Pharmacokinetics, efficacy and toxicity of parenteral halofantrine in uncomplicated malaria

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- 1 The pharmacokinetics, efficacy and toxicity of a new parenteral formulation of halofantrine hydrochloride were evaluated in 12 adults with acute uncomplicated falciparum malaria and nine adults who attended in convalescence.
- 2 Intravenous halofantrine (1 mg kg⁻¹ infused in 1 h) was given every 8 h for a total of three doses in the acute study. Halofantrine cleared parasitaemia rapidly in all but one patient, with a mean (s.d.) parasite clearance time of 71 (29) h. Convalescent patients received a single infusion (1 mg kg⁻¹ in 1 h).
- 3 An open two-compartment model with the following parameters described the pharmacokinetics of halofantrine in acute malaria (mean (s.d.)): $V_1 = 0.36$ (0.18) l kg⁻¹; $CL = 0.355$ (0.18) l h⁻¹ kg⁻¹; $t_{1/2\alpha} = 0.19$ (0.12) h; $t_{1/2\beta} = 14.4$ (7.5) h.
- 4 Intravenous halofantrine in acute malaria produced significant prolongations of the QT and QT_c intervals (mean (s.d.)) of 20 (15%) and 8.2 (5.6)%, respectively ($P < 0.001$) after the third dose, but no clinically significant cardiotoxicity. Eight patients experienced mild to moderate thrombophlebitis at the halofantrine infusion site which had resolved in six by the time of follow-up. In the single treatment failure who received oral quinine, there was a large rise in plasma halofantrine concentration but this did not result in detectable toxicity.
- 5 These data provide the basis for the design of improved dosing regimens for the use of parenteral halofantrine in malaria.

Keywords halofantrine, parenteral uncomplicated *Plasmodium falciparum* pharmacokinetics antimalarial malaria malaria, treatment

Introduction

Halofantrine hydrochloride (originally known as WR 171669) is a 9-phenanthrenemethanol, one of over 300,000 potential antimalarial compounds tested by the Walter Reed Army Institute of Research between 1963 and 1974 [1]. Orally administered halofantrine has already earned an important place in the treatment of uncomplicated malaria and has proved particularly effective for multi-drug resistant *Plasmodium falciparum* infections [2]. Recent studies suggest that halofantrine may be more rapidly acting than quinine or

mefloquine [3]. However, halofantrine like many other arylaminoalcohols is poorly water soluble and a parenteral preparation has been unavailable till now. The pharmacokinetic properties of halofantrine have been difficult to establish because of poor and very variable oral absorption [1]. The development of a solubilised, stable preparation formulated for intravenous administration opens up the prospect of using halofantrine for the treatment of severe malaria, and has allowed a detailed assessment of its pharmacokinetic properties.

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Methods

Patients presenting to Paholpolpayuhasena Hospital, Kanchanaburi, Thailand between June and July 1992 with uncomplicated malaria (asexual parasitaemia with *P. falciparum*) were studied. Patients with severe malaria (coma, jaundice (bilirubin $> 3 \text{ mg dl}^{-1}$), severe anaemia (PCV $< 15\%$), renal impairment (serum creatinine $> 3 \text{ mg dl}^{-1}$), hypoglycaemia (blood sugar $< 2.2 \text{ mmol}$) or hyperparasitaemia ($> 5\%$ infected erythrocytes on admission) [4]), pregnant women and children under 14 years were excluded from the study. All patients denied taking antimalarial drugs prior to admission. Fully informed written consent was obtained from all patients and the study was approved by the Ethics Scientific Review subcommittee of the Ministry of Health, Thailand.

Study design and patient management

After admission to the study, the patient was weighed, a full history was obtained and a physical examination (including lying and standing blood pressure measurements) were carried out. The diagnosis of malaria was confirmed by examination of the peripheral blood film (see below). Peripheral venous catheters were inserted in each arm, one for the administration of halofantrine and for fluid replacement, and the other for blood sampling. Patency was maintained with heparinised saline.

Baseline blood samples were taken for routine biochemical and haematological tests and for the measurement of plasma lactate, glucose and quinine. Three 1 h halofantrine infusions were given (see below): the first on admission, and then 8 and 16 h later. During each infusion patients were observed closely for adverse reactions and vital signs (respiratory rate, pulse, lying blood pressure) were recorded every 15 min.

