Pharmacokinetics of halofantrine in Thai patients with acute uncomplicated falciparum malaria

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Twelve patients with acute uncomplicated falciparum malaria were admitted to the Hospital for Tropical Diseases for 42 days. The patients were treated with halofantrine 500 mg 6 hourly for three doses and halofantrine and its desbutyl metabolite were analysed in plasma by h.p.l.c. $C_{\max}$ values of halofantrine and desbutylhalofantrine ($n = 12$) were 1192 ± 410 (mean $\pm$ s.d.) and 397 ± 160 ng ml⁻¹ with $t_{\max}$ values of 16 ± 2 and 55 ± 26 h, respectively. AUC was 60.6 ± 23.9 and 48.5 ± 22.2 mg l⁻¹ h, respectively, for halofantrine and its metabolite. Halofantrine cured 83% of the patients but in two patients a reduction only in asexual parasitaemia was seen and no overall parasite clearance occurred. One of these, however had relatively low plasma concentrations of both halofantrine and its desbutyl metabolite and it appeared to be a case of inadequate treatment rather than true resistance. We suggest that the large intersubject variability in plasma drug concentrations may relate in part to its poor and inconsistent bioavailability and this rather than true resistance might be responsible for some of the treatment failures.

Keywords halofantrine antimalarial pharmacokinetics

Introduction

The emergence of strains of *Plasmodium falciparum* resistant to chloroquine and other widely used anti-malarials has necessitated a search for alternative drugs for the treatment of this infection. Halofantrine has been shown to be highly active against multi-drug resistant isolates of *Plasmodium falciparum* in preclinical studies (Desjardins *et al.*, 1979; Schmidt *et al.*, 1978). Clinical trials conducted in recent years with oral halofantrine have shown differences in efficacy which may be due to the total dose and dosing regimen used. Information on the absorption kinetics of halofantrine, particularly in patients with falciparum malaria, is limited. This is important since irregular absorption and variable peak drug concentrations are likely to affect the clinical effectiveness of this drug (Boudreau *et al.*, 1988). There are no pharmacokinetic data relating to the use of halofantrine in the treatment of malaria and this may be relevant to the optimisation of treatment regimens and the identification of cases of true drug resistance. The information gained from the present study aims to provide a better understanding of the pharmacokinetics of halofantrine in malaria patients and may assist in the design of more appropriate dosage regimens.

Methods

Patients

Twelve patients with uncomplicated falciparum malaria, aged 15 to 60 years, with a weight range of 45–60 kg, and no history of liver or kidney diseases were recruited into the study. No other drugs were taken concurrently during the study. Written informed consent to participation was obtained from all patients and the study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

On admission each patient had a physical examination, routine blood examination and blood chemistry investigations, plain chest X-ray, urinalysis and ECG. Baseline plasma concentrations of halofantrine, quinine and mefloquine were measured. All patients were admitted to the Bangkok Hospital for Tropical Diseases for 42 days.

Treatment

The patients were treated orally with rac-halofantrine hydrochloride (500 mg) at 6 h intervals for three doses.

Two patients who failed to respond to treatment were

given quinine 500 mg base 8 hourly and tetracycline (250 mg), four times a day for 7 days.

Parasite counts

Parasite counts were performed twice daily until negative, then once daily until day 42.

Blood examination and biochemistry

Haematological examinations and biochemical screens were performed on days 0, 2, 4, 7 then weekly until day 42. These included complete blood count, liver function tests, kidney function tests and electrolyte measurements.

Blood collection for pharmacokinetic studies

Whole blood samples (5 ml) were collected into heparinised tubes at 0, 30, 60 min and 2, 3, 4, 6 h (before dosing), 6.5, 7, 8, 9, 10, 12 h (before dosing), 12.5, 13, 14, 16, 18, 22, 24, 48 h and days 3, 4, 7, 14. Total blood loss was 150 ml within the 2 week period. Plasma was removed immediately following centrifugation (1200 g, 15 min) and frozen (-70°C) prior to transportation to Liverpool for analysis.

Adverse effects

All adverse reactions during the study were recorded with the data and time at which they occurred and disappeared. These included any gastro-intestinal, central nervous system, cardiovascular, dermatological and haematological effects and other changes possibly attributable to halofantrine.

Vomiting and diarrhoea: the frequencies on day 0 (min or h after dosing) and days 1, 2, 3 and 4 were recorded.

