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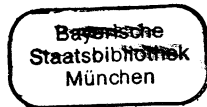
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THE EFFICACY OF HALOFANTRINE IN THE TREATMENT OF ACUTE MALARIA IN NONIMMUNE TRAVELERS

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Abstract. A multicenter prospective trial was performed to investigate the efficacy and the tolerability of halofantrine in nonimmune patients with malaria imported from areas with drug-resistant falciparum parasites (mainly Africa). Forty-five of the 74 subjects were treated with a one-day regimen (3 × 500 mg) of halofantrine, and the other 29 received the same regimen with an additional treatment on day 7. In the second group, a 100% efficacy rate was demonstrated, but in the group receiving the one-day regimen, four recrudescences were observed in patients with falciparum malaria. Only five mild adverse reactions were seen, which disappeared spontaneously after the end of the treatment. We conclude that halofantrine is highly effective in curing malaria in nonimmune subjects. The treatment scheme for such persons should include an additional treatment on day 7 for nonimmune individuals. This drug was well tolerated in our patients, indicating that halofantrine will be useful in the treatment of multidrug-resistant malaria in nonimmune persons.

The spread of multi-resistant *Plasmodium falciparum* strains to many countries where malaria transmission occurs poses a considerable challenge in the treatment of infected patients.¹ Furthermore, severe side effects of other established antimalarial drugs such as pyrimethamine-sulfadoxine (Fansidar®) or amodiaquine restrict their use for prophylaxis or treatment.²⁻⁵ One of the newer drugs, mefloquine, has been shown to produce moderate to severe neuropsychiatric reactions with a frequency of 1 in 215 after therapeutic use;⁶ reduced in vitro sensitivity has also been demonstrated with this drug.⁷ Therefore, new drugs that are efficacious and safe are urgently needed.

Halofantrine, a phenanthrene methanol, is such a new antimalarial drug, and it has been shown to be efficacious in semi-immune patients in various endemic areas.⁸⁻¹³ Data are scanty on non-immune travelers who have contracted malaria during short term stays in the tropics and their treatment with halofantrine.¹⁴ In semi-immune persons, a one-day treatment produced excellent results, but recrudescences were reported in nonimmune patients.¹⁵ The current study was undertaken to investigate the efficacy and tol-

erability of halofantrine hydrochloride in non-immune patients, and to evaluate the need for a regimen with a repetitive dose after one week.

PATIENTS AND METHODS

This multicenter trial was carried out prospectively in four hospitals in Germany. Patients who returned from a stay in the tropics were screened and recruited if they met the following criteria: 1) they had parasitologic evidence of parasites in the blood with clinical symptoms of malaria, 2) they were older than 18 years of age and younger than 65 years of age, and 3) they were nonimmune white individuals living usually in Central Europe, or if the patient is of African/Asian origin, they must have stayed more than one year outside endemic areas. Written informed consent for participation in the study was obtained from all patients.

Parasite densities were calculated by counting asexual parasites against 5,000 red blood cells on Giemsa-stained thin blood films, or against 200 white blood cells on thick blood films when the parasitemia was < 0.1%.

Exclusion criteria were 1) severe or compli-

cated malaria (e.g., renal failure, severe hypotension, central nervous system disorders, vomiting, fever > 41°C) or a parasite count > 500,000/ μ l, 2) being pregnant or nursing, 3) body weight < 40 kg, and 4) concomitant antimalarial treatment.

Forty-five patients were treated orally with halofantrine hydrochloride (3 \times 500 mg tablets) within a 12-hr period (group 1). The other 29 patients were given the same treatment regimen on day 0 and an additional treatment on day 7 (group 2). No differences could be observed between the two groups concerning travel destinations. In those with *P. vivax* malaria, a standard course of primaquine was given after the treatment with halofantrine. Although 80 patients were enrolled in the study, six were not available for followup examinations, and a judgment of drug efficacy in these patients was not possible. The data from these six patients were included only in the evaluation of drug tolerability.

Efficacy and tolerability evaluations included hematologic examinations (hemoglobin level and white blood cell and platelet counts), clinical biochemical tests (levels of creatinine, blood urea nitrogen, bilirubin, liver transaminases and alkaline phosphatase, and serum electrolytes and glucose), urinalysis (glucose and protein levels), recording of body temperature, and parasite count (parasite density). Hematologic and biochemical values were determined on days 1–5, 7, 14, 21, and 28, urinalysis was performed once a week, and temperatures were recorded twice a day. Parasite counts were obtained before treatment, twice a day until blood smears were negative, and on days 5, 7, 14, 21, and 28. Clinical investigations were carried out on days 1–5, 7, 14, 21, and 28. Thus, efficacy could be determined with the following parameters: cure rate, parasite clearance time (hr), fever clearance time (hr), and recrudescence rate. Drug tolerability was measured by determination of the frequency and severity of adverse reactions.