After each infusion, lying and standing blood pressures were measured and vital signs were recorded at the time of blood sampling. Blood samples (2 ml) were taken into heparinised tubes at 0.5, 1, 1.5, 2, 3, 4, 6 and 7.75 h after the start of the first infusion, and then just before the second and third infusions after which the sampling protocols were identical to that following the first infusion. After the third infusion further samples were taken at 30, 36, 48, 60, 72, and 84 h then 12 hourly until the patient was discharged. Samples for glucose and lactate measurements were also taken before each halofantrine infusion and after 24 h in the acute study. All samples were spun immediately at 4°C , and the plasma collected and stored at -60°C until drug assay. Plasma glucose and lactate concentrations were measured on site with glucose and lactate analysers (YSI Instrument Co. Inc., Yellow Springs, Ohio, USA).

Oral temperatures were taken and the peripheral blood film was examined every 6 h after admission until two successive films were negative. Subsequently blood films were taken every 12 h until discharge. An electrocardiogram (1 mV/10 mm, paper speed 25 mm s^{-1}) was recorded on admission, and then immediately

before and after each infusion of halofantrine, 24 h after admission and then at the time of discharge. Haematological and biochemical variables were monitored daily until discharge.

All patients received standard symptomatic care in addition to antimalarial treatment. Rehydration for the first 24 h was with intravenous dextrose saline, and oral paracetamol tablets were given every 4–6 h for headache, myalgia and high fevers (oral temperature $> 38.5^{\circ}\text{C}$). All patients received a normal hospital diet.

Parasitaemia was evaluated on Field's stained thin (asexual parasites/1000 red cells) and thick films (asexual parasites/200 white cells). The time to the first of two successive negative thick films (< 1 parasite/200 white cells) was taken as the parasite clearance time (PCT). The PC_{50} and PC_{90} values were defined as the times for 50% and 90% fall from baseline parasite counts respectively. FCT_A was defined as the first time oral temperature fell below 37.5°C and FCT_B as the time to become and remain afebrile [5].

Drugs

Racemic-halofantrine hydrochloride was supplied by the manufacturers (SmithKline Beecham Pharmaceuticals Ltd, SB House, Brentford, Middlesex, TW8 9BD, UK) in sterile ampoules (2 ml containing 50 mg ml^{-1} drug in dimethylacetamide/polyethylene glycol in a ratio of 40/60 (v/v)). The preparation is a clear, odourless, viscous liquid and can withstand dilution up to fifteen times its original volume in 5% w/v dextrose. It has been well tolerated in earlier phase I studies in doses up to 1 mg kg^{-1} given over 1 h (Dr John Horton, personal communication).

Patients were given three 1 mg kg^{-1} doses by i.v. infusion over 1 h with 8 h between each infusion. Infusions of halofantrine were given directly into a large peripheral vein through a butterfly or a Teflon cannula by a Braun™ perfusor syringe after fifteenfold dilution in 5% w/v dextrose solution. Each dose was followed by an infusion of 200 ml of 5% w/v dextrose given over 1–2 h to minimise the local irritant effects of halofantrine.

To reduce the risk of a recrudescence of infection after halofantrine treatment, tetracycline hydrochloride (250 mg every 6 h, orally for 7 days, Government Pharmaceutical Organisation, Thailand) was given to each patient 48 h after admission. If parasitaemia recrudesced, oral quinine (10 mg kg^{-1} every 8 h for 7 days) was added to the standard tetracycline treatment.

Data and drug analysis

After testing for normality, normally distributed data were analysed using Student's *t*-test or ANOVA and non-normally distributed data were analysed by the Mann-Whitney U or Wilcoxon Sign Rank tests. Repeated measures were analysed by multivariate tests for repeated measures with time as an independent variable. Standard pharmacokinetic parameters were derived using PCNONLIN (v4.0, Statistical Consultants Inc. Lexington, Kentucky). Using the Aikake

information criterion, a two-compartment model gave the best fit to the data.

ECG analysis was based on parameters derived automatically from the ECG machine (Auto Cardiner, Fukuda Denshi Co., Ltd, Tokyo), although all QT intervals were confirmed independently by direct measurement. QT dispersion was calculated by subtracting the longest and shortest QT intervals determined visually from the trace. The QT interval was measured from the start of the QRS complex to the point at which the T wave trace returned to the TP baseline. All patients had at least 10/12 leads which could be assessed on every trace. Plasma halofantrine and *N*-desbutylhalofantrine concentrations were measured within 1 month by the h.p.l.c. method as described by Keeratithakul *et al.* [6]. The limit of detection of halofantrine was 11 ng ml⁻¹, and the coefficients of variation for the halofantrine assays at 50 ng ml⁻¹, 100 ng ml⁻¹, 500 ng ml⁻¹ and 4000 ng ml⁻¹ were, respectively, 9.4%, 6%, 5.1% and 5.3%. Incubation of halofantrine with quinine in plasma prior to extraction for h.p.l.c. did not affect the assay of halofantrine.