Itching/skin rash: If there was any evidence of itching/skin rash after the administration of halofantrine, the intensity and duration of rash were recorded.

Blood pressure (BP) was measured at intervals during the frequent blood sampling and weekly until day 42.

Analysis of halofantrine

Plasma concentrations of halofantrine and its desbutyl metabolite were measured by an h.p.l.c. method (Milton *et al.*, 1988) which is both selective and sensitive with a recovery of 98% for halofantrine and 94% for the desbutyl metabolite. The intra and inter-assay coefficients of variation in plasma were 8.7% for halofantrine ($n = 8$) and 12.3% for desbutylhalofantrine ($n = 8$) at a concentration of 30 ng ml^{-1} . Minimum detectable concentrations were 1.0 ng ml^{-1} (halofantrine) and 0.7 ng ml^{-1} (desbutylhalofantrine).

Pharmacokinetic analysis

Plasma halofantrine concentration-time data were fitted using PC-NONLIN. The metabolite concentration-time data were analysed by compartmental model independent methods (Gibaldi & Perrier, 1982). The area under the plasma concentration-time curve was calculated by the linear trapezoidal rule. C_{max} and t_{max} were the observed values.

Statistical analysis

Student's *t*-test was used to compare the pharmacokinetic parameters for halofantrine and its desbutyl metabolite, rejecting the null hypothesis if $P < 0.05$.

Clinical data

Only those patients who completed a 42-day follow-up were evaluated for efficacy. Clinical evaluations were based on parasite and fever clearance time, recrudescence rate, frequency and severity of adverse clinical effects and incidence of abnormal laboratory observations.

Results

Pre-treatment assessment

Parasite counts (asexual forms) on admission were $3.16\text{--}146.4 \times 10^9\text{ l}^{-1}$.

Clinical response

Ten patients showed a sensitive response with fever and parasite clearance times of $50 \pm 29\text{ h}$ and $78 \pm 20\text{ h}$, respectively. Two patients showed an RII type of response in that a transient reduction in asexual parasitaemia was demonstrated without *total* parasite clearance (Bruce-Chwatt, 1980).

Adverse effects

Three patients had vomiting ranging from 2 to 6 times within 24 h after the first dose of halofantrine. Two patients had diarrhoea. No other drug related side-effects were apparent.

Pharmacokinetics of halofantrine and desbutylhalofantrine

Mean plasma concentrations of halofantrine and its desbutyl metabolite are shown in Figure 1a. The first peak concentration after the first dose was $682 \pm 443\text{ ng ml}^{-1}$, the second peak was $888 \pm 478\text{ ng ml}^{-1}$ and the third peak concentration of $1192 \pm 410\text{ ng ml}^{-1}$ was attained 16 h following the first dose.

Plasma concentrations of halofantrine and its pharmacologically active metabolite desbutylhalofantrine (Horton, 1988) in one patient who vomited six times during treatment were significantly lower than the mean concentrations obtained from 10 patients who showed a sensitive response (Figure 1b). This particular patient had an RII type of response. However, the concentrations obtained from another recrudescing (i.e. showing a short-term relapse with renewed clinical symptoms) patient who vomited were within the same range as those with a sensitive response.

The pharmacokinetic parameters for halofantrine and desbutylhalofantrine are presented in Table 1. Following the first dose a mean apparent absorption half-life of $4.0 \pm 1.9\text{ h}$ ($\pm\text{ s.d.}$) was obtained. The apparent terminal elimination half-life was $4.7 \pm 1.3\text{ days}$. The mean area

Figure 1 a) Mean plasma concentrations of halofantrine (□) and desbutylhalofantrine (■) in 12 Thai patients with uncomplicated *Plasmodium falciparum* malaria following oral administration of halofantrine, 8 mg kg⁻¹ 6 hourly for three doses. b) Mean plasma concentrations of halofantrine (■) and desbutylhalofantrine (◇) in 10 patients who showed a sensitive response compared with one patient who showed an RII response (see text); (○) halofantrine, (□) desbutylhalofantrine. Standard deviations are excluded for purposes of clarity.

