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SHORT REPORT: *IN VIVO* SENSITIVITY OF *PLASMODIUM FALCIPARUM* TO HALOFANTRINE IN SOUTHERN CENTRAL VIETNAM

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Abstract. Drug-resistant *Plasmodium falciparum* is present in Vietnam. We assessed the *in vivo* sensitivity of *P. falciparum* to halofantrine in two villages in the southern part of central Vietnam. Halofantrine (8 mg/kg × 3 doses) was administered to 37 patients with either *P. falciparum* (n = 32) or mixed *P. falciparum/P. vivax* malaria (n = 5). End points were parasite sensitivity or resistance (RI/RII/RIII) determined by parasite clearance, persistence, or recurrence during 28 days of follow-up. By day 28, 31 (93.9%) of 33 (95% confidence interval = 79.8–99.2%) patients were sensitive. Two patients had recurrent *P. falciparum* parasitemia on days 14 and 21. Halofantrine effectively treated uncomplicated *P. falciparum* malaria in these Vietnamese patients.

In Vietnam, *Plasmodium falciparum* is resistant to commonly used antimamalarial drugs.[1] In 1995, we investigated the sensitivity of halofantrine by conducting a 28-day *in vivo* test in two villages in Khanh Hoa province, 40 miles west of the coastal town of Nha Trang in southern central Vietnam. Malaria incidence rates in this area are 1.9 per person-year for *P. falciparum*, 1.1/person-year for *P. vivax*, and 0.03/person-year for *P. malariae* (Nhan DH, unpublished data). Written, informed consent was obtained from all participating patients or their parents/guardians. The study was conducted according to the Vietnamese Ministry of Health and the United States Navy regulations governing the protection of human subjects in medical research. Entry criteria and study conduct have been reported in detail elsewhere.[2] Three doses of halofantrine (Glaxo SmithKline, London, United Kingdom), 8 mg/kg every six hours, was administered in the hospital on an empty stomach (at least one hour before or two hours after a meal) to patients with no clinical signs of cardiac disease and a normal QTc interval. Thick and thin film blood smears (days 1, 2, 4, 7, 11, 14, 18, 21, and 28) were stained with Giemsa, read, and the results were reported as parasites/microliter. Data were analyzed using Epi-Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA).

There were 37 treated patients in the study: 32 with *P. falciparum* monoinfection and 5 with mixed *P. falciparum*/*P. vivax* malaria. Enrollment characteristics are shown in Table 1. On day 0, all patients were either symptomatic or febrile (oral temperature > 37°C). By day 28, four patients were lost to follow-up, and two patients with *P. falciparum* malaria developed recurrent *P. falciparum* parasitemia: a 17-year-old man on day 14 (day 0 parasitemia = 2,120/μL, recurrent parasitemia = 240/μL) and an eight-year-old girl on day 21 (day 0 parasitemia = 18,040/μL, recurrent parasitemia = 280/μL). Using a previously published method,[3] we amplified the small subunit ribosomal RNA of *P. falciparum* by a polymerase chain reaction (PCR) to confirm the microscopic diagnosis of *P. falciparum* of the day 0/day recurrent (day_{rec}) slides. However, technical difficulties unfortunately precluded the genotyping the day_{rec} slides with merozoite surface protein-2 primers.[3] When the four patients lost to follow-up were excluded, the 28-day cure rate was 31 (93.9%) of 33 (95% confidence interval = 79.8–99.2%). The *P. falciparum* parasite clearance rates were 16.2% by day 1, 73.0% by day 2, 91.4% by day 4, and 100% by day 7.

TABLE 1

Enrollment characteristics of Vietnamese patients with *Plasmodium falciparum* (n = 32) or mixed *P. falciparum*/*P. vivax* (n = 5) malaria in a 28-day *in vivo* test assessing halofantrine sensitivity

	Halofantrine group (n = 37)
No. (%) of males	23 (62.2)
Median (range) age in years	12 (5–42)
Prestudy antimalarial drug use*	13 (35.1)
No. (%) symptomatic†	28 (75.7)
No. (%) febrile‡	31 (83.8)
Median (range) day 0 temperature, °C	37.5 (36.3–39.5)
No. (%) with splenomegaly	24 (64.9)
Median (range) *P. falciparum* parasitemia/μL	400 (40–46,480)

* Number (%) consuming any antimalarial drug within one month of enrollment.
† Defined as fever, chills, headache, myalgia, or anorexia.
‡ Defined as an oral temperature > 37.0°C.

This study demonstrates the sensitivity of *P. falciparum* to halofantrine in one small area of southern central Vietnam. Recurrent parasitemia (n = 2) occurred on days 14 and 21, consistent with new infections, RI resistance, or treatment failures due to poor absorption of halofantrine.[4] The expected number of new *P. falciparum* infections in our cohort of 33 who completed the four week follow-up is ≈5 (1.9 infections/person-year × 33 persons × 4 weeks × 1/52 years). These epidemiologic data favor new infections as the cause of our two cases of recurrent parasitemia. However, we cannot exclude drug resistance because of the failure of our PCR genotyping.

Mefloquine, but not halofantrine, was available in local shops when the study was conducted. Mefloquine is cross-resistant to halofantrine; thus, its use would be a factor in the generation of halofantrine resistance.[5,6] Our study used the original World Health Organization (WHO) parasitologic *in vivo* test to assess halofantrine sensitivity. There is now a new WHO *in vivo* test for areas of intense and low/moderate malaria transmission that should be adopted as the standard test for defining drug resistance. Accordingly, our two cases of recurrent parasitemia would have been classified as either late parasitologic or clinical treatment failures, depending on whether they were febrile (axillary temperature ≥ 37.5°C.) at the time of their recurrent parasitemia.[7]

Halofantrine has potentially serious cardiotoxicity that restricts its use to specific clinical indications, e.g., drug-resistant *P. falciparum* malaria in patients with normal electrocardiographic findings who have not recently consumed drugs that prolong the QTc interval.[8–10] These prerequisites make halofantrine unsuitable for widespread use in primary health settings of malaria-endemic countries.

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