Convalescent study

Patients attended between 10 days to 3 weeks after discharge for a follow-up study. This consisted of a history and detailed physical examination, assessment of a blood film, and ECG and baseline haematology and biochemistry. A single infusion of halofantrine was then given (1 mg kg⁻¹ over 1 h) and the specimens and sampling schedule for clinical, biochemical and drug measurements was as in the acute study. Sampling was stopped after 8 h.

Results

Clinical

Twelve patients (11 male, 1 female) with acute uncomplicated falciparum malaria were admitted to the study, and nine attended for follow up. The clinical variables of these patients on admission are shown in Table 1. All patients presented with a history of fever with a mean (s.d.) oral temperature on admission of 38.8 (1.3)°C, 10/12 (83%) complained of headache and 5/12 (42%) of backache. One patient had diarrhoea on admission, another patient had a widespread itchy, erythematous eruption following self-administration of proprietary medication for headache, and another patient had labial *Herpes simplex* infection.

Biochemistry and haematology

None of the patients had evidence of severe malaria on the basis of laboratory investigations (data not shown). The admission haematological and biochemical profiles of patients in our study were typical for patients with uncomplicated malaria, and consisted of mild anaemia, thrombocytopaenia, and minor abnormalities in tests of liver function. These abnormalities improved after treatment. Additionally, however, there was an early

increase in eosinophil count in four patients on the second day of treatment (values of 37%, 8%, 8% and 7%, absolute counts/μl, respectively: 2740, 290, 710 and 340) and this eosinophilia persisted after discharge in three patients who reattended for follow up (11%, 13% and 19%, absolute counts/μl, respectively: 970, 1770, 790). Lactate concentrations were not grossly elevated on admission, and glucose concentrations did not fall significantly after halofantrine (data not shown).

Parasitological responses

The clinical and parasitological responses of the patients are summarised in Table 1 and Figure 1. Parasitaemias began to decline rapidly after the second dose of halofantrine. The mean fever clearance time (FCT_B)

Table 1 Clinical characteristics of the 12 study patients

Variable	Mean ± s.d., median (range) or proportion of patients (%)
<i>Baseline</i>	
Age (years)	21 (16–56)
Weight (kg)	52 (45–74)
Past history of malaria	8 (75%)
Fever (days)	2.8 ± 1.4
Admission temperature (°C)	38.8 ± 1.3
Pulse (beats min ⁻¹)	97 ± 19
Respiration (min ⁻¹)	28 (20–40)
Hepatomegaly	3/12 (25%)
Splenomegaly	2/12 (17%)
Parasitaemia (μl ⁻¹)*	74832 (44839–145822)
Lactate (mmol l ⁻¹)	2.2 ± 0.7
Glucose (mmol l ⁻¹)	6.9 ± 1.7
<i>Drug responses</i> †	
FCT _A (h)	8 (2–28, n = 9)
FCT _B (h)	30 (3–84, n = 11)
PC ₅₀ (h)	13.6 ± 6.0
PC ₉₀ (h)	22.7 ± 8.7
PCT (h)	71 ± 29

*Geometric mean and inter-quartile range.

†For abbreviations see **Methods**.

Figure 1 Mean (± s.e. mean) change in parasitaemia from baseline after parenteral halofantrine (1 mg kg⁻¹ given three times every 8 h) in 12 patients with uncomplicated *P. falciparum* malaria.

was faster than the parasite clearance time (Table 1; $P = 0.013$). There was no significant correlation between estimates of fever and parasite clearance in this small study.

One patient required the addition of oral quinine 65.5 h after the first halofantrine infusion because of a rise in parasitaemia from a nadir of 120 parasites μl^{-1} (at 36 h after admission) to a secondary peak of 15,000 parasites μl^{-1} (66 h after admission). Parasitaemia had subsequently cleared by 96 h after admission. In this patient plasma halofantrine concentrations rose dramatically after quinine had been given (Figure 2), but there were no significant changes in clinical or ECG parameters immediately before and after the administration of quinine. Halofantrine concentrations had fallen to prequinine levels of 96 h.