Table 1 Pharmacokinetic parameters describing the fate of halofantrine and desbutylhalofantrine after oral administration of halofantrine

	Halofantrine (n = 12)	Desbutylhalofantrine (n = 8)
C (ng ml ⁻¹)	1192 ± 410	397 ± 160
t (h)	16 ± 2	55 ± 26
t _{abs} (h)	4.0 ± 1.9	—
t _{1/2} (days)	4.7 ± 1.3	4.9 ± 1.6
AUC (mg l ⁻¹ h)	60.6 ± 23.9	48.5 ± 22.2

under the plasma drug concentration-time curve was 60.6 ± 23.9 mg l⁻¹ h.

Derived pharmacokinetic parameters for desbutylhalofantrine were calculated from plasma concentrations of eight patients as four patients were excluded from the analysis owing to insufficient sampling in the terminal phase. The mean maximum concentration was significantly lower than the parent compound (397 ± 160 vs 1192 ± 410 ng ml⁻¹) and t_{max} was significantly longer, i.e. 55 ± 26 h. The mean terminal half-life (desbutyl metabolite) of 4.9 ± 1.6 days and AUC of 48.5 ± 22.2 mg l⁻¹ h, were not statistically different from those obtained for the parent drug.

Discussion

Halofantrine has been shown to be effective in the treatment of falciparum malaria in several clinical trials over the past 8 years. The most effective dose has been 500 mg every 6 h for three doses for 8 mg kg⁻¹ 6 hourly for three doses in children (Boudreau *et al.*, 1988; Cosgriff *et al.*, 1982; Coulaud *et al.*, 1986; Rinehart *et al.*, 1976; Watkins *et al.*, 1988; Wirima *et al.*, 1988). In the present study, although it cured 83% (10/12) of the patients, two showed a high degree of resistance (i.e. RII type of response). However, one of these patients had relatively low plasma concentrations both of halofantrine and its metabolite when compared with those observed following a sensitive response (Figure 1b). The failure may be attributable to loss of the drug through vomiting but a second patient who vomited achieved therapeutically effective concentrations of halofantrine. Incomplete absorption may also be responsible for the failure to respond. Whatever the mechanism, monitoring of plasma concentrations of halofantrine and desbutylhalofantrine is essential for the identification of true resistance. A comparative study of plasma halofantrine concentrations in patients with a sensitive and resistant response is needed to evaluate accurately the efficacy of halofantrine in multi-drug resistant falciparum malaria.

Peak drug concentrations and the total amount of drug absorbed are two important factors in determining drug efficacy (Boudreau *et al.*, 1988). Previous pharmacokinetic studies of halofantrine in man have shown considerable inter and intra individual variability in healthy volunteers (Broom, 1989; Fleckenstein *et al.*, 1983; Milton *et al.*, 1989). Oral bioavailability appears to be increased by food (Milton *et al.*, 1989) and early clinical evaluations of halofantrine suggested that therapeutic failure was a consequence of wide variation in drug absorption. The maximum concentration of halofantrine observed in the present study was lower than that reported previously in healthy subjects (Broom, 1989). Malaria infection, ethnic differences and food intake during drug administration are possible explanations for these differences. Healthy subjects in the previous study had taken food 2 h before administration of the second and third doses, hence absorption was likely to be enhanced, whereas malaria patients are likely to be in a fasting state during drug administration. Although some patients will have had some food, it would be a mainly light meal with a low fat content which would enhance absorption. The difference in maximum concentrations achieved in different ethnic groups has been demonstrated with mefloquine, another structurally related antimalarial (Karbwan *et al.*, 1987) and a comparative study of Thai healthy subjects may be needed to clarify this discrepancy.

The findings of this study suggest a difference in C_{max} and plasma drug concentrations on the first day after halofantrine administration in patients with falciparum malaria compared with those obtained in healthy subjects (Broom, 1989) and indicate the importance of food intake during drug administration (Milton *et al.*, 1989). However, administration of food during treatment is not practicable as most patients would refuse to eat during acute illness and it may be necessary to increase the total dose of halofantrine in order to obtain the same concentrations as in subjects who took drug with food.

The shorter half-life of halofantrine compared with those of mefloquine and chloroquine may be important in the development of resistance to halofantrine since persistent subtherapeutic concentrations may allow parasite survival and facilitate the development of resistance. Therefore, it is suggested that in areas where parasites have progressively become resistant to halofantrine, such as in the Eastern part of Thailand (Bunnag

et al. unpublished), a higher total dose of halofantrine should be considered to ensure the adequacy of plasma drug concentrations.

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