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Comparison of Artesunate and Chloroquine Activities against *Plasmodium vivax* Gametocytes

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The gametocidal activities of chloroquine and artesunate were compared. The relative risk (RR) of having detectable gametocytes appear after treatment initiation was lower in artesunate-treated patients ($n = 792$) than in chloroquine-treated patients ($n = 695$) (RR = 0.29; 95% CI = 0.2 to 0.40; $P < 0.0001$). The duration and magnitude of gametocyte carriage were also lower for artesunate than chloroquine. By reducing the transmission of *Plasmodium vivax* to the vector, artesunate could therefore reduce the incidence of *P. vivax* malaria.

Plasmodium vivax malaria continues to be a major public health problem in Thailand. On the western Thai border, the spread of drug-resistant *Plasmodium falciparum* has led to the use of artemisinin-based combinations, which, because of their gametocidal properties, have reduced the transmission and the incidence of *P. falciparum* (2). In the meantime, *P. vivax* infections were still treated with chloroquine, which is active on both the asexual and the sexual stages (gametocytes) of the parasite. However, in areas following the same drug policy, there was no reduction in the incidence of *P. vivax* as observed for *P. falciparum* and therefore the incidence of *P. vivax* progressively became greater than that of *P. falciparum*. Relapses might have contributed to complicate the matter because they do not reflect changes in transmission. Another possibility, however, would be that the gametocidal activity of chloroquine was insufficient to markedly influence transmission. In the following historical control trial, we compared the effect of chloroquine and artesunate on gametocyte carriage of patients with *P. vivax* malaria.

Between 1993 and 2002, 2,078 patients aged 4 to 83 years were treated at the Hospital for Tropical Diseases in Bangkok for *P. vivax* malaria. From 1993 to 1998 patients received chloroquine phosphate (Thai Government Pharmaceutical Organization, Bangkok, Thailand) at 10 mg of base/kg of body weight followed by 5 mg of base/kg at h 6, 24, and 36 (n = 1,018). From 1999 to 2002, patients were treated with artesunate (Guilin No. 1 Factory, Guanxi, People's Republic of China) at 3.3 mg/kg on the first day followed by 1.65 mg/kg for the following 4 days (n = 586) or artesunate at a dose of 1.65 mg/kg/day for 7 days (n = 474). All patients gave informed consent, and the study was approved by the Ethical Committee of Mahidol University. Patients received oral paracetamol if they had a temperature above 38°C. Among the above patients, 516 (50.7%) of the patients receiving chloroquine and 607 (57.2%) of the patients receiving artesunate received primaquine at the end of their treatment (on the third day for patients receiving chloroquine and on the fifth or seventh day for patients receiving artesunate) to destroy hypnozoites. However, all but four patients (all in the chloroquine group) had already cleared their gametocytes when primaquine was started; therefore, it was inferred that primaquine was given too late to influence the studied outcome. Gametocytes per 200 leukocytes were counted every 12 h by experienced microscopists on Giemsa-stained thick smears until parasitemia became negative. For all patients, a complete blood count was performed on admission, allowing us to transform asexual parasite counts from thin or thick smears into parasitemia expressed in parasites per microliter of blood. The proportion of gametocyte carriers, the peak gametocyte count, and the gametocyte carriage duration were compared between treatment groups. To compare peak gametocyte counts and the proportion of gametocyte carriers between treatment groups, the analysis did not include 591 patients with gametocytes on admission (total number of patients analyzed = 1,487). The Mann-Whitney test was used to compare medians, and a generalized linear model (binomial family with a log link function) was used to control for the initial parasitemia, age, and fever duration.

After excluding observations of patients with *P. vivax* gametocytes on admission, patients treated with artesunate were less likely to develop gametocyte carriage (Table 1). Among patients with *P. vivax* gametocytes, the median peak gametocyte count was lower in patients treated with artesunate than in those treated with chloroquine, respectively: 465 per mm^3 (interquartile range, 305 to 795 per mm^3) versus 560 per mm^3 (interquartile range, 355 to 975 per mm^3) ($P = 0.001$). Among patients with *P. vivax* gametocytes, patients treated with artesunate had detectable gametocytes for a shorter duration than those treated with chloroquine, respectively: median = 24 h (range, 0 to 96 h) versus 24 h (range, 0 to 264 h) ($P = 0.005$). The lower gametocyte carriage with artesunate followed a tem-

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TABLE 1. Difference in *P. vivax* gametocyte carriage between artesunate and chloroquine

Gametocyte carriage	Artesunate (%)	Chloroquine (%)	Risk ratio (95% CI)	Adjusted risk ratio (95% CI)[a]
+	56 (7)	160 (23)	0.31 (0.23–0.41 [$P < 0.0001$])	0.29 (0.2–0.40 [$P < 0.0001$])
−	736 (93)	535 (77)		

[a] Adjusted for age, initial parasitemia, and fever duration by a generalized linear model.

poral trend for odds ($\chi^2 = 8.94$; $P = 0.002$). When looking at the difference between artesunate regimens, the 5-day regimen, which delivers a larger initial dose, was associated with less gametocyte carriage than the 7-day regimen risk ratio, 0.83 (95% CI = 0.69 to 0.99; $P = 0.04$). All the above results were not affected when controlling for the use of posttreatment primaquine.

Gametocytes do not cause any symptoms, but their presence in sufficient numbers and duration is directly responsible for the infection of the anopheline vector, thus perpetuating the plasmodial cycle. Although both chloroquine and artesunate are able to kill gametocytes (5), the treatment of *P. vivax* malaria with artesunate led to a threefold reduction of gametocyte carriage when compared to chloroquine. Peak gametocyte densities and duration of gametocyte carriage were also lower in patients treated with artesunate. These elements suggest that, as for *P. falciparum* (2), by reducing transmission, the generalized treatment of *P. vivax* with artesunate could predictably be followed by a reduction of *P. vivax* incidence. In addition, hidden *P. falciparum* infections, which occur in 10% of *P. vivax* infections (1), could be effectively treated, thus avoiding their delayed appearance following chloroquine treatment. However, although it has been previously shown that artemisinin derivatives had the strongest activity against asexual parasites (3), the problem of relapses was not affected by these drugs and thus still requires the use of primaquine (4) (if the local treatment policy advocates the prevention of relapses). Thus prospective interventions in target areas should be implemented to measure the potential benefits of artesunate in *P. vivax* malaria for both individuals and populations.

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