Pharmacokinetic analysis

Mean plasma halofantrine concentrations following the three intravenous infusions of halofantrine hydrochloride are shown in Figure 3a. The decline in plasma concentrations of halofantrine after the infusion was biphasic, and a two-compartment open model was fitted to each set of individual data. The derived pharmacokinetic parameters are listed in Table 2.

The concentration of the principal active metabolite, *N*-desbutylhalofantrine (DBH) rose from a mean (s.d.) ng ml^{-1} of 3.7 (6.7) at the end of the first infusion to a peak of 27 (18.5) 35 h later. More than 90% of this peak value had been reached by 15 h after the first infusion

Figure 2 Plasma halofantrine concentrations in the treatment failure who received oral quinine.

following a steady increase in mean values. These low concentrations precluded further pharmacokinetic analysis of the fate of DBH. Mean plasma halofantrine concentrations after a single infusion in the nine patients who attended for follow up are shown in Figure 3b, with the mean drug concentrations from the acute study superimposed. The terminal elimination half-life and MRT of halofantrine were significantly shorter and CL was higher in convalescence than during acute malaria (Table 2).

Figure 3 a) Mean ($\pm$ s.e. mean) plasma halofantrine concentrations following three 1 h infusions (each 1 mg kg^{-1} , at 8 h intervals) in 12 patients with uncomplicated *P. falciparum* malaria. Data from one patient who received quinine at 66 h are omitted beyond this point (see Text and Figure 2). The last time point (84 h) represents data from six patients in whom halofantrine was still detectable. b) Mean ($\pm$ s.e. mean) plasma halofantrine concentrations following a single 1 h infusion (1 mg kg^{-1}) in nine convalescent patients ($\circ$) with mean concentrations from 12 patients with acute malaria ($\blacksquare$) superimposed.

Table 2 Mean ($\pm$ s.d.) and range of pharmacokinetic parameters describing the fate of halofantrine after i.v. administration to patient with acute malaria ($n = 12$) and during convalescence ($n = 9$)

	Acute malaria	Convalescent	P value (95% CI of mean difference)
	$n = 12$	$n = 9$	
$t_{1/2\alpha}$ (h)	0.19 ± 0.12 (0.07–0.52)	0.18 ± 0.16 (0.05–0.55)	NS
$t_{1/2\beta}$ (h)	14.4 ± 7.5 (3.6–27)	7.5 ± 7.7 (3–27)	< 0.02 (0.36–13.4)
$C_{\max}$ (mg l^{-1})	824 ± 159 (560–1112)	918 ± 343 (543–1594)	NS
CL ($\text{l h}^{-1} \text{ kg}^{-1}$)	0.355 ± 0.18 (0.095–0.85)	0.472 ± 0.16 (0.31–0.7)	0.035 (0.03–0.26)
V_{ss} (l kg^{-1})	4.8 ± 2.3 (1.8–9.4)	3.1 ± 2.7 (1.1–9.7)	0.039 (–0.5–3.9)
V_1 (l kg^{-1})	0.36 ± 0.18 (0.17–0.75)	0.35 ± 0.32 (0.07–1.16)	NS
MRT (h)	16.6 ± 8.9 (3.8–30.9)	8.2 ± 8.8 (3.2–30.7)	< 0.02 (0.7–16.1)

Toxicity

The most common and troublesome symptom caused by parenteral halofantrine was local irritation. Six patients complained of mild pain during the infusions of halofantrine. Thirty-six to 48 h following the infusions, three patients developed local symptoms of venous irritation, with a palpable painful vein and surrounding erythematous swelling. The erythema and swelling extended in a strip approximately 10 cm long and 4 cm wide. Two patients developed similar but less marked reactions and a further three complained of mild pain and had slightly tender infusion sites. Four patients had no adverse local reactions.

Two patients developed tender hepatomegaly 22 h after admission; in one patient there was further enlargement of admission splenomegaly as well. Another patient complained of a brief episode of abdominal pain (lasting less than 15 min) 1.5 h after the second halofantrine infusion but there were no abnormalities on examination of the abdomen and, after vomiting, the pain resolved spontaneously. No patient developed diarrhoea, although one patient who did not have diarrhoea on admission experienced one episode of watery stools 24 h afterwards.

