoms of malaria and adverse events was performed daily for the first seven days of admission and weekly thereafter. All patients were closely monitored for the clinical signs of intravascular hemolysis and hemoglobinuria. Fever clearance time was defined as the time from the start of treatment until the oral temperature decreased below 37.5°C for at least 48 hours.

Patients with reappearance of parasitemia after treatment with any of the six regimens were treated with chloroquine (30 mg/kg) and primaquine (15 mg once a day for 14 days) as a standard treatment of the hospital. The patients with subsequent appearance of a sexual form of *P. falciparum* were treated with artesunate (600 mg) followed by mefloquine (25 mg/kg). Patients having recurrent parasitemia on or before day 14 were considered artesunate treatment failures, whereas recurrent parasitemia between days 15 and 28 were considered primaquine treatment failures. All patients with concurrent *P. falciparum* malaria were considered failures to treatment, excluded from the study, and not included in the analysis of the cure rate at 28 days.

The clinical efficacies among groups were estimated by comparing relapse rates observed after 28-day follow-up of patients in each group. Descriptive statistics and statistical analysis were conducted using the Epi Info version 6.04 (USD Inc., Stone Mountain, GA) software package. All statistical tests were two-tailed and a significance level of 0.05 was used.

## RESULTS

Three hundred ninety-nine patients with acute symptomatic *P. vivax* malaria infection were recruited into the study. The baseline demographic, clinical, and pre-treatment characteristic data were comparable (Table 1). Most patients reported recent travel to the Thailand-Myanmar border, where they presumably acquired their infections. There is no risk of malaria in Bangkok, and risk is low in most other areas of Thailand.

During the follow-up period, 77 patients left the hospital before completing 28 days of follow up (8 in group 1, 12 in group 2, 10 in group 3, 16 in group 4, 14 in group 5, and 17 in group 6) for personal reasons unrelated to side effects of treatment. All patients who left the hospital were asymptomatic and without parasitemia before being discharged. None of the patients who left the study before day 28 developed *P. falciparum* malaria. Fever and parasitemia disappeared in all patients within 48 hours (Table 2). No recurrence of parasitemia occurred before day 15; thus, all recurrences were classified as primaquine treatment failures. Almost all recurrences occurred after only 5, 7, or 9 days of daily primaquine dosing with 30 mg (9 of 60 treated, 6 of 57 treated, and 2 of 56 treated, respectively). No recurrences appeared after 11 or 14 days of the same dose. Among patients given twice-a-day primaquine dosing with 30 mg of primaquine for 7 days, 2 recurrences appeared among the 49 persons treated (Table 2). There were no changes in hematocrit

levels (Figure 1). No serious adverse events were observed, and no significant differences in adverse events were observed among the groups (Table 3).

## DISCUSSION

Abbreviated high-dose regimens of primaquine after artesunate therapy provided efficacious, safe, and well-tolerated therapy against relapse by *P. vivax* acquired in Thailand. The complete efficacy of artesunate against *P. vivax* malaria<sup>7</sup> and its short plasma half-life enabled us to evaluate the efficacy of primaquine against early relapse by *P. vivax*. In studies of patients infected by tropical Asian strains of *P. vivax* and not treated with primaquine, 197 (75%) of 263 persons who relapsed did so on or before day 28.<sup>24</sup> We believe the 28-day period of follow-up captured most possible relapses in this study population. Regimens of 30 mg a day for 5 or 7 days proved significantly less efficacious (< 90%) against early relapse than 30 mg a day over 9, 11, or 14 days (> 90%) ( $P < 0.05$ ). The regimen of 2 daily doses of 30 mg for 7 days was 94% efficacious against early relapse. Because of prolonged use of primaquine, which can eliminate the asexual erythrocytic stage of *P. vivax*, none of the patients developed recurrences before day 15.

