Pharmacokinetics of halofantrine in healthy Thai volunteers

Halofantrine has been shown to be highly effective against multi-drug resistant falciparum malaria in Thailand (Boudreau *et al.*, 1988). We have demonstrated that the pharmacokinetics of halofantrine in Thai patients with malaria are different from those in Caucasian volunteers (Karbwang *et al.*, 1991). As both ethnic and disease-related factors might contribute to the differences observed we now report on the pharmacokinetics of halofantrine in healthy Thais.

Eight male volunteers, aged 15 to 60 years, with a weight range of 45–60 kg, and no history of liver or kidney diseases were recruited. No other drugs were taken concurrently and written informed consent was obtained. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University. On admission, each subject had a physical examination, routine blood and blood chemistry investigations, urinalysis and ECG. All subjects were admitted into the Bangkok Hospital for Tropical Diseases for 2 days and returned for follow-up daily for 1 week then weekly until day 35. Dosage with *rac*-halofantrine hydrochloride (500 mg) was at 6 h intervals for three doses with haematological examinations and biochemical screens performed on day 0, then weekly until day 35. Whole blood (5 ml) samples were collected into heparinised tubes at 0, 30, 60 min and 2, 3, 4, 6, 6.5, 7, 8, 9, 10, 12, 12.5, 13, 14, 16, 18, 22, 24, 48 h and days 3, 4, 7, 14, 21, 28 and 35 after the first dose. Any adverse reactions were recorded, notably gastro-intestinal, central nervous system, cardiovascular, dermatological and haematological effects and other changes possibly attributable to halofantrine. Blood pressure was measured frequently during blood sampling and weekly until day 35. Plasma concentrations of halofantrine and desbutylhalofantrine were measured by h.p.l.c. (Milton *et al.*, 1988). Plasma halofantrine concentration-time data were analysed by the non linear least squares regression program PC-NONLIN. A two-compartment model was deemed to offer the best fit as assessed

quantitatively by *F*-test analysis of the residual sums of squares (Boxenbaum *et al.*, 1974). Metabolite concentration-time data were analysed by compartment model independent methods (Gibaldi & Perrier, 1982). $C_{\max}$ and $t_{\max}$ were the observed values. Student's unpaired *t*-test was used in comparisons of AUC, $t_{1/2\text{abs}}$ and $t_{1/2}$ for halofantrine and its desbutyl metabolite obtained in this study with those obtained from patients with falciparum malaria (Karbwang *et al.*, 1991). $C_{\max}$ and $t_{\max}$ values were compared using a Wilcoxon rank sum test for unpaired observations.

No significant drug related changes were seen in any of the haematological or biochemical parameters. The pharmacokinetic variables are listed in Table 1. When estimates of these parameters were compared with those obtained from age and sex matched patients with malaria following an identical protocol (Karbwang *et al.*, 1991) apparent half-life values for absorption and elimination were shorter in the healthy volunteers. In addition, the apparent terminal half-life of desbutylhalofantrine was longer in healthy volunteers when compared with that in patients with malaria. The increase in $C_{\max}$ in healthy subjects was not statistically significant.

We conclude that differences exist in the pharmacokinetics of halofantrine between patients and volunteers within this ethnic group. These observations might relate in part to dietary factors such as food intake, known to increase the plasma concentrations of halofantrine after a single oral dose (Milton *et al.*, 1988). This was not rigorously controlled in the volunteer group but, in contrast to the earlier study, food of a high fat content was not administered either to volunteers or patients. The relatively greater persistence of plasma concentrations of the active metabolite desbutylhalofantrine (Horton, 1988) may lead to relatively greater accumulation on multiple dose administration to volunteers if metabolite elimination is rate-limiting, a factor which might become important should halofantrine be used for malaria prophylaxis.