One patient had symptomatic postural hypotension before receiving his first dose of halofantrine (lying and standing systolic/diastolic blood pressures (mm Hg): pre-halofantrine 115/65 and 65/?; post-halofantrine 100/65 and 80/30). Subsequently, however, there were no episodes of symptomatic postural hypotension.

ECG changes (Table 3)

There were no significant changes in the PR interval during the course of the acute study. Nine hours after admission, the mean QRS duration had increased slightly from baseline values (mean (s.d.) increase 6.4 (9)%) but this change was not significant by repeat measures analysis ($P = 0.08$), and by 24 h the mean duration of the QRS had reverted to baseline values.

The most consistent changes after halofantrine infusions were significant increases in the duration of the

QT and QT_C intervals. The duration of the mean (s.d.) QT interval increased by 16 (10)%, 20 (11)% and 20 (15)% of baseline values immediately after each halofantrine infusion ($P < 0.001$). The initial relatively large increase in QT interval reflected the effects both of halofantrine and a fall in heart rate because of the treatment of fever (Table 3). The corresponding changes in QT_C intervals which attempt a correction for different heart rates were: 4.2 (6.4)%, 7.7 (4.1)% and 8.2 (5.6)% ($P < 0.001$). There was no increase in QT dispersion concomitant with the increase in the duration of the QT interval. The mean (s.d.) values for QT dispersion on admission and 1, 9, and 17 h subsequently were, respectively, 43 (22), 30 (25), 47 (29) and 46 (21) ms. These values were similar to those previously reported in healthy individuals [7, 8].

Two patients had evidence of incomplete right bundle branch block on baseline ECG analysis. In one, the ECG trace had reverted to normal after one infusion of halofantrine. Slight changes in delayed afterpotentials were visible in some patients in the anterior chest leads (V1–V3) and additionally there were some alterations in 'T' wave morphology. A more detailed description of these ECG changes will be reported elsewhere.

Follow-up

On follow up, two patients who had been discharged most recently still had mild residual thrombophlebitis, the remainder were symptomless and had no abnormalities on examination. One patient returned to work, but 10 days after attending for a follow-up study presented with a history of slight headache followed by a major motor seizure. On examination, he was pyrexial (axillary temperature 38.9° C), and was confused and restless. He did not have a stiff neck, but had disconjugate gaze, with symmetrical pupils which reacted consensually and directly to light. There were no retinal haemorrhages or papilloedema, and no localising signs on examination of his peripheries. He had a neutrophilia (total white cell count $14.6 \times 10^9 \text{ l}^{-1}$, 75% neutrophils, 2% eosinophils, 23% lymphocytes),

Table 3 ECG changes in patients receiving parenteral halofantrine

Time (h)	PR(s)	QRS(s)	QT(s)	QT _C (s ^{1/2})	RR(1/s)
Mean $\pm$ s.d., $n = 12$					
0	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.33 $\pm$ 0.04	0.41 $\pm$ 0.02	0.64 $\pm$ 0.13
1	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.38 $\pm$ 0.04	0.43 $\pm$ 0.03	0.73 $\pm$ 0.17
8 ($n = 10$)	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.37 $\pm$ 0.04	0.42 $\pm$ 0.03	0.80 $\pm$ 0.17
9	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.39 $\pm$ 0.04	0.44 $\pm$ 0.03	0.80 $\pm$ 0.13
16 ($n = 10$)	0.15 $\pm$ 0.02	0.11 $\pm$ 0.03	0.37 $\pm$ 0.03	0.42 $\pm$ 0.01	0.80 $\pm$ 0.10
17	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.39 $\pm$ 0.03	0.44 $\pm$ 0.03	0.80 $\pm$ 0.09
24	0.15 $\pm$ 0.02	0.09 $\pm$ 0.01	0.36 $\pm$ 0.03	0.42 $\pm$ 0.02	0.74 $\pm$ 0.11
$n = 9$					
FU0	0.15 $\pm$ 0.02	0.10 $\pm$ 0.01	0.37 $\pm$ 0.04	0.41 $\pm$ 0.01	0.82 $\pm$ 0.17
FU1	0.16 $\pm$ 0.02	0.11 $\pm$ 0.01	0.41 $\pm$ 0.04	0.43 $\pm$ 0.02	0.96 $\pm$ 0.16
FU8 ($n = 8$)	0.16 $\pm$ 0.02	0.10 $\pm$ 0.01	0.41 $\pm$ 0.03	0.41 $\pm$ 0.01	

FU = follow-up patients.

