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Short Report: Therapeutic Efficacy of Chloroquine Combined with Primaquine Against *Plasmodium falciparum* in Northeastern Papua, Indonesia

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SHORT REPORT: THERAPEUTIC EFFICACY OF CHLOROQUINE COMBINED WITH PRIMAQUINE AGAINST *PLASMODIUM FALCIPARUM* IN NORTHEASTERN PAPUA, INDONESIA

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Abstract. Chloroquine combined with primaquine was evaluated for therapy of uncomplicated malaria caused by *Plasmodium falciparum* in nonimmune Javanese migrants to northeastern Papua, Indonesia. Subjects were randomized to treatment with standard chloroquine therapy (25 mg/kg in 3 doses over the course of 48 hours) with 30 mg primaquine administered daily for 28 days (n = 25) or a placebo of primaquine (n = 28). The 14-day cumulative incidence of therapeutic failure was 56% with primaquine and 79% with placebo (odds ratio [OR], 0.35; 95% confidence interval [CI], 0.1–1.3; $P = 0.08$). Primaquine administered daily created a marginally significant improvement in therapeutic efficacy at day 14, but not at day 7 (20% versus 36%; OR, 0.2; 95% CI, 0.1–1.8; $P = 0.2$) or day 28 (82% versus 93%; OR, 0.31; 95% CI, 0.04–2.1; $P = 0.23$). This report corroborates studies suggesting that therapeutic doses of primaquine exert no discernible effect on parasitemia by *P. falciparum.*

INTRODUCTION

Chloroquine and primaquine remain in common use against uncomplicated malaria in the developing world. Chloroquine still constitutes first-line therapy for infection by *Plasmodium falciparum* for most people exposed to risk in Asia—for example, in India, the Philippines, and Indonesia. Primaquine, which is typically used for the prevention of relapse by *Plasmodium vivax* (15 mg daily for 14 days), is also widely used in Asia against *P. falciparum* as a single 45-mg gametocytocidal dose. Although therapeutic regimens of primaquine exert curative activity against blood stages of *P. vivax* organisms,[1,2] most evidence suggests primaquine has no effect on blood stages of *P. falciparum.*[3–5] This may bear on the finding of apparently distinct mechanisms of resistance to chloroquine by these 2 species.[6]

In July 1992 (Arso VIII) and June 1993 (Arso XI), we enrolled subjects in a randomized, blinded, placebo-controlled trial of a primaquine adjunct to standard chloroquine therapy. The findings with *P. vivax* have been published elsewhere in a report that details the conduct of the studies.[2] In brief, 53 subjects (nonimmune Javanese migrants) with uncomplicated malaria caused by *P. falciparum* provided informed consent and were randomized to receive standard chloroquine therapy (Resochin; P. T. Bayer Indonesia, Jakarta, Indonesia; provided as uncoated scored tablets; 10 + 10 + 5 mg/kg at 24-hour intervals) with primaquine (generic label, Sanofi-Winthrop, New York, NY, as coated unscored tablets containing 15 mg base, 0.5 mg/kg daily for 28 days) or a nonidentical placebo (identical to generic primaquine from Kimia Farma, Bandung, as an uncoated, scored tablet containing starch and amylose). Subjects were at least 6 years old and had at least 40 asexual parasites per microliter of blood; in addition, they tested negative for glucose-6-phosphate dehydrogenase deficiency ($NADP^+$ spot test; Sigma Chemical Co., St. Louis, MO). The mean age of the 53 subjects was 23 years (range, 6–40 years), and most were men (n = 45). The geometric mean density of asexual parasites was 2,744/μL. No significant differences in these parameters appeared between the primaquine and placebo groups.

Therapy was directly observed beginning on day 0 of the evaluation and ending with the last dose of primaquine on day 28. Blood films were collected, stained with Giemsa reagents, and read microscopically on days 0, 1, 2, 4, 7, 11, 18, 21, 25, and 28, or at any time a subject complained of illness. Figure 1 illustrates the cumulative incidence of therapeutic failure (persistent or recurrent asexual parasitemia) for both treatment groups estimated by life-table analysis. No significant differences in risk of therapeutic failure occurred between the primaquine and placebo groups. A marginally significant difference appeared only at day 14 (56% versus 79%; odds ratio, 0.35; 95% confidence interval, 0.4–1.3; $P = 0.08$). Daily doses of 0.5 mg/kg primaquine over the 28 days of follow-up exerted

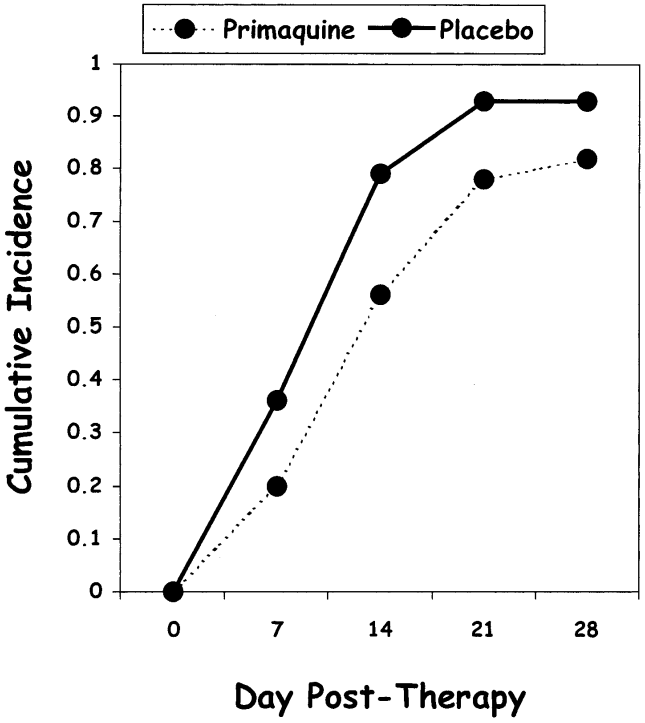

FIGURE 1. Cumulative incidence of recurrent asexual parasitemia by *Plasmodium falciparum* after chloroquine therapy combined with 30 mg daily primaquine **(dashed line)** or a placebo **(solid line).**

no discernible effect on the clearance and recurrence of asexual parasitemia by *P. falciparum.*

Our findings corroborate others suggesting that therapeutic doses of primaquine exert no effect on asexual parasitemia by *P. falciparum,* despite an apparently profound effect against asexual blood forms of *P. vivax* shown in other studies[1] and in parallel[2] with the findings reported here. These findings also corroborate the very high risk of therapeutic failure with chloroquine monotherapy against *P. falciparum* acquired in northeastern Papua, Indonesia.[7–9]

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Informed consent: The work described herein was reviewed and approved by Indonesian and American committees for the protection of human subjects of medical research in accordance with U.S. Navy regulations (SECNAVINST 3900.39B). All subjects of this research provided informed consent.

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