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

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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 x 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 antimalarial 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are 1.9 per person-year for P. falciparum, 1.1/person-year for P. vivax, and 0.03/person-year for P. malariae (Nhan DH, unpublished data).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 parasitemias (days 1, 2, 4, 7, 11, 14, 18, 21, and 28) were stained with Giemsa, read, and the results were reported as 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.

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) |
| Presudy 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.
‡ Exdefined as an oral temperature > 37.0°C.

5 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 (auxiliary 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. These prerequisites make halofantrine unsuitable for widespread use in primary health settings of malaria-endemic countries.

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