a haemoglobin of 13.1 g dl^{-1} , and normal urea, creatinine, electrolytes, liver function tests and urinalysis. Findings of CSF examination were: red cell count of $19/\text{mm}^3$, white cell count of $28/\text{mm}^3$ (4 neutrophils, 24 lymphocytes), protein of $65 \text{ mg\%}$ and a glucose of $75 \text{ mg\%}$. Repeated examinations of thick films did not reveal any evidence of malaria. He had already begun treatment with intravenous quinine, and recovered completely with supportive therapy in 48 h with the differential diagnoses of viral encephalitis or post-malaria neurological syndrome. In convalescent patients a single 1 h infusion of halofantrine significantly prolonged the PR, QT and QT_C intervals ($P = 0.007$, $P = 0.05$ and $P = 0.0006$, respectively, Table 3).

Discussion

Oral halofantrine is well tolerated, rapidly effective against multidrug resistant strains of *Plasmodium falciparum* [1, 2], and arrests parasite development within 6 h of administration unlike quinine and sulphadoxine-pyrimethamine which do not have demonstrable effects even after 24 h of drug exposure [3]. Although these features make halofantrine a potentially attractive treatment, severe malaria should be treated with a parenteral antimalarial whenever possible [5]. However, the development of a parenteral preparation of halofantrine has been hampered by its poor solubility in aqueous solutions.

The antimalarial activity of oral halofantrine is mediated partly by the parent drug and partly by its *N*-desbutyl metabolite [9]. Intravenous administration avoids first-pass metabolism of halofantrine such that the ratio of parent drug to metabolite in the plasma is much higher than after oral administration. Indeed the concentrations of *N*-desbutylhalofantrine measured in this study were too low to allow pharmacokinetic analysis, and would not have contributed to a significant antimalarial effect. Nevertheless, the plasma concentrations of halofantrine were associated with effective clearance of parasitaemia in all but one of the patients with uncomplicated malaria. Peak plasma halofantrine concentrations were similar to those recorded after eight-fold higher oral doses ($824 (159)$ vs $896 (370) \text{ ng ml}^{-1}$ mean (s.d.), respectively, [9]), but concentrations then fell rapidly as the drug distributed. Our data confirm that the oral bioavailability of halofantrine is low and that its total apparent volume of distribution is large.

There was less inter-subject variability in the plasma drug concentrations after i.v. compared with oral dosing and the estimate of the terminal elimination half-life after i.v. administration was less than that observed after oral dosage (Table 3 and [1]), possibly because it was more difficult to define the lower drug concentrations seen after i.v. administration. Alternatively,

rate-limiting absorption could prolong the terminal elimination half-life after oral dosing.

Local toxicity was a significant problem after intravenous infusion. Halofantrine has not previously been considered to have cardiac effects, but our study clearly shows that halofantrine can produce a moderate prolongation of the QT interval, both in patients with acute malaria and in convalescence (Table 3). We have recently confirmed similar ECG changes after oral administration of the drug suggesting that the parent compound and not the drug vehicle is responsible. In addition to more marked QT_C prolongation observed in the larger study of oral halofantrine ($\sim 12\%$ from baseline with a mean combined plasma halofantrine and *N*-desbutylhalofantrine concentration of 1000 ng ml^{-1} [10], Results and Table 3), there was also some evidence of prolongation of the PR interval in patients with malaria. The intravenous regimen of halofantrine used in this study produced a similar degree of prolongation of the QT_C to quinine, and less than that seen with quinidine [11], the drug of choice for the treatment of severe malaria in the USA. In the context of the treatment of severe malaria moderate prolongation of the QT interval would probably be an acceptable side-effect.

In one patient plasma halofantrine concentrations rose markedly when quinine was given to control parasitaemia. This interaction may result from displacement of halofantrine by quinine from tissue binding sites and should be confirmed in future studies. However, there were no evident pharmacodynamic consequences, in particular no additional prolongation of the QT interval. In another patient we have documented a self-limited episode of encephalitis similar to two other episodes in a much larger study of oral halofantrine [12]. Eosinophilia has not been noted previously after oral treatment with halofantrine, although a delayed eosinophilia does follow treatment with oral quinine [13].

The potential role for halofantrine in the treatment of severe malaria remains to be elucidated. An improved continuous infusion regimen based on the pharmacokinetic parameters derived in this study should now be tested, and if it is effective, safe and well tolerated in moderately severe malaria, parenteral halofantrine should be studied in severe malaria.

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