RESULTS

The 74 fully compliant subjects (55 men and 19 women) had a mean age of 35.5 years (age range 23–61) and a mean body weight of 72.9 kg (range 52–101.8). Sixty-two of the 74 patients (83.8%) were white and lived in Central Europe. Ten (13.5%) were of African origin and two (2.7%)

were of Asian origin, but all had lived in Germany for a period of more than one year.

Plasmodium falciparum was detected in 50 patients and *P. vivax* in 20 patients; in four patients, the *Plasmodium* species could not be classified because of very low parasitemias and identification of parasites on thick smears only. The mean pretreatment parasite count was 40, 350/ μ l and the parasite density ranged from < 5,000/ μ l to 250,000/ μ l (Table 1). The patients had contracted their malaria infections in sub-Saharan Africa (78%), South America (6%), the Indian subcontinent (6%), and southeast Asia (10%). Malaria chemoprophylaxis was used by 37 (50%) of the 74 travelers, and consisted mainly of chloroquine (n = 21) or chloroquine plus proguanil (n = 9); 37 (50%) patients did not use any chemoprophylactic agent.

Pretreatment clinical symptoms consisted of fever (n = 71, 95.9%), headache (n = 64, 87%), dizziness (n = 50, 68%), chills/rigors (n = 38, 51%), nausea (n = 45, 61%), diarrhea (n = 8, 11%), and abdominal pain (n = 13, 18%). The median fever clearance time was 53 hr (range 4–185) and was shorter than the parasite clearance time of 65 hr (range 18–225). Clearance times were slightly longer in those with *P. falciparum* infections (fever clearance time = 49 hr and parasite clearance time = 66 hr) compared with those with *P. vivax* infections (42 and 62.5 hr, respectively), but these differences were not statistically significant.

In all patients, clinical symptoms of malaria disappeared and parasites could no longer be detected on day 14 (Table 2). Subsequently, four infections recrudesced in group 1 (treatment on day 0 only) on days 14, 22 (two patients), and 28, respectively, indicating that four (15.4%) of 26 patients in group 1 with *P. falciparum* infections recrudesced. In group 2 (treatment on days 0 and 7), none of the 24 patients with *P. falciparum* malaria recrudesced. Although this difference was not statistically significant, a clinically relevant trend was apparent. The four patients whose infections recrudesced were white individuals; three of them had used a chemoprophylactic (chloroquine), while the fourth patient had not used any chemoprophylactic. Their body weights did not differ significantly from the successfully treated group, and their initial parasite counts were only slightly lower (3,500, 9,500, 10,500, and 48,000/ μ l, respectively). All four patients had returned from tropical Africa. A def-

TABLE 1
Parasitemia in the 74 malaria patients in this study

Parasites/ μ l	No. (%)
<5,000	9 (12.2)
5,000–50,000	48 (64.9)
50,000–100,000	8 (10.8)
100,000–250,000	2 (2.7)
>250,000	3 (4.1)
Not done	4 (5.4)
Total	74 (100.0)

inite cure of these recrudescences was possible by treatment with quinine or mefloquine. No recrudescences were observed in any patients in both groups with *P. vivax* malaria.

Clinical tolerance to treatment with halofantrine was good, with only six patients reporting side effects. One patient each complained of diarrhea, itching, nausea, skin rash, fever, and angioneurotic (Quincke) edema. All reactions were graded as mild and disappeared spontaneously a few days after the end of the halofantrine treatment. Five of these six adverse reactions were confined to those who had a one-day therapy regimen. Only angioneurotic edema occurred in a patient who received two days of therapy; concomitant to falciparum malaria, the same patient had Dengue fever. Treatment of this patient with a second dose of halofantrine on day 7 did not produce any adverse reaction. Therefore, it is more likely that the angioneurotic (Quincke) edema was a reaction that occurred after the onset of Dengue fever. Thus, five (6.25%) of 80 patients developed mild, reversible side effects. Hematologic and clinical biochemical test results remained within the normal limits after treatment in all patients.

In addition, two patients developed neurologic symptoms within the 28-day followup period that were judged to be unrelated to the intake of halofantrine. A 32-year-old woman who received halofantrine on day 0 complained of weakness

in her legs on day 19 post-treatment. She was hospitalized and diagnosed as having Guillain-Barre syndrome (with typical cerebrospinal fluid findings) of unknown etiology. A 50-year-old man who received halofantrine on days 0 and 7 developed viral encephalitis with disorientation and speech disturbance 23 days after initiating treatment. He had a significant influenza A virus titer, indicating that influenza A virus was the probable cause of his encephalitis. Both patients improved spontaneously.