Patients given the dose of 60 mg of primaquine divided into 2 daily doses over 7 days tolerated this drug without serious adverse events and without substantially altered blood or liver function profiles. Although methemoglobin levels were not measured in this study, none of the patients developed clinical signs and symptoms of methemoglobinemia, such as bluish discoloration of the skin. This corroborated similar findings of good tolerability of a 60-mg daily dose given in combination with chloroquine in the setting of a placebo-controlled, double-blinded trial.<sup>30</sup> We consider that regimen a practical alternative to 30 mg of primaquine a day over 9, 11, or 14 days among patients considered good candidates to receive this regimen, i.e., not pregnant and a G6PD deficiency.

Many countries in malaria-endemic regions adopted a dose of 15 mg of primaquine a day for 5 days as standard anti-relapse therapy against *P. vivax* on the basis of findings in poorly controlled clinical trials.<sup>12</sup> Recent well-controlled trials have shown that this regimen was almost completely ineffective against relapse by *P. vivax* in Asia.<sup>31</sup> Health officers responsible for malaria therapy policies cite the impracticality of a 14-day regimen as the basis of opting for the abbreviated regimen. Our findings support the concept of adopting a 30 mg twice a day regimen for 7 days as a safe, well-tolerated, and efficacious alternative that may prove more practical. However, the safety of such a regimen in patients with G6PD deficiency is doubtful and adoption of such a regimen would depend upon availability of reliable G6PD testing prior to drug administration.

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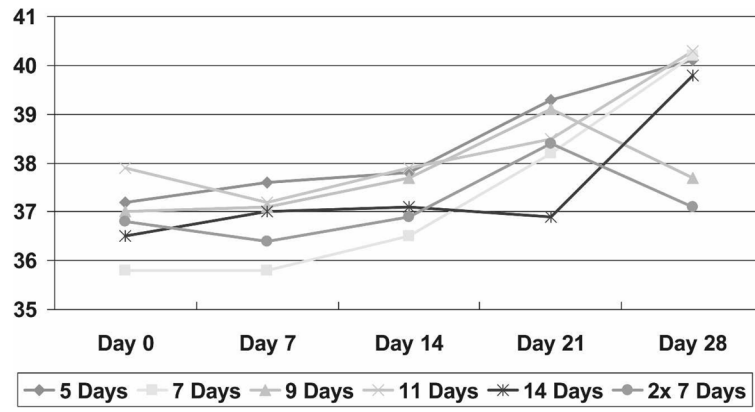
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**Figure 1.**  
Mean hematocrit level of patients receiving high-dose primaquine.

Table 1

Baseline clinical and laboratory characteristics of patients in the study\*

Characteristic	Group 1 (n = 68)	Group 2 (n = 69)	Group 3 (n = 66)	Group 4 (n = 64)	Group 5 (n = 66)	Group 6 (n = 66)
Sex (M:F)	42:26	46:24	46:19	44:21	41:21	37:29
Mean (SD) age, years	26.2 (9.4)	24.5 (8.1)	22.9 (5.8)	23.7 (8.1)	24.1 (8.2)	23.7 (7.2)
Mean (SD) height, cm	160.6 (8.4)	159.2 (7.2)	161.2 (7.1)	160.4 (7.1)	159.8 (6.6)	159.0 (7.6)
Mean (SD) weight, kg	53.6 (7.7)	53.3 (7.9)	53.0 (7.9)	52.8 (8.5)	52.8 (8.2)	51.2 (7.2)
Fever, mean (SD)						
Duration of fever before admission, days	4.8 (3.6)	4.2 (1.8)	5.1 (4.7)	5.2 (5.1)	4.9 (3.1)	4.8 (3.1)
Highest temperature, °C	37.8 (1.0)	38.0 (1.2)	38.0 (1.0)	37.8 (0.9)	37.7 (0.8)	37.9 (1.0)
No. of patients with						
Splenomegaly	0	2	1	1	3	3
Hepatomegaly	21	11	17	10	13	9
First malaria attack	37	28	32	28	38	37
Geometric mean parasitemia (range)/ $\mu$ L	6,410 (75–65,520)	6,016 (63–48,500)	5,993 (42–88,480)	5,192 (22–41,680)	5,616 (49–54,120)	6,323 (105–54,120)
Laboratory results, mean (SD)						
Hematocrit, %	37.2 (5.6)	35.6 (5.9)	37.0 (6.4)	37.6 (5.9)	36.2 (5.6)	36.5 (6.2)
White blood cell count/ $\mu$ L	5.5 (1.6)	5.5 (1.7)	6.3 (2.1)	6.6 (2.1)	6.1 (1.8)	5.6 (1.5)
Blood urea nitrogen, mg/dL	14.9 (4.2)	15.7 (4.6)	14.4 (4.9)	14.8 (4.4)	15.4 (7.1)	14.6 (4.9)
Serum creatinine, mg/dL	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.3)	0.8 (0.1)
Total bilirubin, mg/dL	1.5 (0.8)	1.6 (1.1)	1.7 (1.4)	1.5 (1.0)	1.5 (1.0)	1.3 (0.6)
Serum AST, U/L	34.3 (28.4)	33.9 (21.7)	39.2 (40.1)	29.5 (19.1)	31.5 (16.1)	31.0 (15.2)
Serum ALT, U/L	34.5 (48.4)	35.8 (36.0)	35.0 (37.8)	30.1 (24.0)	34.6 (35.0)	32.6 (31.4)
Alkaline phosphatase, U/L	117.4 (68.4)	120.7 (55.1)	123.9 (63.4)	122.8 (61.0)	127.2 (92.7)	126.6 (62.7)
Albumin, g/dL	3.7 (0.4)	3.7 (0.4)	3.7 (0.5)	3.8 (0.5)	3.7 (0.5)	3.7 (0.4)

