Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers

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Aims

To investigate the effect of tetracycline co-administration on the pharmacokinetics of halofantrine in healthy subjects.

Methods

Eight healthy males were each given 500 mg single oral doses of halofantrine alone, or with tetracycline (500 mg 12 hourly for 7 days), in a crossover fashion. Blood samples collected at predetermined intervals were analyzed for halofantrine and its major metabolite, desbutylhalofantrine (HFM), using a validated HPLC method.

Results

Co-administration of tetracycline and halofantrine resulted in a significant increase ($P < 0.05$) in the maximum plasma concentration ($C_{\max}$), total area under the concentration-time curve (AUC), and terminal elimination half-life ($t_{1/2,z}$), compared with halofantrine alone. ($C_{\max}$ 0.43 ± 0.14 vs 1.06 ± 0.44 $\mu\text{g ml}^{-1}$ (95% CI on the difference 0.30, 0.95); AUC 32.0 ± 13.6 vs 63.7 ± 20.1 $\mu\text{g ml}^{-1} \text{ h}$ (95% CI 14.2, 49.1); $t_{1/2,z}$ 90.8 ± 17.9 vs 157.4 ± 57.4 h (95% CI 21.7, 111.5)). Similarly, tetracycline caused a significant increase ($P < 0.05$) in the AUC and $C_{\max}$ of HFM.

Conclusions

Tetracycline co-administration significantly increases the plasma concentrations of halofantrine and its major metabolite.

Introduction

Halofantrine, a phenanthrene methanol, is an effective antimalarial agent [1, 2] but there are increasing reports of resistance to the drug by the malaria parasite [3]. The declining sensitivity of *P. falciparum* to halofantrine may necessitate an increase in dosage, but the cardiotoxic effects of the drug are a major concern, especially as they are plasma concentration-dependent [4]. Therefore it is important that strategies are devised to prevent the further spread of halofantrine resistance and to delay its onset in areas where the drug is still effective. One such approach is the use of combination ther-

apy [5, 6]. Co-administration of halofantrine with tetracycline may show enhanced therapeutic effect since the antibiotic has antimalarial action and it has been found to improve cure rates when used with other antimalarial drugs such as quinine [7, 8] and mefloquine [9].

Since both halofantrine and tetracycline are known to undergo biliary excretion [3, 10], it is possible that they may interact with each other through competition for this elimination pathway. Furthermore, since *in vitro* data suggest that tetracycline may be a substrate or inhibitor of CYP3A4 [11] and halofantrine is known to

be metabolized by this enzyme [12], a metabolic interaction may occur between both drugs.

The present study examined the effect of a 7-day course of tetracycline on the pharmacokinetics of a single dose of halofantrine in healthy subjects. Because desbutylhalofantrine (HFM), the major metabolite of halofantrine, has antimalarial activity similar to that of the parent drug [13], the disposition of this metabolite in the presence of tetracycline was investigated. Adverse effects of the combination were also monitored.

Methods

Subjects and drug administration

Eight healthy Nigerian males between the ages of 18–38 years, weighing 57–81 kg body weight, participated in this study after clinical assessment, laboratory baseline investigations, serum chemistry tests and ECG measurements.

All the subjects gave their informed consent and the study protocol received approval from the Ethics Committee of the Obafemi Awolowo University Teaching Hospital. None of the subjects was taking any other drugs for at least 1 month before the study and none was a smoker.

A randomized latin-square crossover design was used with a washout period of 2 months. After an overnight fast, each of the subjects received a single oral dose of 500 mg of halofantrine hydrochloride (two tablets of Halfan^R, Smithkline Beecham, Lagos, Nigeria) alone or concurrently with 500 mg tetracycline 12 hourly for 7 days (two capsules of tetracycline, Greenfield International Limited, Kemphouse, London). No other drugs or alcohol were allowed during the study. Subjects were instructed not to take tetracycline with foodstuffs known to interfere with absorption of the drug.

Sample collection

A venous blood sample (5 ml) was collected from all subjects for the determination of full blood count and differential white cell count, and for serum chemistry tests. Thereafter, blood samples were taken immediately prior to the halofantrine dose and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 168 and 336 h after dosing. The samples, which were collected initially through an in-dwelling intravenous Teflon catheter and subsequently by individual venepunctures from the forearm, were placed in EDTA tubes. They were immediately centrifuged at 2000 g to obtain the plasma, which was stored frozen at –20 °C until analysis.

Clinical assessment

ECGs were recorded at 4, 8, 12, and 48 h following drug administration. Vital signs were measured throughout the study. Adverse effects were monitored daily by means of a questionnaire.

Drug analysis

Plasma samples were analyzed for halofantrine and HFM, using a modification of a previously reported HPLC method [14]. Thus imipramine (10 µl of 50 µg ml⁻¹ solution in 1 ml plasma) was used as the internal standard instead of the chloro-substituted derivative of halofantrine [14]. This necessitated the use of a 5 µm C-8 reversed phase column (250 × 4.6 mm I.D.) to achieve peak resolution and to ensure no chromatographic interference from tetracycline. The HPLC equipment consisted of a Model 1100 chromatography pump and a Model 1200 variable wavelength detector (Cecil Instruments Ltd, Milton Technical Centre, Cambridge, UK). The mobile phase consisted of methanol and 0.05 M potassium dihydrogen phosphate (76 : 24 v/v) with 55 mM perchloric acid (pH 3.1) and was pumped through the column at a flow rate of 1.3 ml min⁻¹. Retention times of the internal standard, HFM and halofantrine were 3, 6 and 9 min, respectively. The limits of detection were 2.5 ng ml⁻¹ for halofantrine and 2.0 ng ml⁻¹ for HFM. The intra-assay and interassay coefficients of variation for both compounds were less than 6% at concentrations of 50 and 400 ng ml⁻¹ ($n = 7$), respectively.