DISCUSSION

The role of antimalarial drugs in the control of malaria has undergone major revisions in recent years with the increase of drug resistance in *Plasmodium falciparum*. Thirty years ago, the sensitivity of the parasite was the norm. Today, resistance to chloroquine and other alternative compounds is dominant and still spreading.¹ This has encouraged the development of new drugs. The Walter Reed Army Institute of Research has identified various new antimalarial drugs, including halofantrine in the 1970s.^{16, 17} This compound, a phenanthrene methanol, proved to be more efficacious and less toxic than other new compounds, and has undergone extensive evaluation since that time.^{16, 18} It has proved to be effective in the treatment of drug-resistant strains of *P. falciparum* in semi-immune patients in various geographic localities.^{8–13}

In this study, we show that halofantrine is 100% effective in the treatment of malaria in nonimmune patients if a regimen including a second treatment on day 7 is applied. A similar experience was reported by Bernard and others,¹⁴ who successfully treated 59 patients from tropical Africa with a two-day course of halofantrine on days 1 and 8. The one-day dosing regimen (3×500 mg in group 1) in our study seems to be less effective, since four (15.4%) of 26 patients with *P. falciparum* infections recrudesced. Our results

TABLE 2
Parasite clearance and recovery from fever in the 74 malaria patients

	Day				
	0	2	5	7	14
No. (%) of parasitemic patients	74 (100)	56 (76)	2 (3)	1 (1)	0 (0)
Median parasitemia (parasites/ μ l)	40,350	2,000	0	0	0
Parasite density/ μ l (range)	50–500,000	50–20,000	<50–2,250	<50	0
No. (%) of patients with fever (>38°C)	71 (96)	25 (34)	3 (4)	1 (1)	0 (0)

indicate that the one-day dosing regimen, which is extremely effective in semi-immune persons, is not sufficient in nonimmune travelers. Thus, the manufacturer of halofantrine (Smith Kline Beecham, Munchen, Germany) has taken this into consideration and recommends an adult equivalent dose of 3×500 mg on days 0 and 7. Because of the relatively late recrudescences (days 14, 22, and 28) seen in four patients following treatment with halofantrine, it is essential to follow-up patients for at least one month before a cure may be confirmed. In the interest of the nonimmune patient, a treatment on day 0 only can no longer be justified. These findings confirm the preliminary data of Coulaud and others,¹⁵ who observed three recrudescences in 11 nonimmune individuals and recommended a second treatment on day 14. Since attempts to use a single dose regimen were unsuccessful,¹⁹ we chose the three-dose regimen used in this study.

In general, halofantrine was well tolerated by our patients. We saw no significant effects on hematologic or biochemical parameters, and the few mild reactions observed disappeared spontaneously. A judgment about the frequency of rare severe drug reactions in the order of 1/1,000 or less is usually made only after the drug has been licensed for a few years, as shown by the experience with pyrimethamine-sulfadoxine (Fansidar®)² or mefloquine.^{6, 20, 21} Therefore, a definitive statement concerning rare side effects after treatment with halofantrine cannot be made, but in view of its relatively short half-life of 1–2 days,^{22, 23} (compared with 25 days for mefloquine), long-lasting side effects are not very probable. Another advantage of its short half-life is that this can be of importance in reducing the selection of less susceptible parasites, thereby delaying the emergence of halofantrine resistance. (In this regard, halofantrine will not be used for general chemoprophylaxis, but only as a treatment drug.)

One problem encountered in using halofantrine is that it is poorly soluble in water, which probably explains the wide variation in bioavailability in different subjects.²² This may also account for the recrudescences we observed, although we did not measure drug levels in the sera of our patients. It was possible to exclude reinfection in our patients, since all of them stayed in Germany during the followup period. The recommendation that patients should take halofantrine with a fatty meal to increase absorption is

of limited practicability, since patients with clinical signs of malaria usually do not like to eat fatty food. Since no intravenous formulation of this drug currently exists, this drug has been restricted for use only in mild-to-moderate malaria cases.

Half of our patients took a chemoprophylaxis with chloroquine, and most of these cases originated from sub-Saharan Africa, where chloroquine resistance is well established.¹ Our findings indicate that halofantrine is effective in the treatment of chloroquine-resistant *P. falciparum* malaria, as well as in *P. vivax* infections in non-immune subjects. Given the finding that this drug was both efficacious and well-tolerated, its role in the treatment of multidrug-resistant falciparum malaria appears promising.

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