Table 1 Pharmacokinetics of halofantrine and desbutylhalofantrine in healthy Thai volunteers and Thai patients with falciparum malaria. Values for $t_{1/2\text{abs}}$ and $t_{1/2}$ and AUC are mean $\pm$ s.d. Values for $t_{\max}$ and $C_{\max}$ are median (range) and are the values assessed after the third dose of halofantrine hydrochloride

	Healthy subjects		Malaria patients (Karbwang <i>et al.</i> , 1991)	
	Halofantrine (n = 8)	Desbutylhalofantrine (n = 8)	Halofantrine (n = 12)	Desbutylhalofantrine (n = 8)
$C_{\max}$ (ng ml ⁻¹)	1163* (777–3006)	288* (74–904)	1104 (82–2171)	303 (125–582)
$t_{\max}$ (h)	18* (16–22)	36* (18–72)	16 (13–24)	48 (22–96)
$t_{1/2\text{abs}}$ (h)	1.9 $\pm$ 0.4 [†]	—	4.0 $\pm$ 1.9	—
$t_{1/2}$ (days)	1.8 $\pm$ 0.1 [†]	10.5 $\pm$ 3.6 [†]	4.7 $\pm$ 1.3	4.9 $\pm$ 1.6
AUC (mg l ⁻¹ h)	82.4 $\pm$ 57.3*	58.0 $\pm$ 29.7*	60.6 $\pm$ 23.9	48.5 $\pm$ 22.2

Comparisons between healthy subjects and controls.

*NS ($P > 0.05$); [†]S ($P < 0.05$).

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The effect of metoclopramide on mefloquine pharmacokinetics

Mefloquine is effective in single oral doses of 750–1250 mg against multi-drug resistant falciparum malaria. Side effects include nausea, vomiting, diarrhoea and dizziness (Doberstyn *et al.*, 1979; Patchen *et al.*, 1989; White, 1988). Vomiting is of concern in patients because it may cause treatment failure owing to incomplete absorption (Harinasuta *et al.*, 1985). To reduce vomiting, which can arise from both the disease and the drug, we have considered the concurrent administration of the antiemetic metoclopramide. These antiemetic effects may be the result of both central and peripheral actions but through its peripheral action it increases gastrointestinal motility (Albibi & McCallum, 1983). Since accelerated gastric emptying can lead to an increase in the rate of drug absorption from the small intestine (Harrington *et al.*, 1983) and a shortening of the time to peak plasma concentration, we have examined the effect of metoclopramide on single dose mefloquine pharmacokinetics in healthy Thai male volunteers. We have also monitored side effects since any enhancement of absorption could lead to toxicity.

Seven male volunteers, (24–44 years; 47–60 kg), none of whom was on regular medication, gave written informed consent to participation in the study which was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok,

Thailand. Blood samples were taken for biochemical tests, haematology and measurement of mefloquine concentrations. A 12 lead electrocardiogram (ECG), heart rate and blood pressure were recorded.

The study was of cross-over design with each subject attending the hospital on two occasions at least 12 weeks apart. Subjects remained in hospital for the first 5 days of the study. All were fasted overnight until 2 h after mefloquine administration. On the first occasion, the subjects were randomised to receive either mefloquine or coadministration of metoclopramide and mefloquine. Metoclopramide (10 mg) was given orally 15 min prior to a single oral dose of mefloquine (750 mg). Blood samples (4 ml) were collected at 0, 15, 30, 45, 60, 75, 90, 105, 120, 150 min, then 3, 4, 6, 8, 12, 18, 24 h and 2, 3, 4, 7, 14, 21, 28, 35, 42 and 56 days after dosing; a total of 27 samples. Whole blood mefloquine concentrations were measured by h.p.l.c. (Karbwang *et al.*, 1989).

Adverse effects (gastrointestinal, central nervous system and cardiovascular) were monitored by questionnaires daily for 7 days then weekly until day 56. ECG monitoring, heart rate and blood pressure were recorded at 1, 2, 4, 6, 8, 24 h then daily for 7 days and after that weekly until day 56.

The pharmacokinetic parameters of mefloquine were calculated using standard non-compartmental methods