Pharmacokinetic and statistical analysis

The peak plasma concentrations ($C_{\max}$) and the time to reach peak concentration ($t_{\max}$) were noted directly from the concentration vs time profiles. Other pharmacokinetic parameters were calculated using standard non-compartmental methods [15] with the software package WinNonlin Standard Edition, Version 1.5 (Scientific Consultant Inc. Apex, NC, USA). The Wilcoxon matched pairs signed-ranked test was used to evaluate the effects of tetracycline on halofantrine pharmacokinetics. A P value of <0.05 was considered significant.

Results

Figure 1 shows the mean ($\pm$ SD) plasma concentration-time profiles of halofantrine and HFM when the former was given alone and together with tetracycline. $C_{\max}$ and AUC were significantly higher ($P < 0.05$), when halofantrine was co-administered with tetracycline compared with halofantrine alone (Table 1). The mean $\pm$ SD values of elimination half-life ($t_{1/2,z}$) of halofantrine was also increased by tetracycline (90.8 ± 17.9 h vs

Figure 1

Mean ($\pm$ SD) plasma concentration vs time profiles for halofantrine (A) HF alone ($\square$), HF with TCN ($\blacksquare$); and HFM (B) HFM (without TCN) ($\square$), HFM (TCN presence) ($\blacksquare$); following oral administration of single doses of 500 mg of halofantrine HCl alone, and with tetracycline (TCN, 500 mg 12 hourly for 7 days), to eight subjects

Table 1

Some pharmacokinetic parameters of halofantrine and its major metabolite (desbutylhalofantrine) in eight volunteers following oral administration of 500 mg single dose of the drug alone, and with tetracycline (500 mg 12 hourly for 7 days)

Drug	Volunteer	Halofantrine		Desbutylhalofantrine	
		C_{max} ($\mu\text{g ml}^{-1}$)	AUC_T ($\mu\text{g ml}^{-1} \text{ h}$)	C_{max} ($\mu\text{g ml}^{-1}$)	$AUC(0,336 \text{ h})$ ($\mu\text{g ml}^{-1} \text{ h}$)
A	1	0.39	15.9	0.15	11.6
	2	0.30	15.1	0.26	19.2
	3	0.47	26.3	0.32	18.8
	4	0.19	18.9	0.29	17.3
	5	0.42	50.7	0.43	32.3
	6	0.60	46.7	0.56	31.7
	7	0.63	40.1	0.50	27.2
	8	0.47	42.6	0.45	20.8
	Mean $\pm$ SD	0.43 ± 0.14	32.0 ± 13.6	0.37 ± 0.13	22.4 ± 6.8
B	1	0.49	43.4	0.73	48.0
	2	1.37	40.8	1.21	45.7
	3	0.89	42.8	1.12	31.3
	4	0.46	96.5	0.58	26.4
	5	0.85	86.1	0.67	60.3
	6	1.26	54.1	0.83	40.8
	7	1.82	76.7	0.98	33.2
	8	1.33	68.9	1.21	32.9
	Mean $\pm$ SD	1.06 ± 0.44	63.7 ± 20.1	0.92 ± 0.23	39.8 ± 10.4
	Difference of mean	0.60*	31.6*	0.54*	17.4*
	(95% CI)	(0.30, 0.95)	(14.2, 49.1)	(0.32, 0.77)	(8.1, 22.5)

*Statistically significant ($P < 0.05$). A = Halofantrine alone; B = Halofantrine plus tetracycline. 95% CI 95% confidence interval on the difference.

157.4 ± 57.4 h, 95% confidence interval on the difference (CI) 21.7, 111.5, $P < 0.05$). $t_{\max}$ was unchanged by tetracycline (median (range) 6 (4–8) h alone vs 7 (4–8) h with tetracycline (95% CI –1.0, 2.5)).

$C_{\max}$ and AUC for HFM were significantly increased in the presence of tetracycline (Table 1). There was no significant change ($P > 0.05$) in $t_{\max}$ (median (range) 10 (8–12) alone vs 12 (8–12) h with tetracycline (95% CI –3.3, 2.3)).

No significant drug-related adverse effects were reported by the subjects following administration of the drug combination. The results of the blood counts and ECGs were comparable during the two treatment periods.

Discussion

The pharmacokinetic parameters obtained for halofantrine showed the usual high interindividual variation and were in agreement with values from the literature [2, 16, 17]. The increase in plasma concentrations of halofantrine in the presence of tetracycline is similar in magnitude to that found for mefloquine when administered with tetracycline [9]. Tetracycline, mefloquine and halofantrine are all excreted into the bile [3, 10, 18] and competition for this pathway of elimination could result in increased plasma drug concentrations.

Based on a report [11] which suggests that tetracycline is a substrate or inhibitor for CYP3A4, the enzyme that metabolizes halofantrine [12], a metabolic interaction between the two compounds might be expected. However, the increased plasma concentrations of the metabolite HFM in the presence of tetracycline and the finding that doxycycline, a tetracycline analogue, does not inhibit the metabolism of halofantrine in human liver microsomes [19] suggests that the interaction between tetracycline and halofantrine does not have a metabolic basis.

In summary, tetracycline was shown to increase significantly plasma concentrations of halofantrine and HFM in healthy subjects. Since the toxicity of halofantrine is concentration dependent, there may be an increased risk of adverse effects with this drug combined with higher doses of tetracycline.

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