\* For definition of groups, see Patients and Methods. AST = aspartate aminotransferase; ALT = alanine aminotransferase.



Table 2

Therapeutic responses of patients in the study\*

Characteristic	Group 1 (n = 68)	Group 2 (n = 69)	Group 3 (n = 66)	Group 4 (n = 64)	Group 5 (n = 66)	Group 6 (n = 66)
No. of dropouts	8	12	10	16	14	17
No. of patients who completed follow-up	60	57	56	48	52	49
Cure rate at day 28 (%)	51 (85)	51 (89)	54 (94)	48 (100)	52 (100)	47 (96)
Relapse rate at day 28 (%)	9 (15)	6 (11)	2 (4)	0	0	2 (4)
Day of appearance	19, 20, 22, 23, 25, 28	20, 21, 23, 24, 28	14, 21	NA	NA	22, 23
Mean (SD) fever clearance time, hr	16.8 (14.4)	20.0 (21.6)	14.5 (9.3)	13.8 (11.4)	19.6 (22.2)	21.4 (23.5)
Mean (SD) parasite clearance time, hr	34.9 (8.4)	36.0 (10.5)	35.7 (10.1)	34.2 (9.9)	37.2 (11.4)	36.8 (10.4)

\* NA = not available. Group 1 ≠ group 4 and group 5 ( $P = 0.004$  and  $0.003$ ), Group 2 ≠ group 4 and group 5 ( $P = 0.015$  and  $0.014$ ).

Table 3

Potential adverse effects after treatment in patients in the study\*

Characteristic	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Headache	1 (1.47)	3 (4.34)	3 (4.54)	2 (3.12)	3 (4.54)	3 (4.54)
Weakness	0	0	0	0	0	0
Dizziness	3 (4.41)	2 (2.89)	5 (7.57)	1 (1.56)	2 (3.03)	1 (1.51)
Anorexia	2 (2.94)	2 (2.89)	4 (6.06)	4 (6.05)	1 (1.51)	2 (3.03)
Nausea	2 (2.94)	1 (1.44)	2 (3.03)	1 (1.56)	1 (1.51)	1 (1.51)
Vomiting	1 (1.47)	0	1 (1.51)	0	0	1 (1.51)
Insomnia	0	0	0	0	0	0
Abdominal pain	3 (4.41)	4 (5.79)	1 (1.51)	2 (3.12)	2 (3.03)	3 (4.54)
Diarrhea	0	1 (1.44)	0	0	1 (1.51)	0

\* Values are no. (%).